CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020511

Trade Name : APHTHASOL ORAL PASTE 5%

Generic Name: Amlexanox Oral Paste

Sponsor : Block Drug Company

Approval Date: December 17, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 17 1996

NDA 20-511

Block Drug Company, Inc.
Attention: Richard K. Bourne, Ph.D.
Vice President Regulatory Affairs
257 Cornelison Avenue
Jersey City, New Jersey 07302-9988

Dear Dr. Bourne:

Please refer to your September 6, 1994, new drug application, and your resubmission dated April 17, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aphthasol (amlexanox oral paste) Oral Paste, 5%.

Please refer to your approvable letter dated April 16, 1996.

We acknowledge receipt of your amendments and correspondence dated April 19, May 23, June 21, July 16, August 2, September 6 and 24, October 8 (two), 15, 16 and 18, and December 2 and 4, 1996.

This new drug application provides for the treatment of signs and symptoms of aphthous ulcers in immunocompetent individuals.

We have completed the review of this application, as amended, including the enclosed revised draft labeling which was submitted August 2, 1996, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling. Accordingly, the application is approved effective the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling submitted on August 2, 1996. The enclosed revised draft labeling was stated to be acceptable in your letter dated December 4, 1996. Marketing the product with FPL that is not identical to this enclosed revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated 'FINAL PRINTED LABELING for approved NDA 20-511". Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug

become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated August 2, 1996. The commitments are listed below:

Protocols for the studies on immunocompromised and pediatric patients should be submitted to the Division of Dermatologic and Dental Drug Products within six months of approval for evaluation prior to initiation of the studies.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments".

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock up form, not final print. Please submit one copy to this Division, and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

Should you have any questions concerning this application, please contact:

Roy Blay, Ph.D.
Project Manager
Telephone: (301) 827-2023

Sincerely yours,

Michael Weintraub 12/1/98

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

The reviewers of this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540
Linda Katz, M.D., Deputy Division Director, DODDDP, HFD-540
Peter Cooney, Ph.D., Microbiology Team Leader, ONDC, HFD-805
David Hussong, Ph.D., Microbiologist, ONDC, HFD-805
Ralph Harkins, Ph.D., Director, DOBIV, HFD-725
Alaka Chakravarty, Ph.D., Biostatistician, HFD-725
Phyllis Huene, M.D., Medical Officer, DODDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Ernie Pappas, B.S., Chemist, DNDCIII, HFD-540
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Frank Pelsor, Biopharmaceutist, DPEIII, HFD-880
Ene Ette, Ph.D. Biopharmaceutist, OCPD, HFD-855
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DODDDP, HFD-540
Mary J. Kozma-Fornaro, Supervisor, Project Management Staff, DODDDP, HFD-540
Roy Blay, Ph.D., Regulatory Management Officer, DODDDP HFD-540

cc:

Original NDA 20-511
HFD-540/Div File
HF-2/MED WATCH/w/labeling
HFD-2/CDER DEP DIR/MLumpkin/w/labeling
DISTRICT OFFICE
HFD-105/w/labeling
HFD-613/w/labeling
HFD-92/w/labeling
HFD-40/w/labeling)
HFD-735/w/labeling
HFD-222/New Drug Chemistry Division Director
HFD-540/DIV DIR/Wilkin/12/4/96
HFD-540/MO/Huene
HFD-540/CHEM/Pappas/12/6/96
HFD-805/MICRO/Cooney/Hussong
HFD-725/BIOSTAT/Harkins/Chakravarty
HFD-880/BIOPHARM/Pelsor
HFD-855/BIOPHARM/Ette
HFD-540/PROJ MGR/Blay
Concurrence:
HFD-540/PHARM TEAM LEADER/Jacobs/
HFD-540/CHEM TEAM LEADER/DeCamp/12/6/96
HFD-540/SPMS/Fornaro12/6/96
HFD-880/BIOPHARM TEAM LEADER/Bashaw/
HFD-830/ACTDIR/DNDCIII/CHEN/12/11/96

drafted:12/9/96
revised:12/12/96
file: 20511ap

PHASE 4 COMMITMENTS
APPROVAL (AP)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-511

APR 16 1996

Block Drug Company, Inc.
Attention: Richard K. Bourne, Ph.D.
Vice President, Regulatory Affairs
257 Cornelison Avenue
Jersey City, NJ 07302-9988

Dear Dr. Bourne:

Please refer to your September 6, 1994, new drug application (and your resubmission dated April 17, 1995) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aphthasol (amlexanox oral paste) oral paste, 5%.

We acknowledge receipt of your communications and those of Chemex Pharmaceuticals, Inc., dated September 15 and 29, November 10, and December 1 and 5, 1994; July 31, August 15, September 21 (three), October 12, and December 21, 1995; and February 7 and March 7, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable for the indication of treatment of signs and symptoms of aphthous ulcers in immunocompetent individuals. Before this application may be approved, however, it will be necessary for you to address the following:

Clinical issues:

1. Revised draft labeling for the drug product that is identical to the enclosed draft labeling. Please note that because of extensive revisions to the draft labeling, editing notation such as strikeouts have been omitted for the sake of legibility. Redlining indicates those sections of labeling where the majority of revisions have taken place. Line numbering is provided solely as a reference aid. We recommend that you compare in a line-by-line fashion the attached draft labeling with your proposed labeling. Should additional information relating to the safety and effectiveness of this drug become available, further revision of the labeling may be required.

2. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

   A. Retabulate all safety data including results of trials that were still ongoing at the time of the NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs. now will certainly facilitate review.

B. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

C. Provide details of any significant changes or findings, if any.

D. Summarize worldwide experience on the safety of this drug.

E. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led up to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including but not limited to: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels.

Chemistry issues:

1. Please resolve the inconsistency between the particle size specification for bulk amlexanox and finished product specifications; the specification for the finished product should not be less than that for the bulk drug.

2. Environmental Assessment (EA)

   A. Please note that the EA is a stand-alone document that summarizes information that is available elsewhere. The non-confidential parts of the EA will be made public by the FDA in accordance with regulations prescribed by the Council on Environmental Quality, 40 CFR 1508.9 (see 21 CFR 25.31). The current version of the EA contains addenda that are labeled "Confidential" while other sections of the EA are unlabeled. Please revise the EA to contain three distinct parts: (1) the non-confidential EA summary, (2) non-confidential appendices, and (3) confidential appendices. References to non-confidential and confidential appendices may be included in the EA summary document as appropriate. Confidential data and information which are pertinent to the environmental review of a proposed action and which are submitted in confidential appendices should be summarized in the EA summary document to the extent possible. The EA summary document, non-confidential appendices, and finding of no significant impact will be made available for public inspection.

B. Please note that the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* is available from the Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville MD 20855, (301) 594-1012. It is also available by FAX on Demand, 1-800-342-2722, Document # 0803, or via Internet by connecting to the CDER File Transfer Protocol (FTP) server (CDVS2.CDER.FDA.GOV).

C. Regarding Section 4, Description of the proposed action:

1) The EA did not indicate the basis for the submission of this abbreviated format. The requested approval should indicate that an abbreviated EA has been submitted pursuant to 21 CFR 25.31a(b)(3). It should state the qualifying basis for submission of an abbreviated EA and describe the attributes of the drug that make the submission of an abbreviated EA appropriate. Also, this section of the EA should state the NDA identification number, 20-511, and provide a brief description of the packaging of the drug product.

2) Please submit a description of the need for the action. Also please submit a description of the medical indications for the drug product.

3) Please indicate whether proprietary intermediates are used in the production of the drug substance. If proprietary intermediates are used in the production process, the locations of their manufacture and manufacturing site information (format item 6) must be addressed in the EA. If proprietary intermediates are not used in the production process, the EA should clearly state this fact.

Also, please submit the complete addresses for the manufacturing facility for both the drug substance and drug product. Please provide the street addresses and postal codes for these facilities. Please submit a brief description of the type of environment at and near these production locations.

4) Please indicate whether the product will be used in residences and/or clinics and hospitals throughout the United States.

D. Regarding Section 5, Identification of chemical substances that are subject to the proposed action, please identify any impurities likely to be found in the drug substance at a level greater than 1%. The CAS registration number should be provided if available. Also the EA should include an MSDS for the drug substance as non-confidential information.

E. Regarding Section 6.b, Manufacture of drug product:

1) In the subsection concerning controls of air, liquid and solid effluents for the drug product manufacturing facility, a brief description of the control devices used should be included. Briefly describe any devices or techniques which serve to minimize or eliminate discharges to the environment. For example, in regard to air, describe any use of closed containers for transport of the drug substance, vacuum loading of ingredients, or filtering or scrubbing of the air exhausted from the facility.

2) Although the EA does provide the numbers of the environmental permits for each applicable matrix for the Puerto Rico facility, the expiration dates and issuing agency for these permits should be identified.

3) The facilities currently used to dispose of rejected, expired, returned or waste drug product should be identified as well as the license or permit number, issuing authority and permit expiration date, if any.

Phase 4 commitments:

Although the following comments are not approvability issues, your response to these comments is requested, particularly as they address the subsequent development of this drug.

Biopharmaceutics issues:

1. Should you plan future submissions regarding the use of this agent, please note the following comments:

   A. There was no control over the amount of amlexanox applied/administered per patient in the multiple dose studies; therefore, the extent of absorption could not be characterized. Future submissions involving this type of agent should describe well controlled multiple dose studies.

   B. Please note that individual data were not provided in the oral administration study; therefore, no conclusion could be made regarding the linearity or nonlineartity of amlexanox pharmacokinetics following administration.

   C. Please note that the type of food used in the food effect study was not specified. Please provide such specifics in any future submission(s).

Microbiology issues:

Please note that in reference to the microbiological test procedures provided, it is not necessary to test each lot for microbiological attributes; however, if testing is done, then the product must conform to existing specifications. Microbial Limits (USP) testing is not usually performed on each lot as an end-product release test.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Dr. Roy Blay, Consumer Safety Officer, at (301) 827-2020.

Sincerely yours,

Michael Weintraub 4/16/96

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure: Draft labeling dated March 28, 1996

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540
Linda Katz, M.D., Deputy Division Director, DODDDP, HFD-540
Peter Cooney, Ph.D., Microbiology Supervisor, ONDC, HFD-805
David Hussong, Ph.D., Microbiologist, ONDC, HFD-805
Ralph Harkins, Ph.D., Biostatistics Supervisor, DOBIV, HFD-725
Alaka Chakravarty, Ph.D., Biostatistician, HFD-725
Phyllis Huene, M.D., Medical Officer, DODDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Ernie Pappas, B.S., Chemist, DNDCIII, HFD-540
Dennis Bashaw, Ph.D. Biopharmaceutics Team Leader, DPEIII, HFD-880
Frank Pelsor, Biopharmaceutics Team Leader, DPEIII, HFD-880
Ene Ette, Ph.D., Biopharmaceutist, OCPB, HFD-855
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DODDDP, HFD-540
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DODDDP, HFD-540
Roy Blay, Ph.D., Regulatory Management Officer

cc:
Original NDA 20-511
HFD-540/Div. Files
HFD-540/Derm File
HFD-2/M.Lumpkin (with labeling)
HFD-80(with labeling)
HFD-100
HFD-160/MICRO/Hussong
HFD-105/Weintraub (with labeling)
HFI-20/Kupec/(with labeling)
HF-2/Medwatch (with labeling)
HFD-613 (with labeling-only for applications with labeling)
HFD-29/Sherman (with labeling)
HFD-130
HFD-730
HFD-40/DDMAC/Raymond (with labeling)
HFD-725/BIOSTAT/Chakravarty
HFD-725/BIOSTAT SUPV/Harkins/4.2.96
HFD-540/DIV DIR/Wilkin/4.8.96
HFD-540/MO/Huene
HFD-540/CHEM/Pappas/4.2.96
HFD-540/PROJ MGR/Blay/4.3.96
HFD-855/BIOPHARM/Ette
HFD-638
DISTRICT OFFICE
Concurrence:
HFD-540/DEP DIR/Katz/4.3.96
HFD-540/CHEM SUPV/DeCamp/4.2.96
HFD-540/PHARM SUPV/Jacobs
HFD-805/MICRO SUPV/Cooney
HFD-880BIOPHARM SUPV/Pelsor
HFD-550/BIOPHARM SUPV/Bashaw/4.2.96
HFD-540/PROJ MGT SUPV/Cook/4.1.96
drafted: RAB/March 27, 1996/c:\royblay\letters\nda\approval\20511.002
r/d Intials: RAB
Final:

APPROVABLE (AE)


mor

Patent Certification

Chemex Pharmaceuticals, Inc. has a license agreement with Takeda Chemical Industries, Ltd. for the use of the drug substance, amlexanox, in topical drug products. As noted in Section 13, Chemex has received a patent for the use of amlexanox in the treatment of aphthous ulcers and other mucocutaneous disorders. Thus, Chemex will not be infringing on any patents, if allowed to market amlexanox oral paste, 5%, for the treatment of aphthous ulcers.

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA/PLA # 20511 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade (generic) name/dosage form: Aphthasol (Amlexanox Oral paste) Oral paste, 5% Action: (AP) AE NA

Applicant Block Drug Co. Therapeutic Class 1P

Indication(s) previously approved NA

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Treatment of the signs + symptoms of aphthous ulcers in immunocompetent individuals

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- X (4) If no protocol has been submitted, explain the status of discussions on the back of this form. (ODE)

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Mary Jean Lynn Jenkins SCPM 12/9/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20511
HFD 540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

12/30/96

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

cc. HFD 540 /Kling

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-511 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: AMLEXANOX ORAL PASTE, 5% [redacted] Action: AP (AE) NA

Applicant Block Drug Co Therapeutic Class 1P

Indication(s) previously approved _____

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application TREATMENT OF SIGNS AND SYMPTOMS OF APTHOUS ULCERS IN IMMUNOCOMPETENT INDIVIDUALS.

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use. NOTE DR. KATZ IN LETTER WHETHER THE SPONSOR WILL COMPLY WITH A REQUEST TO CONDUCT PEDIATRIC STUDIES

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Ray Blay CSO/PM 4/3/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

4/7/96

cc: Orig NDA/PLA # 20-511
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Certification Regarding Debarment

Chemex Pharmaceuticals, Inc. has not and will not use the services of any debarred firm or individual.

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.

OCT 10 1996

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-511

October 4, 1996

SPONSOR: Chemex Pharmaceuticals
Fort Lee, NJ

DRUG: Amlexanox oral paste 5%

PROPOSED TRADE NAME: Aphthasol

INDICATION: Aphthous ulcers

DATE OF PRESENT SUBMISSION: August 2, 1996

REASON FOR SUBMISSION: Response to approvable letter of April 16, 1996.

This submission provides a revised package insert, which is in response to the approvable letter of April 16, 1996 and to the discussion at the meeting between the sponsor and FDA on July 8, 1996. A response to the other clinical issues in the approvable letter is also provided.

Package insert

The meeting of July 8 concerned the Clinical Studies and the Indications and Usage sections of the package insert. It was agreed that for the Indications and Usage section, the phrase could be deleted, so that this section will now read

In regard to the Clinical Studies section, the following agreements were reached between the sponsor and the FDA.

1. Inclusion of data comparing amlexanox oral paste to no treatment is acceptable.

2. Data from the two pivotal studies containing no treatment groups may be combined for the comparison of amlexanox oral paste to no treatment, and the data from all three studies may be combined to compare amlexanox paste to the vehicle.

3. The data on the percentage of patients healed at certain days of treatment may be presented in the form of a graph or table. If presented in a graph, the y-axis (percent of patients healed) must be extended to 100%, and the x-axis (days on treatment) must originate at day 0, and error bars must be included for each data point.

4. The statement

may be revised to state

Reviewer's comments: The package insert has been revised in accordance with the draft labeling in the approvable letter of April 16, 1996, and with the subsequent discussion at the meeting of July 8, 1996, and is acceptable. There is a typographical error in the last line of the Dosage and Administration section.

Other clinical issues

Additional requests in the approvable letter concerned an update of safety information; these requests, denoted by capital letters, and the sponsor's responses, are as follows.

A. Retabulate all safety data including results of trials that were still ongoing at the time of the NDA submission.

There were no ongoing trials at the time of the NDA submission. All safety data were submitted in the NDA.

B. Retabulate drop-outs with new drop-outs identified.

There were no ongoing trials at the time of the NDA submission; therefore, there are no new drop-outs.

C. Provide details of any significant changes or findings.

There are no significant changes or findings since the NDA submission.

D. Summarize worldwide experience on the safety of the drug.

Four periodic reports on adverse events with oral amlexanox in Japan are provided, which cover the period from January 1995 through the first half of 1996. These consist of a number of cases of rash, or nausea and vomiting. There were single cases of dizziness, dyspnea, headache, numbness of the fingers, and numbness of the limbs. On followup one patient with a rash was unchanged; the remainder were either lost to followup, improved, or recovered.

E. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

There were no patient deaths during any of the clinical studies conducted under IND . The case report forms for the premature discontinuations were submitted in the NDA.

F. Update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led up to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including but not limited to: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels.

There were no ongoing trials at the time of the NDA submission; therefore, there is no new safety information with respect to amlexanox oral paste, 5%. A world wide safety report for Amlexanox, which covers uses of the drug including those involving indications not being sought in NDA 20-511 and other dosage forms, has been provided in this submission. (This is reviewed and summarized under D. above.)

Reviewer's evaluation: The package insert has been revised in accordance with the draft labeling in the approvable letter of April 16, 1996, and with the subsequent discussion at the meeting of July 8, 1996, and is acceptable. There is a typographical error in the last line of the Dosage and Administration section.

The sponsor has also provided an adequate response to the other clinical requests in the approvable letter.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.
10/10/96.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Blay
HFD-540/DeCamp
HFD-540/Jacobs

10/10/96

Supervisory Medical Officer's Review
Division of Dermatologic and Dental Products

NDA: 20-511
Sponsor: Chemex Pharmaceuticals
Fort Lee, New Jersey
Drug: Amlexanox oral paste 5% (Aphthasol)
Indication: Aphthous Ulcers
Date of Submission: April 19, 1995
Date of Review: March 5, 1996
Primary Medical Reviewer: Phyllis Huene, MD
Secondary Medical Reviewer: Linda M. Katz, MD, MPH

(Refer to Medical Officer's Review of NDA 20-511, dated August 29, 1995, for complete discussion of the relevant trials submitted by the Sponsor in support of approval of Amlexanox oral paste 5% for the indication of the treatment of the signs and symptoms of aphthous ulcers. This review will focus on the results of the two pivotal trials described.)

BACKGROUND:

As of this writing, Amlexanox has been approved for marketing only in Japan, for the treatment of bronchial asthma (1987) and allergic rhinitis (1989) - 25 and 50 mg tablets, nasal solution 0.25% for allergic rhinitis (1988), and ophthalmic solution 0.025% for allergic conjunctivitis, pollinosis and vernal conjunctivitis (1989). Infrequently reported side effects that have been reported for these indications include: hypersensitivity reactions (such as rash and pruritus), gastrointestinal symptoms (including nausea, vomiting, anorexia, gastric discomfort, gastric pain, abdominal pain, and diarrhea), psychoneurologic symptoms (including headache, sleepiness, tremor), elevations of SGOT and SGPT, and eosinophilia. Rare side effects have included: jaundice, elevation of alkaline phosphatase, LDH or GGPT, elevation of BUN or urine protein or pollakiuria, dizziness, palpitations, hot flashes, generalized malaise or edema.

The Phase I-II clinical trials, which includes the irritation potential, sensitization potential, tolerance under conditions of clinical use, and pharmacokinetic studies have been reviewed and discussed in detail by Dr. Huene in her review. As such, no additional discussion of these trials will be undertaken by this reviewer.

The results of the clinical effectiveness studies will be discussed in the section below.

CLINICAL EFFECTIVENESS STUDIES:

(Refer to Medical Officer's Review and Statistical Review for specific details.)

Two trials were presented to discuss the efficacy of Amlexanox oral paste for individuals having aphthous ulcers.

Trial 34, 787-107

Trial 34,787-107 was a double-blind, multicenter, randomized, parallel, vehicle controlled trials, designed to determine the safety and efficacy of Amlexanox oral paste 5% when applied four times a day to minor aphthous ulcers for a maximum of 7 days. The primary efficacy variables assessed were the percentage of patients in each treatment group with all ulcers healed, and the percentage of patients in each treatment group with all ulcer pain resolved.

Efficacy was assessed by the intent-to-treat analysis , in which all patients enrolled into the study were assessed. A second analysis was performed in those patients who were considered to be efficacy evaluable (i.e, patients who discontinued prematurely and those who were protocol violators were excluded). For consistency with both the Medical Officer's Review and the Statistical Review, only the results of the efficacy evaluable population will be discussed. (The tables of raw data can be found in both the Medical Officer Review and the Statistical Review, and, as such, will not be copied into this text.)

On all evaluation days (day 3 through 7), the mean ulcer size in the Amlexanox group was significantly smaller than in the vehicle group ($p<0.05$). The mean change in the ulcer size from baseline was not significantly different in the two treatment groups. There were no significant differences between the treatment groups in the amount of ulcer pain at any time period and no differences in the change in ulcer pain from baseline at any of the time periods.

The percentage of patients with healed ulcers in the Amlexanox group was significantly greater than in the vehicle on day 5 ($p=0.027$) and day 7 ($p=0.003$). The percentage of patients with complete resolution of pain in the Amlexanox group was significantly higher than in the vehicle group on day 3 ($p=0.03$) and day 6 ($p=0.052$). Time to ulcer healing was significantly lower in the Amlexanox group (5.0 days for Amlexanox versus 5.6 days for vehicle ($p=0.022$)). The estimated median time for complete pain relief was 3.4 days in the Amlexanox group versus 3.9 days in the vehicle group. (These results were significantly different by Wilcoxon comparison ($p=0.035$)).

There were no reports of adverse events in the Amlexanox group. The two reports were in the vehicle group, which consisted of increased pain at the ulcer site, and nausea after 6 days of treatment.

Trial 34, 787-108

Trial 34,787-108 was a double-blind, multicenter, randomized, parallel, vehicle and no treatment, controlled trial, designed to determine the safety

and efficacy of Amlexanox oral paste 5% when applied four times a day to minor aphthous ulcers for a maximum of 7 1/2 days. The primary efficacy variables assessed were the percentage of patients in each treatment group with all ulcers healed, and the percentage of patients in each treatment group with all ulcer pain resolved.

Efficacy was assessed by the intent-to-treat analysis , in which all patients enrolled into the study were assessed. A second analysis was performed in those patients who were considered to be efficacy evaluable (i.e, patients who discontinued prematurely and those who were protocol violators were excluded). For consistency with both the Medical Officer's Review and the Statistical Review, only the results of the efficacy evaluable population will be discussed. (The tables of raw data can be found in both the Medical Officer Review and the Statistical Review, and, as such, will not be copied into this text.)

On days 4 through 8, the mean ulcer size in the Amlexanox group was significantly smaller than in the vehicle group ($p<0.05$) and was significantly smaller than in the untreated group on days 3 through 8 ($p<0.05$). The mean change in the ulcer size from baseline was significantly greater in the Amlexanox group than both the vehicle and the untreated groups at all evaluation times ($p<0.05$). The mean pain measurement in the Amlexanox group was significantly less than in the vehicle group on days 5 and 7. It was significantly less than the untreated group at days 3 through 8 ($p<0.05$). The mean change in pain from baseline was significantly greater in the Amlexanox group over vehicle on days 4 through 7 and days 3 through 8 for the untreated patients ($p<0.05$).

The percentage of patients with healed ulcers in the Amlexanox group was significantly greater than in the vehicle on day 8 ($p=0.031$) and on days 3 thought 8 ($p<0.05$) for the untreated patient group. The percentage of patients with complete resolution of pain in the Amlexanox group was significantly higher than in the vehicle group on days 5 through 8 and on days 3 through 8 ($p<0.05$). Time to ulcer healing was significantly lower in the Amlexanox group than in both the vehicle group ($p=0.053$) and the untreated group ($p=0.001$). The estimated median time for complete pain relief was 3.6 days in the Amlexanox group versus 4.2 days in the vehicle group and 5.0 days in the untreated group. The time to complete pain relief was marginally significantly less in the Amlexanox group than in the vehicle group ($p=0.047$) and significantly less than in the untreated group ($p=0.000$).

There were few reports of adverse events. No patients discontinued therapy as a result of an adverse event. Stinging pain was reported in 4 (2.0%) of Amlexanox patients and 1 (0.5%) of vehicle patients. Dry mouth was reported in 1 (0.5%) of Amlexanox patients and superficial mucocele was reported in 1 (0.5 %) of vehicle patients.

Trials 34, 787-102 and 34,787- 106

These trials will not be discussed in this review, as they did not measure the efficacy variables assessed in the above two trials. (For additional information regarding these trials, the readers are referred back to the Primary Medical Officer Review and the Statistical Review).

CONCLUSION:

The results of the two pivotal trials indicate significant differences in the established primary efficacy variables assessed: the percentage of patients in each treatment group with all ulcers healed, and the percentage of patients in each treatment group with all ulcer pain resolved. There was a significant difference in the rate of ulcers healed, which translates into a median reduction of 0.6 days in Trial 107 and 0.8 days in Trial 108. Further, a median reduction for reduction in pain of 0.5 days was seen in Trial 107 and 0.6 days in Trial 108. It is noteworthy, that the Amlexanox group versus the no treatment population revealed greater statistical significance for all efficacy variables assessed, which would be expected if the product were effective. The primary medical reviewer felt that these results, although statistically significant, were not clinically meaningful. Despite the small reductions observed in the clinical trials reviewed to support efficacy of Amlexanox, statistically significant results were obtained that would support the approval of Amlexanox to treat the signs and symptoms of aphthous ulcers in the general population.

This application did not assess the efficacy of this product in immunocompromised hosts, which will need to be addressed by the Sponsor as part of their Phase 4 commitments. Further, because of the way in which pain relief was assessed, the sponsor cannot be given an analgesic or anesthetic type claim for pain relief. The labeling will be addressed separately and attached at the end of the medical reviews.

Linda M. Katz, M.D., M.P.H.
Deputy Director,
Dermatologic and Dental Products

cc: Orig NDA
HFD-540
HFD-540\Katz
HFD-540\Huene
HFD-540\Blay
HFD-540\DeCamp
HFD-540\Jacobs

3/26/96

Minutes of Meeting

DRAFT

Date: March 4, 1996
Sponsor: Block Drug
Drug: Amlexanox, NDA 20-511
Purpose: Discussion of Approvability

FDA Attendees:

Roy Blay, Ph.D., Consumer Safety Officer
MaryJane Walling, ODEV
Linda Katz, M.D., Deputy Division Director
Jonathan Wilkin, M.D., Division Director
Michael Weintraub, M.D., Office Director
Mac Lumpkin, M.D., Director, CDER

Dr. Lumpkin noted that there was a positive statistically significant difference between Amlexanox treatment and no treatment at all time points. Amlexanox treatment was also generally more efficacious than the vehicle-treated control.

Dr. Katz said that the company wished a two-fold indication for its product: (1) accelerated wound healing, and (2) decreased pain. Dr. Katz noted that the statistical and clinical reviews of this NDA did not provide substantive support for the pain indication; therefore, the agent should not be presented as an analgesic. The decreased time of pain sensation correlated with the healing of the mucosa, not from any intrinsic analgesic effect of the agent. In view of the above information, Dr. Lumpkin indicated that it would be appropriate to use language in the labeling indicating accelerated healing but not pain relief.

In response to Dr. Lumpkin's question regarding population definition, Dr. Katz noted that the trials took place in immunocompetent individuals and that the labeling for the agent should state this fact.

cc:
NDA 20-511
HFD-540\Wilkin\Katz\Blay
HFD-105\Weintraub\Walling
HFD-002\Lumpkin
HFD-101\Temple

DRAFT

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MEDICAL OFFICER'S REVIEW OF NDA 20-511

3/19/96

MEDICAL OFFICER'S REVIEW OF NDA 20-511
ORIGINAL SUBMISSION

August 29, 1995

SPONSOR: Chemex Pharmaceuticals
Fort Lee, NJ

DRUG: Amlexanox oral paste 5%

Chemical name: 2-amino-7-isopropyl-5-oxo-5H-benzopyranol-pyridine-3-carboxylic acid.

PROPOSED TRADE NAME: Aphthasol

INDICATION: Aphthous ulcers

FORMULATION:

Amlexanox	5.0%
Mineral oil	%
Gelatin	%
Pectin	%
Carboxymethylcellulose sodium ..	%
Carboxymethylcellulose sodium ..	%
Glyceryl monostearate	%
White petrolatum	%
Benzyl alcohol	%

DOSAGE AND ADMINISTRATION: Applications QID until ulcer healing occurs.

DATE OF SUBMISSION: April 19, 1995

RELATED SUBMISSIONS: INDs

PHARMACOLOGY AND CONTROLS REVIEWS: These are not as yet available.

Scientific rationale

Amlexanox has been shown in preclinical studies to be an antiallergic, anti-inflammatory agent. The mechanism of action for accelerating the healing of aphthous ulcers is not known.

Foreign marketing history

Amlexanox has been approved for marketing only in Japan in the following formulations.

1. Amlexanox tablets, 25 and 50 mg (Solfa tablets); approved in 1987 for bronchial asthma and in 1989 for allergic rhinitis.

2. Amlexanox nasal solution 0.25% (Solfa); approved in 1988 for allergic rhinitis.

3. Amlexanox ophthalmic solution 0.25% (Elics); approved in 1989 for allergic conjunctivitis, pollinosis, and - vernal conjunctivitis.

The dosage of Amlexanox tablets for asthma and allergic rhinitis is 25 to 50 mg TID. Side effects listed in the package insert as occurring infrequently are hypersensitivity reactions such as rash and pruritus, gastrointestinal symptoms such as nausea, vomiting, anorexia, gastric discomfort, gastric pain, abdominal pain, and diarrhea, psychoneurologic symptoms such as headache, sleepiness, or tremor, and elevation of GOT and GPT, and eosinophilia. Side effects occurring rarely are jaundice, elevation of alkaline phosphatase, LDH or GTP, elevation of BUN or urine protein or pollakiuria, and dizziness, palpitations, hot flushes, generalized malaise or edema.

The dosage of Amlexanox nasal solution is a single dose of spray, which provides 0.225 mg Amlexanox, inhaled into each nasal cavity three to six times a day, at intervals of about three hours. Side effects are the infrequent occurrence of a sensation of irritability of the nose, sensation of dry nose, epistaxis, contact dermatitis in the anterior nares, nausea, stomachache, and headache, and the rare occurrence of a rash.

The dosage of Amlexanox ophthalmic solution is 1 to 2 drops instilled in the eye four times a day. Side effects are contact dermatitis, blepharitis, eye discharge, irritation, conjunctival congestion, formation of conjunctival follicles, and itching.

Phase I-II clinical studies

1. Irritation potential. The investigator for this study was William Jordan, M.D., Richmond, VA. Twenty-five subjects, 4 males and 21 females, were studied. Applications of 200 mg of 1% and 5% Amlexanox paste and the paste vehicle were made to skin sites on the back under occlusive patches for 24 hours on three consecutive days. The sites were evaluated for skin reactions at 24 hours after each application and at 48 hours after the last application, with grading done on the following scale:

0	=	normal skin
0.5	=	barely perceptible redness, < 25% of test area
1	=	macular, faint erythema involving at least 25% of test area.
1.5	=	mild to moderate erythema without induration.
2	=	moderately intense erythema with or without induration and involving at least 25% of the test area.

3	=	strong, indurated erythema and accompanying vesicles or superficial erosions involving at least 25% of the test area.
3.5	=	deep intense erythema with some bullae.
4	=	bullae (skin necrosis) or extensive erosions involving at least 50% of the test area.

Twenty-four subjects completed the study. One subject discontinued prematurely due to Grade 3 reactions, considered to be allergic contact dermatitis, at all three test sites at 24 hours after the first application. This subject had a previous history of contact dermatitis with sunscreens.

There were no reactions with 5% Amlexanox paste in the remaining 24 subjects. One subject had a reaction score of 0.5 with 1% Amlexanox paste. Six subjects had reactions with the vehicle paste; these were scored at 1.5 in one, 1 in two, and 0.5 in four. There were no reactions in any subject at 48 hours after removal of the third patch.

2. Sensitization potential. This was performed by William Jordan, M.D., Richmond, VA. on 195 subjects. In the induction period, applications of 200 mg of 5% Amlexanox paste and the vehicle paste were made to test sites on the back under occlusive patches for 48 hours, three times weekly for three weeks. After a two week rest period, two consecutive 48 hour challenge applications under occlusive patches were made to new skin sites on the back. Evaluations for skin reactions were done at each patch removal, with grading according to the same scale as in the previous study on irritation potential.

Two hundred and fourteen subjects, 183 females and 31 males, were entered into the study, of which 195 completed the study. Nineteen subjects discontinued from the study prematurely. Only one discontinuation was due to study-related adverse effects; this was a case of severe itching due to the tape used to secure the patches.

During the induction phase there were no irritation scores higher than 1.5. From 6% to 15% of the subjects had a score of 0.5 with the active paste or the vehicle during the induction period. From 0.5% to 1.0% of the subjects had a score of 1.0 with the active paste or the vehicle during the last few days of the induction period, and 0.5% of the subjects had a score of 1.5 with the vehicle during the end of the induction period; none of the subjects had a score of 1.5 with the active paste.

At the challenge a few subjects had a reaction score of 0.5 at either the active or vehicle sites. There was no evidence of contact sensitization.

3. Tolerance under conditions of clinical use. This was an open label study to assess the safety and tolerance of 5% Amlexanox paste under conditions of clinical use. The investigators were dentists with additional training in oral pathology. These were as follows.

Carl Allen, D.D.S., M.S.D.
Ohio State University
College of Dentistry
Columbus, Ohio

William Binnie, D.D.S.
Baylor College of Dentistry
Dallas, TX

Michael Rohrer, D.D.S., M.S.
Stephen Young, D.D.S., M.S.
The University of Oklahoma
College of Dentistry
Oklahoma City, OK

Steven Vincent, D.D.S.,M.S.
University of Iowa
College of Dentistry
Iowa City, IA

The patients entered into the study were males and females 18 years or more with from one to three minor aphthous ulcers located such that they were easily accessible for evaluation and treatment, and that normally took more than five days to resolve. The patients were treated with applications of 5% Amlexanox paste to the oral mucosa at the sites of the ulcers four times daily for 28 days, regardless of when the ulcers healed. Treatment was also given to any new ulcers that developed.

The following safety evaluations were made weekly during the treatment period and at one week after discontinuation: adverse events, serum amlexanox levels, and local irritation. Laboratory evaluations were made at baseline and at the post-treatment followup. No assessments were made of efficacy parameters.

Irritation was evaluated in terms of the severity of erythema on the following scale.

0	=	no erythema.
0.5	=	faint, barely perceptible erythema, light red/pink in color; no clearly defined borders.
1	=	mild, definite erythema, red/pink in color; borders may be defined.
1.5	=	mild to moderate erythema.
2	=	moderate erythema, red but not dark in color, with defined borders.
2.5	=	moderate to severe erythema, red, dark in color.
3	=	strong erythema, very red, dark in color, may show additional symptoms.

If erythema were present, the investigators were asked to determine whether the erythema was related to the medication or was simply a symptom of the aphthous ulcer.

The following laboratory tests were performed: CBC with differential, platelets, BUN, creatinine, total bilirubin, SGPT, SGOT, AP, albumin, total protein, cholesterol, triglycerides, glucose, uric acid, phosphorus, calcium, sodium, potassium, chloride, and urinalysis. The laboratory tests done at weeks 1 through 4 included the same parameters except for cholesterol, glucose, and triglycerides. Serum samples for Amlexanox determinations were obtained prior to and two hours after the first application, prior to the first application each week throughout the treatment period, prior to and two hours after the last application, and at one week following completion of the study.

Results were as follows.

a. Patient enrollment and disease characteristics. One hundred patients were enrolled in the study, of which one patient was discontinued after one week of treatment for lack of compliance with the visit schedule. Of the 100 patients, 45 were female and 55 were male. All patients entered had at least one aphthous ulcer; 15 patients had two ulcers and 6 patients had three ulcers. The average ulcer size at entry was 9 mm^2.

b. Local irritation. The average erythema scores and the frequency distribution of erythema scores were as follows.

Severity of erythema						
	Baseline	Week 1	Week 2	Week 3	Week 4	Followup
Average erythema score	1.3	0.3	0.2	0.1	0.06	0.02
Erythema scores (# pts)						
0	7	52	76	88	91	96
0.5	15	26	13	6	4	1
1.0	32	13	8	3	4	1
1.5	12	2	1	0	0	0
2.0	21	5	1	2	0	0
2.5	13	1	0	0	0	0

The erythema at baseline was attributed to the aphthous ulcers, and in all cases but one the observations of erythema were associated with aphthous ulcers and were not attributed to the use of Amlexanox paste.

One patient developed hemorrhagic petechiae and local mucosal erythema of mild severity on days 27-28 of the study. The investigator felt that the clinical findings were consistent with a diagnosis of contact mucositis due to Amlexanox paste. All symptoms had resolved at the one week followup visit.

c. Adverse events. No patient discontinued the study due to an adverse event. Three patients experienced adverse events that might have been related to the test material.

One patient experienced mild nausea and indigestion at the time of each application, which lasted about 20 minutes; this was considered to be definitely related to the application of Amlexanox. This patient also developed several bumps or ridges in the area of application during the second week which persisted throughout the duration of the study. Another patient had contact mucositis considered to be due to Amlexanox, as described previously. A third patient had a transient rash on the arms, hands, and neck, which was not noticed by the investigator; no intraoral symptoms occurred and no definite etiology could be determined.

d. Laboratory evaluations. There were no changes in clinical laboratory parameters that were considered by the investigators to be clinically significant or related to the test product.

e. Amlexanox levels. The mean serum Amlexanox concentrations and ranges at each time period were as follows.

Mean serum Amlexanox concentrations ng/ml (serum concentration ranges)	
Day 1, pre-dose	0.3 (0-14)
Day 1, 2-hour	25.7 (0-193)
Week 1, pre-dose	27.4 (0-559)
Week 2, pre-dose	33.2 (0-406)
Week 3, pre-dose	38.9 (0-599)
Week 4, pre-dose	37.5 (0-561)
Week 4, 2 hour	74.1 (0-761)
Followup	0.6 (0-29)

4. Pharmacokinetic studies. Three single and multiple dose pharmacokinetic studies have been performed with 5% Amlexanox paste. The sponsor's conclusions were that Amlexanox was absorbed systemically after topical application of the 5% oral paste. Those pharmacokinetic parameters that are usually dose-independent were similar for the 5% oral paste and the tablets. Comparison of the serum level vs time curves and Tmax values indicated that the absorption from the 5% oral paste is more like the absorption from the tablets than from the nasal solution. This was felt to indicate that direct absorption through the aphthous ulcer is a minor

component of the total systemic absorption of the paste.

According to the sponsor, none of the multiple dose studies indicated accumulation of Amlexanox. Studies with the oral paste indicated that steady state levels were achieved by one week and there were no further increases when dosing was extended to four weeks. Studies with tablets, nasal solution, and ophthalmic solution also did not indicate accumulation.

Reviewer's note: These studies have not been evaluated by this reviewer. A review and evaluation is to be done by the Division of Biopharmaceutics.

Clinical effectiveness studies

I. Study 107.

The report of this study provided in the original submission of the NDA was later found on audit of the clinical sites to be incorrect, because of an error in the drug assignment in the database for eight patients at one clinical center. This was corrected and the data were re-analyzed; the submission of 4/19/95 provides the corrected study report, as follows.

The investigators for the study were:

1	Thomas Aufdemorte, D.D.S UT Health Science Center School of Dentistry San Antonio, TX	7	James Cade, D.D.S. Louisiana State Univ. Med. Ctr. School of Dentistry New Orleans, LA
2	James Burns, D.D.S. Medical College of Virginia School of Dentistry Richmond, VA	8	Alan Gould, D.D.S., M.S. University of Louisville School of Dentistry Louisville, KY
3	Michael Hall, D.D.S. Medical College of Georgia School of Dentistry Augusta, GA	9	Richard Wesley, D.D.S, M.S.D. University of Detroit Dental School Detroit, MI
4	Karen Rossie, D.D.S., M.S. University of Pittsburgh School of Dental Medicine Pittsburgh, PA	10	Joan Phelan, D.D.S. VA Medical Center Northport, NY
5	Steven Vincent, D.D.S, M.S. University of Iowa College of Dentistry Iowa City, IA	11	Charles Shuler, D.M.D., Ph.D. University of Southern California Center for Craniofacial Mol. Bio. Los Angeles, CA
6	Sook-Bin Woo, D.M.D., M.S. Brigham Dental Group Boston, MA	12	Mario Martinez, D.M.D., M.S. University of Alabama School of Dentistry Birmingham, AL

The conduct of the study was as follows.

1) Study objective: This was to determine the safety and efficacy of 5% Amlexanox paste when applied four times daily to minor aphthous ulcers.

2) Study design: This was a double blind, multicenter, randomized, parallel group comparison with the product vehicle in patients with minor aphthous ulcers.

3) Patient selection: Patients selected were males and females 18 years or older, with one to three aphthous ulcers of less than 48 hours duration, in locations easily accessible for evaluation and treatment, including the buccal mucosa, labial mucosa, floor of the mouth or the tongue. The patients were to have a history of recurrent minor aphthous ulcers and an expectation that their ulcers normally take five days or more to resolve.

4) Patient exclusions: Patients with the following conditions were excluded from the study.

a. Pregnancy or lactation.
b. Normal resolution of aphthous ulcers in less than 5 days.
c. Concurrent clinical conditions that might pose a health risk to the patient or could potentially influence the outcome of the study.
d. Ulcers which are a manifestation of a systemic disease such as ulcerative colitis, Crohn's disease, Behcet's disease, or anemia.
e. Treatment with systemic steroids, oral retinoids, or other immunomodulatory agents within one month of study entry.
f. Chronic use of NSAIDs, acetaminophen, or oral antihistamines within one month of study entry. Patients who had occasionally used these products were enrolled if the medications had not been used within three days of study entry.
g. Treatment with any topical medication within two weeks of study entry.
h. Treatment of the ulcer with any preparation or medication within 48 hours of study entry.
i. Treatment with a systemic antibiotic within two weeks of study entry.
j. Dental surgery within two weeks of study entry.
k. Orthodontic braces or retainer that might come into contact with the ulcer.
l. Use of chewing tobacco products or cigars, or history of drug or alcohol abuse.

5) Dosage and administration: The patient applied the test product to each of up to three ulcers four times a day for seven days, or until all the ulcers had healed, whichever occurred first. The applications were made after meals and at bedtime.

6) Efficacy evaluations: The patients returned daily for measurements of the ulcer size and evaluation of the pain associated with the ulcer.

a. Ulcer size: This was measured with a calibrated dental probe. Two measurements were taken, one of the longest diameter and the other perpendicular to this measurement. These were then multiplied to obtain the ulcer size.

b. Ulcer pain: The investigator estimated the amount of pain by marking a 10 cm line which had the following descriptive assessments at equal distances from one end:

- No pain
- Pain with rough aggravation of the ulcer
- Pain with moderate aggravation of the ulcer
- Pain with slight aggravation of the ulcer
- Constant pain
- Severe pain

The primary efficacy variables were the percentages of patients in each treatment group with all ulcers healed, and the percentages of patients in each treatment group with all ulcer pain resolved.

7) Safety parameters: Adverse events were recorded daily as they occurred, together with the severity and the perceived relationship to the test product.

Results were as follows.

1) Patient enrollment and demographic characteristics: A total of 424 patients were enrolled into the study, of which 385 were considered to be evaluable for efficacy. The demographic and disease characteristics of all patients enrolled were as follows:

Demographic characteristics				
	Amlexanox (n=211)		Vehicle (n=213)	
	Male	Female	Male	Female
	99 (47%)	112 (53%)	102 (48%)	111 (52%)
Age				
Mean	26.2	29.4	26.7	27.7
Range	18-49	18-64	19-64	18-54
Race				
Caucasian	90 (42%)	97 (46%)	86 (40%)	89 (42%)
Black	1 (0.5%)	6 (2.8%)	3 (1.4%)	6 (2.8%)
Hispanic	3 (1.4%)	4 (1.9%)	0	4 (1.9%)
Asian	5 (2.4%)	5 (2.4%)	12 (5.6%)	10 (4.7%)
Other	0	0	1 (0.5%)	2 (0.9%)

Baseline ulcer assessment		
	Amlexanox (n=211)	Vehicle (n=213)
Duration of outbreak Mean (hrs)	24.2	24.8
# Patients with 1 ulcer	165 (78%)	172 (81%)
# Patients with 2 ulcers	38 (18%)	37 (17%)
# Patients with 3 ulcers	8 (4%)	4 (2%)
Mean ulcer size (mm^2)	6.04	6.75
Mean pain severity	4.37	4.66

Ulcer history		
	Amlexanox	Vehicle
Recurrences per year Mean Range	11.2 1 - 100	11.1 1 - 100
Ulcers per outbreak Mean Range	1.6 1 - 6	1.6 1 - 6
Anticipated days for ulcer to heal Mean Range	7.8 3 - 30	8.2 5 - 21

2) Discontinuations and protocol violations: Sixteen patients discontinued the study prematurely; this included 7 Amlexanox patients and 9 vehicle patients. Two of the discontinuations, both involving vehicle patients, were related to treatment; one patient requested discontinuation because the medication was not effective, and another had an aggravation of pain at the application site. Other discontinuations were either patients lost to followup or were unrelated to the study.

Twenty-four patients had protocol violations; this included 10 in the Amlexanox group and 14 in the vehicle group. The violations included application of study material more than 48 hours after first noticing the ulcer, concomitant medications, missed visits, too short an anticipated time for healing, and missed applications.

3) Efficacy evaluations: In the study report the sponsor provided an analysis for all patients enrolled into the study for the duration that they were in the study (intent-to-treat analysis). A second analysis of only those patients that were considered to be efficacy evaluable is provided in the statistical report. This latter analysis excludes those patients who discontinued prematurely and patients who had protocol violations. Only the results of this analysis (efficacy evaluable) is included in this review.

The sponsor's conclusions in this regard were that there were no differences between the two analyses in the levels of significance, interpretations of the data, and conclusions of the study.

The mean ulcer size and the mean change in ulcer size from baseline at each return visit were as follows.

Mean ulcer size (mm^2)				
	Amlexanox		Vehicle	
	# pts	Mean	# pts	Mean
Day 1	201	6.01	199	6.74
Day 3	194	5.48	194	7.05
Day 4	196	4.55	193	6.05
Day 5	197	3.23	188	5.14
Day 6	195	2.52	190	4.10
Day 7	194	1.87	191	3.23

Mean change in ulcer size from baseline				
	Amlexanox		Vehicle	
	# pts	Mean	# pts	Mean
Day 3	194	-0.61	194	0.26
Day 4	196	-1.46	193	-0.70
Day 5	197	-2.81	188	-1.60
Day 6	195	-3.56	190	-2.51
Day 7	194	-4.01	191	-3.50

On all evaluation days, days 3 through 7, the mean ulcer size in the Amlexanox group was significantly smaller than in the vehicle group ($p<0.05$). The mean change in ulcer size from baseline, however, was not significantly different in the two treatment group at any of the evaluation times.

The mean pain measurement and the mean change from baseline at each return visit were as follows.

Mean pain measurement				
	Amlexanox		Vehicle	
	# pts	Mean	# pts	Mean
Day 1	200	4.35	199	4.69
Day 3	195	2.99	194	3.29
Day 4	194	1.84	192	2.22
Day 5	193	1.23	187	1.45
Day 6	192	0.70	187	1.00
Day 7	188	0.37	188	0.59

Mean change in pain measurement from baseline				
	Amlexanox		Vehicle	
	# pts	Mean	# pts	Mean
Day 3	195	-1.35	194	-1.38
Day 4	194	-2.50	192	-2.43
Day 5	193	-3.09	187	-3.17
Day 6	192	-3.61	187	-3.64
Day 7	188	-3.93	188	-4.05

There were no significant differences between the treatment groups in the amount of ulcer pain at any time period. There were also no differences between the treatment groups in the change in ulcer pain from baseline at any of the time periods.

The percentages of patients with ulcers healed and with the pain healed at each return visit were as follows.

# and % of patients with ulcers healed		
	Amlexanox	Vehicle
Day 3	3.5% (7/198)	2.1% (4/195)
Day 4	14.1% (28/198)	15.4% (30/195)
Day 5	35.9% (71/198)	25.3% (49/194)
Day 6	49.2% (97/197)	42.1% (82/195)
Day 7	68.5% (135/197)	53.6% (104/194)

# and % of patients with pain healed		
	Amlexanox	Vehicle
Day 3	19.7% (39/198)	11.8% (23/195)
Day 4	39.4% (78/198)	33.5% (65/194)
Day 5	57.6% (114/198)	50.0% (97/194)
Day 6	73.2% (145/198)	63.9% (124/194)
Day 7	82.2% (162/197)	75.7% (146/193)

The percentage of patients with healed ulcers in the Amlexanox group was significantly greater than in the vehicle group on day 5 ($p=0.027$) and day 7 ($p=0.003$); there were no significant differences at the other time periods. The percentage of patients with complete resolution of pain in the Amlexanox group was significantly higher than in the vehicle group on day 3 ($p=0.03$) and day 6 ($p=0.052$); there were no significant differences at the other time periods.

The time to first occurrence of ulcer healing was as follows.

Ulcer healing Time to first occurrence				
	Amlexanox		Vehicle	
Followup days[a]	# pts at risk[b]	% healed (Cum.)[c]	# pts at risk[b]	% healed (Cum.)[c]
0 - 2	198	3.5%	195	2.1%
2 - 3	190	14.2%	191	15.4%
3 - 4	169	36.0%	163	25.2%
4 - 5	126	49.2%	143	42.5%
5 - 6	97	69.1%	109	54.1%
6 - 7	0	69.1%	0	54.1%

[a] time from the beginning of treatment to ulcer healing or last ulcer assessment.
[b] number of patients at the beginning of each time interval without ulcer healing.
[c] the estimated percent of patients with all ulcers healed by the end of the time interval.

The estimated median time for healing was 5.0 days in the Amlexanox group and 5.6 days in the vehicle group.

The time to healing was significantly less in the Amlexanox group than in the vehicle group ($p=0.022$).

The time to complete pain relief was as follows:

Complete pain relief Time to first occurrence				
	Amlexanox		Vehicle	
Followup days[a]	# pts at risk[b]	% healed (Cum.)[c]	# pts at risk[b]	% healed (Cum.)[c]
0 - 2	198	19.7%	195	11.8%
2 - 3	158	41.6%	171	34.5%
3 - 4	115	59.9%	125	51.8%
4 - 5	79	74.6%	92	65.4%
5 - 6	48	83.6%	65	76.1%
6 - 7	0	83.6%	0	76.1%

[a] time from the beginning of treatment to pain relief or last pain evaluation.
[b] number of patients at the beginning of each time interval without complete pain relief.
[c] the estimated percent of patients with complete pain relief by the end of the time interval.

The estimated median time for complete pain relief was 3.4 days in the Amlexanox group and 3.9 days in the vehicle group.

The time to complete pain relief in the Amlexanox group was not significantly less than in the vehicle group by the Log rank comparison ($p=0.083$), but was significantly less than in the vehicle group by the Wilcoxon comparison ($p=0.035$). As specified in the protocol, either method of analysis was to be used.

4) Adverse experiences: Two patients, both in the vehicle group, discontinued due to adverse events. One had an aggravation of pain at the ulcer site, which was considered definitely related to treatment. The other patient had nausea after six days of treatment; the relationship to the test medication was considered by the investigator to be remote.

The adverse events that were considered to be possibly, probably, or definitely related to treatment were as follows.

Adverse events		
	Amlexanox	Vehicle
Nausea	3 (1.4%)	1 (0.5%)
Diarrhea	1 (0.5%)	0
Stinging/pain	2 (1%)	1 (0.5%)
Numbness	0	1 (0.5%)
White plaque	0	1 (0.5%)
Dryness	1 (0.5%)	0
Facial flushing	1 (0.5%)	0

Reviewer's comments: In summary, the results of the efficacy parameters in Study 107 were as follows:

a) Mean change in ulcer size and amount of pain: The mean change in ulcer size in the Amlexanox group was not significantly different from the vehicle group at any of the evaluation times on days 3 through 7. The mean change in pain with Amlexanox was not significantly different from that with the vehicle at any of the evaluation times, and in fact was somewhat greater with the vehicle.

b) Percentage of patients with healed ulcers and with resolution of pain: The percentage of patients with ulcers healed with Amlexanox was significantly greater than with the vehicle at days 5 and 7, and the percentage of patients with resolution of pain with Amlexanox was significantly greater at days 3 and 6.

c) Estimated median times for healing and for resolution of pain: The estimated median time for ulcer healing was 5.0 days in the Amlexanox group and 5.6 days in the vehicle group; the difference was significant. The estimated median time for pain resolution was 3.4 days in the Amlexanox group and 3.9 days in the vehicle group; the difference was significant by one method of analysis but not by another method.

The sponsor was queried as to the differences in the numbers of patients in the different tabulations. In the group of evaluable patients, with the exclusion of the protocol violators and the patients that were discontinued prematurely, there should be 194 patients in the Amlexanox group and 190 patients in the vehicle group. However, certain of the tabulations list a larger number of patients than this in each treatment group. The sponsor's reply was

that in all the tables that directly summarize the ulcer size and the amount of pain the patient numbers represent the actual numbers of patients from whom data were collected for each of the time points, with the only exception being a carrying forward of data from patients with healed ulcers. For tables on derived calculations on ulcer healing and resolution of pain scoring, certain rules were imposed to handle missing values; thus the numbers in these tables represent the number of data points used for each of the calculations. This reviewer feels that a statistical review is needed to determine the validity of these methods of analyses.

However, it is the conclusion of this reviewer that the results of this study do not demonstrate adequate effectiveness for the labeling claim that the product accelerates the healing of aphthous ulcers. It is felt that an acceleration of healing by 0.6 days is not clinically significant, and is not sufficient to justify use of this product.

II. Study . 108.

The report of this study provided in the original submission of the NDA was later found on audit of the clinical sites to have a potential inconsistency in the way the pain measurements were handled for one patient. The data analyses were re-generated with a correction of this potential inconsistency; the submission of 4/19/95 provides the corrected study report, as follows.

The investigators for the study were:

1	Stephen Ahing, D.D.S. University of Manitoba School of Dentistry Mainitoba, Canada	7	Catherine Flaitz, D.D.S. UT Health Science Center School of Dentistry Houston, TX
2	Bruce Barker, D.D.S. University of Missouri School of Dentistry Kansas City, MO	8	Michael Kahn, D.D.S. University of Tennessee School of Dentistry Memphis, TN
3	Ron Baughman, D.D.S. University of Florida School of Dentistry Gainesville, FL	9	Brad Neville, D.D.S. Medical University of South Carolina School of Dentistry Charleston, SC
4	Steven Budnick, D.D.S. Emory University School of Medicine Decatur, GA	10	Brad Rodu, D.D.S. University of Alabama School of Dentistry Birmingham, AL
5	Douglas Damm, D.D.S. University of Kentucky College of Dentistry Lexington, KY	11	Michael Rohrer, D.D.S. University of Oklahoma College of Dentistry Oklahoma City, OK
6	John Fantasia, D.D.S. Long Island Jewish Medical Center Department of Dental Medicine New Hyde Park, NY	12	Roy Eversole. D.D.S. UCLA Health Sciences Center School of Dentistry Los Angeles, CA

The conduct of the study was as follows.

1) Study objective: This was to determine the safety and efficacy of 5% Amlexanox paste when applied four times daily to minor aphthous ulcers.

2) Study design: This was a double blind, multicenter, randomized, uneven parallel group comparison of 5% Amlexanox paste with the product vehicle and with no treatment in patients with minor aphthous ulcers. Patients were randomly assigned to one of three treatment groups; each block of eight patients consisted of three patients treated with 5% Amlexanox paste, three patients treated with the vehicle, and two patients who received no treatment.

3) Patient selection: Patients selected were males and females 18 years or older, with one to three aphthous ulcers of less than 48 hours duration, in locations easily accessible for evaluation and treatment, including the buccal mucosa, labial mucosa, floor of the mouth or the tongue. The patients were to have a history of recurrent minor aphthous ulcers and an expectation that their ulcers normally take five days or more to resolve.

4) Patient exclusions: Patients with the following conditions were

excluded from the study.

a. Pregnancy or lactation.
b. Normal resolution of aphthous ulcers in less than 5 days.
c. Concurrent clinical conditions that might pose a health risk to the patient or could potentially influence the outcome of the study.
d. Ulcers which are a manifestation of a systemic disease such as ulcerative colitis, Crohn's disease, Behcet's disease, or anemia.
e. Treatment with systemic steroids, oral retinoids, or other immunomodulatory agents within one month of study entry.
f. Chronic use of NSAIDs, acetaminophen, or oral antihistamines within one month of study entry. Patients who had occasionally used these products were enrolled if the medications had not been used within three days of study entry.
g. Treatment with any topical medication within two weeks of study entry.
h. Treatment of the ulcer with any preparation or medication within 48 hours of study entry.
i. Treatment with a systemic antibiotic within two weeks of study entry.
j. Dental surgery within two weeks of study entry.
k. Orthodontic braces or retainer that might come into contact with the ulcer.
l. Use of chewing tobacco products or cigars, or history of drug or alcohol abuse.

5) Dosage and administration: Patients in the Amlexanox and vehicle groups applied the test products four times daily to the ulcer sites for up to 7 1/2 days or until the ulcers healed, whichever occurred first. Applications were made after meals and at bedtime. A third group of patients received no treatment during an eight day period.

6) Efficacy evaluations: The patients returned daily on days 3 through 8 for measurement of the ulcer size and evaluation of the pain associated with the ulcer.

a. Ulcer size: This was measured with a calibrated dental probe. Two measurements were taken, one of the longest diameter and the other perpendicular to this measurement. These were then multiplied to obtain the ulcer size.

b. Ulcer pain: The investigator estimated the amount of pain by marking a 10 cm line which had the following descriptive assessments at equal distances from one end:

- No pain
- Pain with rough aggravation of the ulcer
- Pain with moderate aggravation of the ulcer
- Pain with slight aggravation of the ulcer
- Constant pain
- Severe pain

The pain score was obtained by measuring the distance of the mark from the origin of the scale (no pain) in centimeters.

The primary efficacy variables were the percentages of patients in each treatment group with all ulcers healed, and the percentages of patients in each treatment group with all ulcer pain resolved.

7) Safety parameters: Adverse events were recorded as they occurred, together with the severity and the perceived relationship to the test product.

Results were as follows.

1) Patient enrollment and demographic characteristics: A total of 528 patients were enrolled into the study, of which 505 were evaluable for efficacy. The demographic and disease characteristics of all patients enrolled were as follows.

Demographic characteristics						
	Amlexanox (n=197)		Vehicle (n=198)		No treatment (n=133)	
	Male	Female	Male	Female	Male	Female
	85 (43%)	112 (57%)	101 (51%)	97 (49%)	74 (56%)	59 (44%)
Age Mean Range	28.0	27.8	26.4	28.3	28.2	27.7
Race Caucasian Black Hispanic Asian Other	 77 (39%) 1 (0.5%) 2 (1.0%) 5 (2.5%) 0	 98 (50%) 2 (1.0%) 3 (1.5%) 9 (4.6%) 0	 89 (45%) 0 3 (1.5%) 9 (4.5%) 0	 82 (41%) 5 (2.5%) 6 (3.0%) 4 (2.0%) 0	 65 (49%) 0 3 (2.2%) 6 (4.5%) 0	 51 (38%) 1 (0.8%) 1 (0.8%) 6 (4.5%) 0

Baseline ulcer assessment			
	Amlexanox (n=197)	Vehicle (n=213)	No treatment (n=133)
Duration of outbreak Mean (hrs)	25.8	24.7	24.0
# Patients with 1 ulcer	167 (85%)	162 (82%)	114 (86%)
# Patients with 2 ulcers	26 (13%)	31 (16%)	16 (12%)
# Patients with 3 ulcers	4 (2%)	5 (3%)	3 (2%)
Mean ulcer size (mm^2)	6.92	6.74	6.94
Mean pain severity	4.67	4.55	4.40

Ulcer history			
	Amlexanox	Vehicle	No treatment
Recurrences per year Mean Range	14.5	11.0	11.5
Ulcers per outbreak Mean Range	1.6	1.7	1.6
Anticipated days for ulcer to heal Mean Range	7.9	8.0	8.1

2) Discontinuations and protocol violations: Twelve patients discontinued the study prematurely; this included four patients in each of the three treatment groups. No patient was known to have discontinued because of an adverse event. The reasons for discontinuations were as follows.

Discontinuations			
	Amlexanox	Vehicle	No treatment
Lost to followup	3	0	4
Lost medication	1	2	0
Unrelated illness	0	1	0

Twenty-three patients had protocol violations; this included 7 in the Amlexanox group, 13 in the vehicle group, and three in the untreated group. The violations included application of study material more than 48 hours after first noticing the ulcer, concomitant medications, missed visits, and too short an

anticipated time for healing.

3) Efficacy evaluations: In the study report the sponsor provided an analysis for all patients enrolled into the study for the duration that they were in the study (intent-to-treat analysis). Another analysis of the efficacy evaluable patients, which excluded those patients that had protocol violations, is provided in the statistical report. Only the results of this analysis (efficacy evaluable) are included in this review.

The mean ulcer size and the mean change in ulcer size from baseline at each return visit were as follows.

Mean ulcer size (mm^2)						
	Amlexanox		Vehicle		Untreated	
	# pts	Mean	# pts	Mean	# pts	Mean
Day 1	190	6.92	185	6.57	130	6.84
Day 3	189	6.39	184	7.45	130	8.41
Day 4	187	5.11	177	6.68	125	8.49
Day 5	186	3.96	182	6.15	123	6.96
Day 6	184	3.11	178	5.26	126	6.21
Day 7	182	2.39	178	4.32	124	5.01
Day 8	187	1.88	182	3.67	126	4.29

Mean change in ulcer size from baseline						
	Amlexanox		Vehicle		Untreated	
	# pts	Mean	# pts	Mean	# pts	Mean
Day 3	189	-0.38	184	0.86	130	1.57
Day 4	187	-1.61	177	-0.32	125	1.56
Day 5	186	-2.80	182	-0.50	123	0.33
Day 6	184	-3.66	178	-1.34	126	-0.56
Day 7	182	-4.49	178	-2.33	124	-1.66
Day 8	187	-4.91	182	-2.96	126	-2.49

The mean ulcer size was significantly smaller in the Amlexanox group than in the vehicle group on days 4 through 8 ($p<0.05$), and was significantly smaller than in the untreated group on days 3 through 8 ($p<0.05$). The mean change in ulcer size from baseline was

significantly greater in the Amlexanox group than in the vehicle group and the untreated group at all evaluation times ($p<0.05$).

The mean pain measurement and the mean change from baseline at each return visit were as follows.

Mean pain measurement						
	Amlexanox		Vehicle		Untreated	
	# pts	Mean	# pts	Mean	# pts	Mean
Day 1	190	4.70	185	4.51	130	4.40
Day 3	189	3.08	184	3.26	130	3.94
Day 4	187	2.08	179	2.43	125	3.44
Day 5	186	1.37	181	1.84	121	2.14
Day 6	184	0.89	178	1.29	124	1.56
Day 7	183	0.52	179	0.88	122	1.11
Day 8	186	0.32	180	0.55	123	0.81

Mean change in pain measurement from baseline						
	Amlexanox		Vehicle		Untreated	
	# pts	Mean	# pts	Mean	# pts	Mean
Day 3	189	-1.63	184	-1.25	130	-0.46
Day 4	187	-2.62	179	-2.04	125	-0.98
Day 5	186	-3.32	181	-2.69	121	-2.14
Day 6	184	-3.82	178	-3.22	124	-2.80
Day 7	183	-4.19	179	-3.61	122	-3.23
Day 8	186	-4.38	180	-3.93	123	-3.54

The mean pain measurement in the Amlexanox group was significantly less than in the vehicle group at days 5 and 7 only, and was significantly less than in the untreated group at days 3 through 8 ($p<0.05$). The mean change in pain from baseline in the Amlexanox group was significantly greater than in the vehicle group at days 4 through 7, and was significantly greater than the untreated group at all return visits, days 3 through 8 ($p<0.05$).

The percentages of patients with ulcers healed and with resolution of pain at each return visit were as follows.

# and % of patients with ulcers healed			
	Amlexanox	Vehicle	Untreated
Day 3	5.8% (11/189)	4.3% (8/185)	0.8% (1/130)
Day 4	19.3% (36/187)	13.0% (24/184)	7.8% (10/128)
Day 5	35.1% (66/188)	26.5% (49/185)	19.2% (25/130)
Day 6	50.0% (93/186)	41.1% (76/185)	31.5% (41/130)
Day 7	62.2% (117/188)	53.9% (98/182)	46.2% (60/130)
Day 8	70.9% (134/189)	60.5% (112/185)	49.2% (64/130)

The percentage of patients in the Amlexanox group in whom the ulcers were healed was significantly greater than in the vehicle group at day 8 ($p=0.031$), and was significantly greater than in the untreated group at all return visits, days 3 through 8 ($p<0.05$).

# and % of patients with pain healed			
	Amlexanox	Vehicle	Untreated
Day 3	14.3% (27/189)	16.2% (30/185)	6.9% (9/130)
Day 4	39.2% (74/189)	34.6% (64/185)	16.2% (21/130)
Day 5	55.9% (105/188)	45.1% (83/184)	35.9% (46/128)
Day 6	74.9% (140/187)	59.2% (109/184)	47.7% (61/128)
Day 7	84.5% (158/187)	69.0% (127/184)	59.1% (75/127)
Day 8	88.2% (165/187)	79.9% (147/184)	73.2% (93/127)

The percentage of patients in the Amlexanox group with complete resolution of pain was significantly higher than in the vehicle group at days 5 through 8, and was significantly higher than in the untreated group at all return visits, days 3 through 8 ($p<0.05$).

The time to first occurrence of ulcer healing was as follows.

Ulcer healing Time to first occurrence						
	Amlexanox		Vehicle		Untreated	
Followup days[a]	# pts at risk[b]	% healed (Cum.)[c]	# pts at risk[b]	% healed (Cum.)[c]	# pts at risk[b]	% healed (Cum.)[c]
0 - 2	189	5.8%	185	4.5%	130	0.8%
2 - 3	177	19.1%	176	13.0%	128	7.8%
3 - 4	152	35.1%	159	26.7%	117	19.6%
4 - 5	122	49.5%	134	41.5%	102	32.2%
5 - 6	95	62.2%	106	53.6%	85	47.4%
6 - 7	70	71.4%	84	61.4%	66	50.5%

[a] time from the beginning of treatment to ulcer healing or last ulcer assessment.
[b] number of patients at the beginning of each time interval without ulcer healing.
[c] the estimated percent of patients with all ulcers healed by the end of the time interval.

The estimated median time for healing was 5.0 days in the Amlexanox group, 5.7 days in the vehicle group, and 6.8 days in the untreated group.

The time to healing was marginally significantly less in the Amlexanox group than in the vehicle group ($p=0.053$), and was significantly less than in the untreated group ($p=0.001$).

The time to complete pain relief was as follows.

Complete pain relief
Time to first occurrence

	Amlexanox		Vehicle		Untreated	
Followup days[a]	# pts at risk[b]	% healed (Cum.)[c]	# pts at risk[b]	% healed (Cum.)[c]	# pts at risk[b]	% healed (Cum.)[c]
0 - 2	189	14.3%	185	16.2%	130	6.9%
2 - 3	161	39.8%	154	35.8%	119	16.3%
3 - 4	112	57.0%	116	46.3%	104	36.4%
4 - 5	79	75.0%	97	60.7%	79	50.1%
5 - 6	46	85.3%	70	70.3%	60	60.9%
6 - 7	27	88.6%	52	81.7%	47	75.9%

[a] time from the beginning of treatment to pain relief or last pain evaluation.
[b] number of patients at the beginning of each time interval without complete pain relief.
[c] the estimated percent of patients with complete pain relief by the end of the time interval.

The estimated median time for complete pain relief was 3.6 days in the Amlexanox group, 4.2 days in the vehicle group, and 5.0 days in the untreated group.

The time to complete pain relief was marginally significantly less in the Amlexanox group than in the vehicle group ($p=0.047$), and was significantly less than in the untreated group ($p=0.000$).

4) Adverse experiences: No patient was known to have discontinued due to adverse events. The adverse events that were considered to be possibly, probably, or definitely related to treatment were as follows.

Adverse events

	Amlexanox (n=197)	Vehicle (n=198)
Stinging/pain	4 (2.0%)	1 (0.5%)
Dry mouth	1 (0.5%)	0
Superficial mucocele	0	1 (0.5%)
Total	5 (2.5%)	3 (1.5%)

The severity and duration of the adverse events in the 5% Amlexanox group were as follows.

Adverse events Severity and duration in the Amlexanox group			
Pt #	Symptom	Severity	Duration
	Burning, tongue	moderate	3 days
	Burning, application site	mild	3 days
	Stinging, application site	mild	< 1 day
	Dryness, mouth	mild	2 days
	Stinging, application site	mild	4 days

Reviewer's comments: *In summary, the results of the efficacy parameters in Study 108 were as follows:*

a) Mean change in ulcer size and amount of pain: The mean change in ulcer size with Amlexanox was significantly greater than with the vehicle or at the untreated sites at all evaluation times, days 3 through 8. The mean change in pain in the Amlexanox group was significantly greater than in the vehicle group at days 4 through 7 and was significantly greater than the untreated group at all return visits, days 3 through 8.

b) Percentage of patients with healed ulcers and with resolution of pain: The percentage of patients in the Amlexanox group with ulcers healed was significantly greater than in the vehicle group at day 8 and was significantly greater than in the untreated group at all return visits, days 3 through 8. The percentage of patients in the Amlexanox group with complete resolution of pain was significantly higher than in the vehicle group at days 5 through 8, and was significantly higher than in the untreated group at all return visits, days 3 through 8.

c) Estimated median times for healing and for resolution of pain: The estimated median time for ulcer healing was 5.0 days in the Amlexanox group, 5.7 days in the vehicle group, and 6.8 days in the untreated group. The difference was not significant between Amlexanox and the vehicle group, but was significant between Amlexanox and the untreated group. The estimated median time for pain resolution was 3.6 days in the Amlexanox group, 4.2 days in the vehicle group, and 5.0 days in the untreated group. The difference between Amlexanox and the vehicle was marginally significant, and that between Amlexanox and no treatment was significant.

As with Study 107, a statistical review is needed to determine the validity of the methods of analyses. However, it is the conclusion of this reviewer that the results of this study do not demonstrate adequate effectiveness for the labeling claim that the product accelerates the healing of aphthous ulcers. It is felt that an acceleration of healing by 0.7 days is not clinically significant, and is not sufficient to justify approval of this product.

III. Study 106.

The investigators for this study were:

1	William Binnie, D.D.S. Baylor College of Dentistry Dallas. TX	4	John Kalmar, D.M.D. Eastman Dental Center Rochester, NY
2	Robert Greer, D.D.S. University of Colorado Denver, Colorado	5	Stuart Fischman, D.M.D. SUNY School of Dental Medicine Buffalo, NY
3	Carl Allen, D.D.S. OSU College of Dentistry Columbus, Ohio	6	Michael Newman, D.D.S. UCLA School of Dentistry Los Angeles, CA

The conduct of the study was as follows.

1) Study objective: This was to determine the median time to healing of minor aphthous ulcers when treated with 5% Amlexanox paste or the paste vehicle applied four times daily, as compared with no treatment.

2) Study design: This was a double blind, multicenter, randomized, parallel group comparison of 5% Amlexanox paste, the product vehicle, and no treatment in patients with minor aphthous ulcers.

3) Patient selection: Patients selected were males and females 18 to 65 years of age, with one to three aphthous ulcers of less than 48 hours duration, located on the buccal mucosa, labial mucosa, floor of the mouth or the tongue. The patients were to have a history of recurrent minor aphthous ulcers and an expectation that their ulcers normally take five days or more to resolve.

4) Patient exclusions: Patients with the following conditions were excluded from the study.

a. Pregnancy or lactation.
b. Normal resolution of aphthous ulcers in less than 5 days.

c. Concurrent clinical conditions that might pose a health risk to the patient or could potentially influence the outcome of the study.
d. Ulcers which are a manifestation of a systemic disease such as ulcerative colitis, Crohn's disease, Behcet's disease, or anemia.
e. Treatment with systemic steroids, oral retinoids, or other immunomodulatory agents within one month of study entry.

f. Chronic use of NSAIDs, acetaminophen, or oral antihistamines within one month of study entry. Patients who had occasionally used these products were enrolled if the medications had not been used within five days of study entry.
g. Treatment with any topical medication within two weeks of study entry.
h. Treatment of the ulcer with any preparation or medication within 48 hours of study entry.
i. Treatment with a systemic antibiotic within two weeks of study entry.
j. Dental surgery within two weeks of study entry.
k. Orthodontic braces or retainer that might come into contact with the ulcer.
l. A history of drug or alcohol abuse.

5) Dosage and administration: The patient applied the test product to the ulcers four times a day for ten days, or until all the ulcers had healed, whichever occurred first. The applications were made after meals and at bedtime.

6) Efficacy evaluations: The patients returned daily for the following evaluations.

a. Ulcer size: This was measured in millimeters with a calibrated dental probe. Two measurements were taken which were perpendicular to each other; these were then multiplied to obtain the ulcer size.

b. Ulcer pain: The investigator estimated the amount of pain by marking a 10 cm line which had the following descriptive assessments at equal distances from one end:

- No pain
- Pain with rough aggravation of the ulcer
- Pain with moderate aggravation of the ulcer
- Pain with slight aggravation of the ulcer
- Constant pain
- Severe pain

c. Erythema: The amount of erythema was graded on the following scale.

0 = no erythema
1 = faint erythema, light red/pink in color, not uniformly surrounding the ulcer; no clearly defined borders.
2 = faint definite erythema, light red/pink in color, completely surrounding the ulcer; borders may be defined.
3 = moderate erythema, red but not dark in color, with defined borders.
4 = strong erythema surrounding the ulcer, very red, dark in color.

d. Physician's assessment of improvement: The amount of improvement was graded on the following scale.

+3 = ulcer is completely healed.
+2 = ulcer is almost completely healed.
+1 = ulcer is in the process of healing.
0 = ulcer still apparent, can not determine if healing or getting worse.
-1 = ulcer appears to be getting worse.

e. Patient's global assessment: At the end of the study, either at day 10 or when the ulcer had healed, the patient graded the effect of treatment on the ulcer healing time, according to the following scale.

+3 = marked improvement (marked decrease of anticipated healing time).
+2 = moderate improvement (moderate decrease of anticipated healing time).
+1 = slight improvement (slight decrease of anticipated healing time).
0 = no perceptible improvement.
-1 = slight negative effect (slight increase of anticipated healing time).
-2 = moderate negative effect (moderate increase of anticipated healing time).
-3 = marked negative effect (marked increase of anticipated healing time).

7) Safety parameters: Adverse events were recorded as they occurred, together with the severity and the perceived relationship to the test product.

Results were as follows.

1) Patient enrollment, demographic and disease characteristics: A total of 181 patients were enrolled into the study, of which 170 were considered to be evaluable for efficacy. The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics			
	Amlexanox (n=60)	Vehicle (n=59)	No treatment (n=62)
Sex			
Male	31 (52%)	26 (44%)	23 (37%)
Female	29 (48%)	33 (56%)	39 (63%)
Age			
Mean	25.9	27.5	27.0
Range			
Race			
Caucasian	53 (88%)	48 (81%)	48 (77%)
Black	2 (3%)	2 (3%)	2 (3%)
Hispanic	0	3 (5%)	3 (5%)
Asian	5 (8%)	6 (10%)	9 (15%)
Other	0	0	0

The baseline ulcer assessment and ulcer history for the evaluable patients, plus one patient that discontinued after one day of treatment, were as follows.

Baseline ulcer assessment			
	Amlexanox (n=56)	Vehicle (n=53)	No treatment (n=62)
# Patients with 1 ulcer	52 (93%)	47 (89%)	53 (86%)
# Patients with 2 ulcers	3 (5%)	6 (11%)	8 (13%)
# Patients with 3 ulcers	1 (2%)	0	1 (2%)
Mean ulcer size (mm^2)	4.69	6.16	5.42
Mean erythema severity	2.0	2.2	2.0
Mean pain severity	4.27	4.09	4.34

Ulcer history			
	Amlexanox (n=56)	Vehicle (n=53)	No treatment (n=62)
Recurrences per year Average	9.9	9.8	10.2
Ulcers per outbreak Average	1.3	1.4	1.4
Anticipated days for ulcer to heal Average	7.6	7.6	7.7

2) Discontinuations and protocol violations: The distribution among the treatment groups was as follows.

Discontinuations and protocol violations			
	Amlexanox	Vehicle	No treatment
Adverse event	0	1	0
Lost to followup/failure to cooperate	0	3	1
Protocol violations	4	6	0

The four patients who were lost to followup were included in the efficacy analysis for as long as they were in the study. One vehicle patient discontinued at one day after study entry due to a rash on both hands which was considered possibly related to the test product. This patient was not included in the efficacy analysis. Of the protocol violations, eight patients did not meet the entry requirement that the ulcers be less than 48 hours old, one patient may not have used the medication, and one patient was not felt to have a true aphthous ulcer.

Of the 170 evaluable patients, 166 patients completed treatment until their ulcers healed.

3) Efficacy evaluations: The results for the five efficacy parameters were as follows.

a) Ulcer size: The cumulative number and percent of patients with ulcers completely healed at each return visit were as follows.

Patients with healed ulcers			
	Amlexanox (n=56)	Vehicle (n=53)	Untreated (n=62)
Day 1	0	0	0
Day 2	0	1 (2%)	1 (2%)
Day 3	6 (11%)	8 (17%)	4 (7%)
Day 4	17 (30%)	16 (33%)	6 (10%)
Day 5	28 (50%)	18 (38%)	17 (28%)
Day 6	34 (61%)	24 (50%)	22 (36%)
Day 7	43 (77%)	31 (65%)	29 (48%)
Day 8	46 (82%)	34 (71%)	36 (59%)
Day 9	47 (84%)	38 (79%)	43 (70%)
Day 10	47 (84%)	38 (79%)	47 (77%)
Median time to heal (days)	5	6	8

Amlexanox was not statistically significantly different from the vehicle in the percentage of patients with ulcer healing at any time point, nor in the median time to healing. Amlexanox was significantly superior to no treatment in the percentage of patients with ulcer healing on days 4 through 8, but not on days 9 and 10. Amlexanox was also significantly superior to no treatment in the median time to healing.

b) Erythema: The cumulative number and percentage of patients at each return visit with resolution of the erythema associated with the ulcers were as follows.

Patients with resolution of erythema *			
	Amlexanox (n=55)	Vehicle (n=53)	Untreated (n=58)
Day 2	4 (7%)	5 (10%)	2 (4%)
Day 3	16 (30%)	9 (18%)	6 (11%)
Day 4	23 (43%)	19 (39%)	9 (16%)
Day 5	31 (58%)	24 (49%)	19 (34%)
Day 6	38 (72%)	31 (61%)	25 (41%)
Day 7	42 (79%)	33 (70%)	30 (54%)
Day 8	45 (85%)	34 (70%)	36 (64%)
Day 9	46 (87%)	39 (80%)	41 (73%)
Day 10	48 (91%)	39 (80%)	46 (82%)
Median time to cure (days)	5	6	7
* includes only those patients with at least mild erythema at study entry.			

Amlexanox was not statistically significantly different from the vehicle in the percentage of patients with resolution of erythema at any time point, nor in the median time to cure. Amlexanox was significantly superior to no treatment in the percentage of patients with resolution of erythema on days 3 through 8, but not on days 9 and 10. Amlexanox was also significantly superior to no treatment in the median time to resolution of erythema.

c) Pain: The cumulative number and percentage of patients at each return visit with resolution of the pain associated with the ulcers were as follows.

Patients with resolution of pain			
	Amlexanox (n=54)	Vehicle (n=47)	Untreated (n=57)
Day 1	0	0	0
Day 2	6 (12%)	4 (9%)	3 (5%)
Day 3	21 (40%)	13 (20%)	9 (16%)
Day 4	33 (63%)	18 (41%)	20 (36%)
Day 5	39 (75%)	24 (55%)	27 (49%)
Day 6	41 (79%)	31 (70%)	39 (71%)
Day 7 *	43 (83%)	35 (81%)	43 (78%)
Day 8	44 (85%)	37 (87%)	48 (87%)
Day 9	45 (89%)	40 (95%)	51 (93%)
Day 10	48 (88%)	40 (95%)	52 (95%)
Median time to resolution (days)	4	5	6
* includes only those patients with at least a mark at 0.5 cm on the pain scale at study entry.			

Amlexanox was significantly superior to the vehicle in the percentage of patients with resolution of pain on days 4 and 5. There was no significant difference in the median time to resolution. Amlexanox was significantly superior to no treatment in the percentage of patients with resolution of erythema on days 3 through 6, and was significantly superior to no treatment in the median time to resolution of pain by the Wilcoxon test but not by the log rank test.

d) Physician's assessment: The cumulative number and percentage of patients with complete resolution of all signs and symptoms of ulcers at each return visit were as follows.

Physician improvement assessment Patients with complete healing			
	Amlexanox (n=56)	Vehicle (n=52)	Untreated (n=62)
Day 1	0	0	0
Day 2	1 (2%)	1 (2%)	1 (2%)
Day 3	7 (13%)	6 (13%)	5 (8%)
Day 4	17 (30%)	15 (31%)	8 (13%)
Day 5	29 (53%)	18 (38%)	18 (30%)
Day 6	35 (63%)	24 (50%)	24 (39%)
Day 7*	43 (77%)	31 (65%)	30 (49%)
Day 8	46 (82%)	33 (69%)	36 (59%)
Day 9	47 (84%)	38 (79%)	43 (70%)
Day 10	47 (84%)	38 (79%)	48 (79%)
Median time to cure (days)	5	6	8
* includes only those patients with a score of +3 on the physician's improvement scale.			

Amlexanox was not statistically significantly different from the vehicle in the percentage of patients with complete ulcer healing at any time point. There was also no significant difference in the median time to healing. Amlexanox was significantly superior to no treatment in the percentage of patients with complete ulcer healing on days 4 through 8 only, and was significantly superior to no treatment in the median time to resolution of the ulcer by the Wilcoxon test but not by the log rank test.

e) Patient's assessment: There was no significant difference between the percent of patients treated with Amlexanox and the percent of patients treated with the vehicle with marked improvement in ulcer healing time during this study as compared to previously treated episodes and/or previously untreated episodes of aphthous ulcers. However, both treated groups were significantly superior to the untreated group in this assessment.

4) Adverse experiences: One patient discontinued participation in the study because of an adverse event that was considered to be possibly related to the test medication. This patient developed a rash on both hands after four applications of the vehicle. The rash resolved within one day of discontinuation of treatment with no additional therapy required.

The adverse events that were considered to be possibly or probably related to treatment were as follows.

Adverse events Amlexanox patients			
Pt #	Symptom	Severity	Duration
[redacted]	Stinging of mouth	mild	<1 day
	Pain in mouth	mild	<1 day
	Pain in mouth	mild	<1 day
	Pain in mouth	mild	<1 day
Vehicle patients			
[redacted]	Rash on hands	moderate	1 day
[redacted]	Upset stomach	mild	1 day
[redacted]	Stinging of mouth	moderate	1 day
	Stinging of mouth	moderate	<1 day
[redacted]	Stinging of mouth	mild	<1 day
[redacted]	Pain in mouth	mild	<1 day

The events listed as pain or stinging in the mouth were at the application site.

Reviewer's comments: In summary, the results of the efficacy parameters for the comparison between Amlexanox and the vehicle in Study 106 were as follows:

a) Percentage of patients with healed ulcers and with resolution of pain: The percentage of patients with ulcers healed with Amlexanox was not significantly greater than with the vehicle at any time point. The percentage of patients with resolution of pain with Amlexanox was significantly greater than with the vehicle on days 4 and 5 of a ten day treatment period.

b) Estimated median times for healing and for resolution of pain: Amlexanox was not statistically significantly different from the vehicle in the median time to healing nor in the median time to resolution of pain.

c) Physician's assessment: Amlexanox was not significantly different from the vehicle in the percentage of patients with complete ulcer healing at any time point, nor in the median time to healing.

d) Patient's assessment: There was no significant difference between Amlexanox and the vehicle in the percentage of patients with marked improvement in ulcer healing as compared with previous episodes.

It is the conclusion of this reviewer that the results of this study do not demonstrate effectiveness for the labeling claim that the product accelerates the healing of aphthous ulcers.

IV. Study 102.

The investigators for this study were:

1	William Binnie, D.D.S. Baylor College of Dentistry Dallas. TX	6	Samuel Yankell, Ph.D. University of Pennsylvania Philadelphia, PA
2	Sadru Kabani, D.M.D. Tufts University Boston, MA	7	Francina Lozada-Nur, D.D.S. UCSF San Francisco, CA
3	Craig Fowler, D.D.S. Lackland Air Force Base San Antonio, TX	8	Peter Polverini, D.D.S. Northwestern University Chicago, IL
4	Robert Greer, D.D.S., Sc.D. University of Colorado Denver, CO	9	Roy Rogers, M.D. Mayo Clinic Rochester, MN
5	Francis Howell, D.D.S. Pathology medical Laboratories San Diego, CA	10	Dwight Weathers, D.D.S. Emory University Atlanta, GA

The conduct of the study was as follows.

1) Study objective: This was to determine the tolerance and efficacy of 1% and 5% Amlexanox paste as compared with vehicle in the treatment of aphthous ulcers.

2) Study design: This was a double blind, multicenter, randomized, uneven parallel group comparison of 1% and 5% Amlexanox paste and the paste vehicle, when applied QID for up to four days in patients with aphthous ulcers.

3) Patient selection: Patients selected were males and females 18 to 70 years of age, with one to three aphthous ulcers of less than 48 hours duration, located on the buccal mucosa, labial mucosa, floor of the mouth or the tongue. The patients were to have a history of recurrent aphthous ulcers.

4) Patient exclusions: Patients with the following conditions were excluded from the study.

a. Pregnancy or lactation.
b. Resolution of aphthous ulcers within 72 hours.
c. Ulcers which are a manifestation of a systemic disease such as ulcerative colitis, Crohn's disease, Behcet's disease, or anemia.
d. Treatment with systemic steroids within one month of study entry.
e. Treatment with any topical medication to the areas of treatment within two weeks of study entry.
f. Treatment with an antibiotic within two weeks prior to study entry.
g. Dental surgery within two weeks of study entry.
h. Orthodontic braces or retainer that might come into contact with the ulcer.
i. A history of drug or alcohol abuse.

5) Dosage and administration: The patient applied the test product to the ulcers four times a day for four days, or until all the ulcers had healed, whichever occurred first. The applications were made after meals and at bedtime.

6) Efficacy evaluations: The patients returned daily for the following evaluations.

a. Ulcer size: This was measured in millimeters with a calibrated dental probe. Two measurements were taken which were perpendicular to each other; these were then multiplied to obtain the ulcer size. The changes in ulcer size were categorized as follows.

    Marked improvement = > 70% decrease
    Moderate improvement = 41% to 70% decrease
    Some improvement = 10% to 40% decrease
    Little or no improvement = 10% change
    Worse = > 10% increase

b. Erythema: At baseline the investigator scored the amount of erythema on the following scale.

    0 = none (no erythema)
    1 = very mild (light red/pink)
    2 = moderate (red but not dark in color)
    3 = strong (very red, dark in color)

At daily return visits the change in erythema was rated on the following scale.

-4 = no erythema.
-3 = marked decrease in erythema.
-2 = moderate decrease in erythema.
-1 = slight decrease in erythema.
0 = no change from day 1.
1 = slight increase in erythema.
2 = moderate increase in erythema.
3 = marked increase in erythema.

c. Pain: At baseline the patient rated the pain on the following scale.

0 = none (no pain).
1 = mild (awareness of easily tolerated discomfort).
2 = moderate (discomfort causing interference with usual activities).
3 = severe (significant discomfort).

At daily return visits the change in pain was rated on the following scale.

-4 = no pain.
-3 = marked decrease in pain.
-2 = moderate decrease in pain.
-1 = slight decrease in pain.
0 = no change from day 1.
1 = slight increase in pain.
2 = moderate increase in pain.
3 = marked increase in pain.

d. Physician's global assessment: The amount of improvement as compared to baseline was graded on the following scale.

4 = ulcer cleared.
3 = marked improvement.
2 = moderate improvement.
1 = slight improvement.
0 = no change from day 1.
-1 = ulcer worsened.

7) Safety parameters: Adverse events were recorded as they occurred, together with the severity and the perceived relationship to the test product.

Results were as follows.

1) Patient enrollment and demographic characteristics: 202 patients were enrolled into the study, of which 189 patients were evaluable for effectiveness at day 5. The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics						
	Vehicle (n=42)		1% Amlexanox (n=79)		5% Amlexanox (n=81)	
	Male	Female	Male	Female	Male	Female
	12 (29%)	30 (71%)	42 (53%)	37 (47%)	38 (47%)	43 (53%)
Age Mean Range	32.9	34.2	33.4	30.4	31.3	31.8
Race Caucasian Black Asian Other	12 (28%) 0 0 0	25 (60%) 0 3 (7%) 2 (5%)	31 (39%) 2 (3%) 4 (5%) 5 (6%)	35 (44%) 0 0 2 (3%)	34 (42%) 1 (1%) 3 (4%) 0	41 (51%) 0 0 2 (6%)

The baseline ulcer assessment and ulcer history were as follows.

Baseline ulcer assessment			
	Vehicle (n=42)	1% Amlexanox (n=79)	5% Amlexanox (n=81)
# Patients with 1 ulcer	29 (69%)	58 (73%)	64 (79%)
# Patients with 2 ulcers	8 (19%)	9 (11%)	13 (16%)
# Patients with 3 ulcers	5 (12%)	12 (15%)	4 (5%)
Mean # of ulcers per patient	1.4	1.4	1.3
Mean ulcer size (mm^2)	7.8	7.5	7.8
Mean erythema severity	1.9	1.8	1.9
Mean pain severity	1.7	1.7	1.5

Ulcer history			
	Vehicle (n=42)	1% Amlexanox (n=79)	5% Amlexanox (n=81)
Recurrences per year Average	11.1	10.3	10.8
Ulcers per outbreak Average	2.3	1.7	1.6
Anticipated days for ulcer to heal Average	9.9	8.7	9.9

2) Discontinuations and protocol violations: The distribution among the treatment groups was as follows.

Discontinuations and protocol violations			
	Vehicle	1% Amlexanox	5% Amlexanox
Ulcers gone, unable to return	1	1	0
Lost study material	0	0	1
Returned after day 5	1	7	0
Unable to return	0	1	1

No patients were discontinued or dropped out because of an adverse reaction.

3) Efficacy evaluations: A total of 166 patients were evaluable for efficacy on day 3 and 189 patients were evaluable for efficacy on day 5.

a) Ulcer size: The mean ulcer size at baseline, days 3 and 5, and the change in size at days 3 and 5 were as follows.

Ulcer size - day 3			
	Vehicle (n=34)	1% Amlexanox (n=66)	5% Amlexanox (n=66)
Baseline			
Mean	8.6	7.4	7.6
Median	6.0	5.0	5.3
Range			
Day 3			
Mean	6.9	5.8	5.3
Median	4.0	5.7	4.0
Range			
Change from baseline			
Mean change	-1.7	-1.7	-2.3
Mean % change	-14.5%	-5.5%	-18.9%
Median % change	-11.8%	0	-38.8%
% cured	0	5%	12%
% worse	24%	23%	20%

Ulcer size - day 5			
	Vehicle (n=40)	1% Amlexanox (n=70)	5% Amlexanox (n=79)
Baseline			
Mean	7.7	7.5	7.9
Median	4.8	4.5	5.5
Range			
Day 5			
Mean	5.0	2.8	2.9
Median	1.8	0.5	0.3
Range			
Change from baseline			
Mean change	-2.7	-4.7	-5.0
Mean % change	-46.5%	-53.2%	-58.3%
Median % change	-66.7%	-88.0%	-93.8%
% cured	30%	41%	43%
% worse	10%	11%	9%

Data from those patients who were cured prior to day 5 were carried over and included in the day 5 analysis; thus the baseline values were different for the day 3 and the day 5 analyses.

Statistical analyses were done on the mean change and the mean percent change in ulcer size from baseline and on the percentage of patients that were cured. At day 3 neither 1% nor 5% Amlexanox were superior to the vehicle in these parameters. At day 5, both 1% and 5% Amlexanox were superior to the vehicle in the mean change from baseline (p=0.033 and 0.028, respectively), but not in the mean percent change from baseline nor in the percentage that were cured. There was no significant difference in ulcer size reduction between the 1% and 5% Amlexanox pastes.

The changes in ulcer size at days 3 and 5 were categorized as follows.

Change in ulcer size - day 3

Ulcer size *	1% Amlexanox (n=66)	5% Amlexanox (n=66)	Vehicle (n=34)
Marked improvement	13 (20%)	13 (20%)	6 (18%)
Moderate improvement	10 (15%)	18 (27%)	6 (18%)
Some improvement	7 (11%)	8 (12%)	6 (18%)
Little or no improvement	21 (32%)	14 (21%)	8 (24%)
Worse	15 (23%)	13 (20%)	8 (24%)
Ulcer cure			
Cured	3 (5%)	8 (12%)	0
Not cured	63 (95%)	58 (88%)	34 (100%)

* Marked improvement = > 70% decrease
Moderate improvement = 41% to 70% decrease
Some improvement = 10% to 40% decrease
Little or no improvement = 10% change
Worse = > 10% increase

For patients with multiple ulcers, size = mean size

Change in ulcer size - day 5			
Ulcer size *	1% Amlexanox (n=70)	5% Amlexanox (n=79)	Vehicle (n=40)
Marked improvement	44 (63%)	48 (61%)	20 (50%)
Moderate improvement	8 (11%)	8 (10%)	4 (10%)
Some improvement	7 (10%)	9 (11%)	5 (13%)
Little or no improvement	3 (4%)	7 (9%)	7 (18%)
Worse	8 (11%)	7 (9%)	4 (10%)
Ulcer cure			
Cured	29 (41%)	34 (43%)	12 (30%)
Not cured	41 (59%)	45 (57%)	28 (70%)

* Marked improvement = > 70% decrease
Moderate improvement = 41% to 70% decrease
Some improvement = 10% to 40% decrease
Little or no improvement = 10% change
Worse = > 10% increase

For patients with multiple ulcers, size = mean size

No statistical analyses are provided for the tabulations of categories of improvement.

b) Pain scores: Baseline pain and the change in pain on days 3 and 5 was as follows.

Baseline pain scores			
	1% Amlexanox (n=79)	5% Amlexanox (n=81)	Vehicle (n=42)
0 (none)	0	4 (5%)	0
1 (mild)	36 (46%)	37 (46%)	15 (36%)
2 (moderate)	32 (41%)	35 (43%)	24 (57%)
3 (Severe)	11 (14%)	5 (6%)	3 (7%)
Mean score	1.68	1.51	1.71
Median score	2.00	1.00	2.00

Pain assessment - day 3			
	1% Amlexanox (n=66)	5% Amlexanox (n=66)	Vehicle (n=34)
No pain	17 (26%)	23 (35%)	11 (32%)
Marked decrease	12 (18%)	11 (17%)	5 (15%)
Moderate decrease	12 (18%)	14 (21%)	3 (9%)
Slight decrease	7 (11%)	10 (15%)	3 (9%)
No change	10 (15%)	4 (6%)	6 (18%)
Slight increase	7 (11%)	4 (6%)	3 (9%)
Moderate increase	1 (2%)	0	3 (9%)
Marked increase	0	0	0
Mean	- 1.9	- 2.4	- 1.7
Median	- 2	- 3	- 2

Pain assessment - day 5			
	1% Amlexanox (n=70)	5% Amlexanox (n=79)	Vehicle (n=40)
No pain	49 (70%)	55 (69%)	23 (58%)
Marked decrease	7 (10%)	11 (14%)	2 (5%)
Moderate decrease	4 (6%)	7 (9%)	4 (10%)
Slight decrease	2 (3%)	2 (2%)	6 (15%)
No change	4 (6%)	2 (3%)	3 (8%)
Slight increase	0	3 (4%)	2 (5%)
Moderate increase	4 (6%)	0	0
Marked increase	0	0	0
Mean	- 3.1	- 3.3	- 2.8
Median	- 4	- 4	- 4

No statistical analyses are provided for the tabulation of categories of change.

c) Erythema scores: Similar tabulations are provided for the changes in erythema scores; these have not been reproduced here.

d) Global score: The physician's global assessment at days 3 and 5 was as follows.

Physician's global assessment - day 3			
	1% Amlexanox (n=66)	5% Amlexanox (n=66)	Vehicle (n=34)
4 - Ulcer healed	3 (5%)	6 (9%)	2 (6%)
3 - Marked improvement	18 (27%)	12 (18%)	9 (26%)
2 - Moderate improvement	9 (14%)	22 (33%)	3 (9%)
1 - Slight improvement	13 (20%)	12 (18%)	7 (21%)
0 - No change	14 (21%)	9 (14%)	4 (12%)
-1 - Worse	9 (14%)	5 (8%)	9 (26%)
Mean	1.3	1.7	1.1
Median	1	2	1

Physician's global assessment - day 5			
	1% Amlexanox (n=70)	5% Amlexanox (n=79)	Vehicle (n=40)
4 - Ulcer healed	28 (39%)	31 (39%)	15 (38%)
3 - Marked improvement	19 (26%)	26 (33%)	9 (23%)
2 - Moderate improvement	9 (13%)	4 (5%)	2 (5%)
1 - Slight improvement	6 (9%)	13 (16%)	9 (23%)
0 - No change	4 (6%)	1 (1%)	1 (3%)
-1 - Worse	5 (7%)	4 (5%)	4 (10%)
Mean	2.6	2.8	2.4
Median	3	3	3

No statistical analyses are provided for the tabulations of categories of improvement.

e) Comparative efficacy scores: A summary of the p values for the statistical analyses of between group efficacy comparisons of the mean scores is as follows.

Between group efficacy comparisons (p values) Baseline			
	1% Amlexanox vs vehicle	5% Amlexanox vs vehicle	1% vs 5% Amlexanox
Ulcer size			
Erythema	ns	ns	ns
Pain	ns	ns	ns

Between group efficacy comparisons (p values) Day 3			
	1% Amlexanox vs vehicle	5% Amlexanox vs vehicle	1% vs 5% Amlexanox
Ulcer size			
Change	ns	ns	ns
% change	ns	ns	ns
Cured	ns	ns	ns
Erythema	ns	0.020	ns
Pain	ns	ns	ns
Global score			
Median	ns	ns	ns
Cured	ns	ns	ns

Between group efficacy comparisons (p values) Day 5			
	1% Amlexanox vs vehicle	5% Amlexanox vs vehicle	1% vs 5% Amlexanox
Ulcer size			
Change	0.033	0.028	ns
% change	ns	ns	ns
Cured	ns	ns	ns
Erythema	ns	ns	ns
Pain	ns	0.033	ns
Global score			
Median	ns	ns	ns
Cured	ns	ns	ns

4) Adverse experiences: The adverse events which were considered to be possibly or probably related to the test medications were mild transient dryness of the mouth in one patient on 1% Amlexanox, and mild transient stinging of the mouth in another 1% Amlexanox patient.

Reviewer's comments: In summary, the results of the efficacy parameters for the comparison between 5% Amlexanox and the vehicle in Study 102, on which statistical analyses were performed, were as follows:

a) Percentage of patients with healed ulcers: The percentage of patients with ulcers healed with Amlexanox was not significantly greater than with the vehicle at either of the two time points studied.

b) Mean change in ulcer size: At the end of the treatment period Amlexanox was superior to the vehicle in the mean change from baseline, but not in the mean percent change from baseline.

The estimated median times for healing and for resolution of pain apparently were not subjected to statistical analysis.

It is the conclusion of this reviewer that the results of this study do not demonstrate effectiveness for the labeling claim that the product accelerates the healing of aphthous ulcers.

V. Pooled results of Studies 106 and 102.

The sponsor felt that there was sufficient justification for combining the data from these two studies, based on the similarities in study design, inclusion/exclusion criteria, dosing, and efficacy evaluations. The treatment duration differed in the two studies (4 days vs 9 days), so the analyses of the pooled data were performed on the day 5 data. Results of the pooled studies were as follows.

1) Patient population: A total of 383 patients participated in Studies 106 and 102; this comprised 141 patients on 5% Amlexanox, 79 patients on 1% Amlexanox, 101 patients on the vehicle, and 62 patients who received no treatment. Of these, 132 patients treated with 5% Amlexanox and 91 patients treated with the vehicle were evaluable for efficacy at day 5. Eleven of the patients were treated in both studies, and two of the sites participated in both studies, which were conducted several months apart.

2) Demographics and baseline disease characteristics: The two groups were comparable in racial composition, but a larger proportion in the vehicle group were female. The numbers of ulcers per patient at entry appear to be comparable in the two groups.

Other characteristics, including the mean age, age range, and mean ulcer size and pain severity at baseline in each treatment group are provided for the separate studies, but not for the pooled studies.

3) Efficacy parameters: The percentages of patients healed, based on ulcer size measurements, and the percentage of patients with complete resolution of pain, on days 3 and 5, were as follows.

Patients with healed ulcers Ulcer size measurements			
	5% Amlexanox	Vehicle	p value
Day 3	14/122 (12%)	8/86 (9.3%)	NS
Day 5	62/132 (47%)	30/91 (33%)	0.023

Patients with resolution of pain			
	5% Amlexanox	Vehicle	p value
Day 3	46/122 (38%)	27/86 (31%)	NS
Day 5	95/131 (73%)	51/91 (56%)	0.01

The percentages of patients that were healed, based on the physician's improvement assessment, were as follows.

Patients with healed ulcers Physician improvement assessment			
	5% Amlexanox	Vehicle	p value
Day 3	13/122 (11%)	6/86 (7%)	NS
Day 5	54/131 (41%)	30/90 (33%)	0.13

The median time to healing was not analyzed.

Reviewer's note: In summary, the pooled data for Studies 106 and 102 show a significantly larger percentage of patients in the Amlexanox group with healing of the ulcers and with resolution of pain at day 5 as compared to the vehicle group. In the physician's assessment of improvement there was no difference between the Amlexanox and the vehicle groups at day 5.

There is a question which needs to be addressed by the statistician as to whether these two studies may be pooled, in view of the differences in treatment duration and effectiveness variables. The comparability of the demographic and baseline disease

characteristics, in particular the mean ulcer size and pain severity, also needs to be assessed. The median time to healing, which is the primary efficacy variable in Studies 107 and 108, in accordance with the labeling claims, has not been provided for the pooled Studies 106 and 102. Thus, the analysis of the pooled data does not appear to contribute to an evaluation of the effectiveness for the labeling claims.

Labeling review

The indication in the proposed package insert is

This reviewer feels that the margin of acceleration of healing over that with the vehicle as demonstrated in the clinical studies is not clinically significant, and thus the product should not be approved. Further labeling review is therefore deferred.

Summary and evaluation

The product is felt to be safe, but is not felt to be sufficiently efficacious for the labeling claims.

Safety

The safety studies consist of cutaneous irritation, sensitization, local and systemic tolerance, and pharmacokinetics.

a. Cutaneous irritation. The cutaneous irritation study was performed on 25 subjects, using occlusive applications of the product and the vehicle for three consecutive days. One subject developed a contact dermatitis with both the active product and the vehicle after the first application. There were otherwise no reactions with 5% Amlexanox paste, while several subjects showed faint reactions with the vehicle.

We usually require that a cutaneous irritation study be a repeat insult study of 21 days duration; however, it is felt by this reviewer that this study, together with the repeat insult patch testing performed in the sensitization study, is adequate to conclude that the product has a low potential for cutaneous irritation.

*b. **Sensitization.** This was performed on 195 subjects, according to a standard protocol for cutaneous sensitization. In the induction phase the product and the vehicle were applied three times weekly under occlusive patches for three weeks. There were no reactions with Amlexanox paste stronger than a faint, spotty erythema during the last few days of the induction period; a few subjects had a mild to moderate erythema with the vehicle. With the challenge patches there were no reactions that were indicative of sensitization.*

*c. **Cutaneous and systemic tolerance.** This study was performed on 100 patients with aphthous ulcers, to determine the tolerance under conditions of clinical use. Applications of 5% Amlexanox paste were made to the sites of the ulcers and to any new ulcers that developed, regardless of whether the ulcers healed, four times daily for 28 days. Laboratory tests, including hematology and liver and renal function tests, were performed at baseline and at one week post-treatment. Results were that one patient developed a mild local reaction which was felt to be a contact mucositis, one patient had transient mild nausea after application and also had several 'bumps' at the area of application, and a third patient had a transient rash of the hands, arms, and neck which was of indeterminate etiology. There were no clinically significant or drug-related alterations in the laboratory parameters.*

It is felt that this study is adequate to demonstrate the safety of the product under conditions of clinical usage.

*d. **Pharmacokinetic studies.** These studies showed that steady state levels are achieved by one week, and that accumulation did not occur with further dosing. These studies are to be reviewed by the Division of Biopharmaceutics.*

*e. **Adverse experiences in clinical studies.** The adverse experiences in the clinical effectiveness studies were infrequent, mild, or transient in nature.*

<u>Effectiveness</u>

Four clinical effectiveness studies were performed, designated Studies 107, 108, 106, and 102. For efficacy analysis the results of Studies 106 and 102 were pooled. Each study was a double blind, multicenter, parallel group comparison of 5% Amlexanox paste with the paste vehicle in patients with from one to three minor aphthous ulcers. Studies 108 and 106 also included an untreated group, and Study 102 included a 1% Amlexanox group. In each study applications were made QID; the duration of treatment was from four to ten days in the various studies. In accordance with the proposed labeling claims, the primary efficacy variable is considered to be the time to healing. The results were as follows.

1) Study 107: This study had 385 evaluable patients, and the treatment duration was 7 days. The efficacy parameters were ulcer size and categorization of the amount of ulcer pain. The median time for healing was significantly less in the Amlexanox group than in the vehicle group; the estimated median time for healing was 5.0 days in the Amlexanox group and 5.6 days in the vehicle group.

It is felt by this reviewer that an acceleration of healing by 0.6 days is not clinically significant, and is not sufficient to justify use of the product. A statistical review is needed to determine the validity of the methods of analyses for Studies 107 and 108, as described in the reviewer's notes on Study 107.

2) Study 108: This study had 505 evaluable patients in the three treatment groups, and the treatment duration was 8 days. The efficacy parameters were as in Study 107. The median time to healing was marginally significantly less in the Amlexanox group than in the vehicle group, and was significantly less than in the untreated group. The estimated median time for healing was 5.0 days in the Amlexanox group, 5.7 days in the vehicle group, and 6.8 days in the untreated group.

It is felt by this reviewer that an acceleration of healing by 0.7 days over that with the vehicle is not clinically significant, and is not sufficient to justify use of the product.

3) Study 106: This study had 170 evaluable patients in the three treatment groups, and the treatment duration was ten days. The efficacy parameters were ulcer size, categorization of the amount of ulcer pain, and a physician and patient assessment of improvement. The median time to healing in the Amlexanox group was not significantly less than in the vehicle group. There was no difference between Amlexanox and the vehicle in the physician or patient assessment of improvement.

4) Study 102: This study had 189 evaluable patients in the three treatment groups, and the treatment duration was four days. The efficacy parameters were ulcer size, categorization of ulcer pain, and a physician global assessment. Statistical analyses of the median time to healing are not provided. There was no significant difference between Amlexanox and the vehicle in the physician global assessment.

5) Pooled Studies 106 and 102: These studies had 223 evaluable patients in the 5% Amlexanox and vehicle groups. The validity of pooling of these data needs to be assessed by the statistician, for the reasons given in the reviewer's notes on the pooled studies. The median time to healing is not provided, and so it is felt that the analysis of the pooled data does not contribute to an evaluation of the effectiveness for the labeling claims.

The NDA is currently under review by our statistician.

Recommendations: It is recommended that this application for 5% Amlexanox paste for the treatment of aphthous ulcers not be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540\Huene
HFD-540\Holmes
HFD-540\DeCamp
HFD-540\Jacobs

3/18/96.

420
3/15/96

Pharm/Tox

Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products, HFD-540

NDA: # 20-511 (Resubmission Dated April 19, 1995) Amendment No. 1

Date Submitted: July 31, 1995

Date CDER Received: August 2, 1995

Assigned Date: August 14, 1995

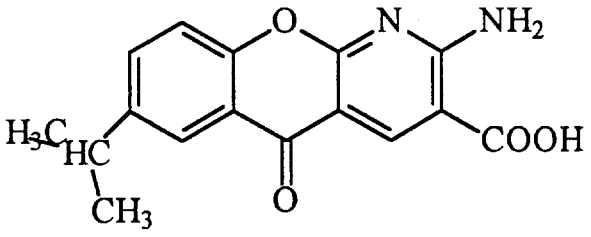
Date Review Completed: August 1995

Date Review Accepted By Supervisor:

Name of Drug: Amlexanox Oral Paste, 5% **Code Name:** AA-673; CHX 3673

Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2,3-b] pyridine-3-carboxylic acid

Structure:



Molecular Formula: $C_{16}H_{14}N_2O_4$

Molecular Weight: 298.30

Pharmacological Category: Antiallergic and anti-inflammatory; the mechanism of action for accelerating the healing of aphthous ulcers is unknown

Sponsor: Chemex Pharmaceuticals, Inc
Fort Lee Executive Park 1
One Executive Drive
Ft. Lee, NJ 07024

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs
Phone (201) 944-1449

Proposed Indication: Treatment of aphthous ulcers on the oral mucosal lining.

Dosage Form and Route of Administration: The 5% oral paste is to be dabbed on the ulcer four times a day, preferably following oral hygiene after breakfast, lunch, dinner and at bedtime. The projected maximum human dose would be approximately 1mg/kg/day.

This amendment was to define what constitutes a dab of 5% Amlexanox paste to be applied to an ulcer. A dab was described as an amount of paste squeezed from the tube which constituted a line approximately 1/4 inch (0.5cm) long on a finger tip. A reasonable estimate of approximately 60 mg of paste per application was determined from patient use (data from five clinical trials). If all of the paste was actually ingested by the patient, assuming a body weight of 60 kilograms, the mean body burden [using 12.4 mg amlexanox/day per patient] would be about 0.2 mg/kg/day. [This would be equivalent to 6.7 mg/m^2/day in a 1.88 m^2 person]. The appropriate information was incorporated into the package insert. The sponsor satisfactorily responded to the question.

John Wedig, Ph.D.
Toxicologist

Original NDA
HFD-540
HFD-540/Pharm/JWedig
HFD-540/MO/EToombs
HFD-540/Chem/EPappas
HFD-540/CSO/JHolmes

Concurrence Only
HFD-540/DD/JWilkin
HFD-540/SPharm/AJacobs

JUL 19 1995

NDA 20-511

Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products, HFD-540

NDA: # 20-511 (Resubmission Dated April 19, 1995)

Date Submitted: April 17, 1995

Date CDER Received: April 19, 1995

Assigned Date: April 21, 1995

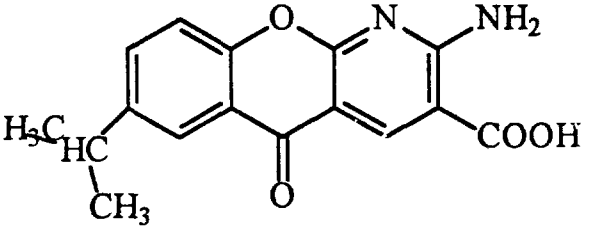
Date Review Completed:

Date Review Accepted By Supervisor:

Name of Drug: Amlexanox Oral Paste, 5% **Code Name:** AA-673; CHX 3673

Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2,3-b] pyridine-3-carboxylic acid

Structure:



Molecular Formula: $C_{16}H_{14}N_2O_4$

Molecular Weight: 298.30

Pharmacological Category: Antiallergic and anti-inflammatory; the mechanism of action for accelerating the healing of aphthous ulcers is unknown

Sponsor: Chemex Pharmaceuticals, Inc
Fort Lee Executive Park 1
One Executive Drive
Ft. Lee, NJ 07024

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs
Phone (201) 944-1449

Proposed Indication: Treatment of aphthous ulcers on the oral mucosal lining

Formulation:	Ingredient	Composition (% w/w)
	Amlexanox	5.0
	Mineral oil, USP	
	Gelatin, NF	
	Pectin, NF	
	Carboxymethylcellulose sodium, USP	
	Carboxymethylcellulose sodium, USP	
	Glycerol monostearate,	
	White petrolatum, USP	
	Benzyl alcohol, NF	

Related Submissions: IND
IND
NDA 89-066 Stiefel Research
NDA 19-940 Actinex-Chemex
DMF

Dosage Form and Route of Administration: The 5% oral paste (formulation noted above) is to be dabbed on the ulcer four times a day, preferably following oral hygiene after breakfast, lunch, dinner and at bedtime. The projected maximum human dose would be approximately 1mg/kg/day.

The pharmacology and pharmacokinetic studies have been previously summarized by Dr. Browder in the original review of IND . The following studies were reviewed under IND

1) Acute Exposure Oral Toxicity Study With 5% CHX 3673 Cream (PH 402-CX-001-88; GLP).
2) Acute Exposure Dermal Toxicity Study In Rabbits With 5% CHX 3673 Cream (PH 22-CX-001-88; GLP).
3) Primary Dermal Irritation Study With 5% CHX 3673 Cream (PH 420-CX-001-88; GLP).
4) Delayed Contact Hypersensitivity Study In Guinea Pigs With CHX 3673 Cream (PH 424-CX-001-88; GLP).
5) Hamster Cheek Pouch Irritation Study (Multiple Dose) With CHX 3673 (PH 418-CX-001-90; GLP).

6) 8-Day Dermal Toxicity Study In Rabbits With CHX 3673 Cream (PH 430-CX-001-88)

Review Objectives: To assist in the safety evaluation of a 5% oral paste preparation for the treatment of aphthous ulcers by the evaluation of nonclinical laboratory studies for clinical studies.

Index Of Preclinical Studies:

Acute Evaluations
Oral, dermal, skin and sensitization

Subacute Evaluations
5 Week Oral Toxicity Study In Rats
26 Week Oral Toxicity Study In Rats
5 Week Oral Toxicity Study In Beagle Dogs
5 Week Oral Toxicity Study In Beagle Dogs Followed By 5 And 10 Week Recovery Periods
26 Week Oral Toxicity Study In Beagle Dogs

Chronic Studies
18 Month Dietary Oncogenicity Study In Mice
2 Year Dietary Oncogenicity Study In Rats

Special Toxicity Studies
Nasal Mucosal Irritation Study In Rats
5 Week Toxicity Study Of AA-673 Into The Nasal Cavity In Rats
Ocular Irritation From Repeated Instillation
Ocular Toxicity of Aged AA-673 Ophthalmic Solution-4 Weeks Of Instillation
Four Week Ocular Toxicity of AA-673 Ophthalmic Solution In Rabbits

Reproductive Studies
Segment I In Rats
Segment II In Rats and Rabbits
Segment III In The Rats

Mutagenicity Studies
Ames Test
Micronucleus Test-Mouse

Absorption And Kinetic Studies

Protein Binding And Erythrocyte Distribution

Tissue Distribution And Accumulation Studies

Enzyme Induction

Metabolism

Excretion

Nasal Administration

Intraocular Penetration

Acute Studies

1) Acute Toxicity Of AA-673 In Mice And Rats (Report # A-16-145, GLP)

Laboratory:
Number of Animals: 10/sex/group
Animal Strain: Mice-Ta:ICR, Rats-Jcl:Wistar
The test material was suspended in 5% gum arabic. The animals were observed for 7 days after treatment and then necropsied. The LD50 (95% confidence limits) was found to be:

Mouse- mg/kg	Male	Female
Subcutaneous injection	3310(2960-3680)	3760(3370-4200)
Intraperitoneal injection	480(440-520)	450(410-490)
Oral gavage	2370(2160-2540)	2320(2120-2540)
RAT-mg/kg	Male	Female
Subcutaneous injection	1560(1320-1820)	1400(1180-1620)
Intraperitoneal injection	520(470-560)	500(460-540)
Oral gavage	ca 10000	ca 10000

A difference in LD50 values was noted between rats and mice. The major clinical

signs noted after treatment were decreased activity and respiratory depression. The study is acceptable for its intended purpose.

2) Acute Oral Toxicity Study In Rats (Report # 70903807; GLP)

Laboratory:

Number Of Animals: 5/sex/group

Animal Strain: Sprague Dawley, Charles Rivers

Study Design: The test material was suspended in 0.5% hydroxypropyl methylcellulose. The rats were observed for 14 days following dosing and then necropsied.

Results: The LD50(mg/kg) and 95% confidence limits were found to be : Male-5000(3346-7473) female-2828(1964-4073). Combined values were 3810 mg/kg. The major clinical sign noted after dosing was hypoactivity. The study is acceptable for its intended purpose.

3) Acute Dermal Toxicity Study In Rabbits (solution of Amlexanox; Report # 70903808 GLP)

Laboratory:

Number Of Animals: 5 males and 5 females

Animal Strain: New Zealand Albino

Study Design: The test material was dissolved in trolamine and water to yield a 10% solution which was applied at 2 gm/kg. One-half of the animals had abraded skin sites. A pilot study using two animals per sex indicated no mortality.

Results: The study using 10 animals indicated no mortality at 2 gm/kg. This study is acceptable for its intended purpose.

4) Publication- Hairya, et al, Allergenicity and tolerogenicity of amlexanox in the guinea pig, Contact Dermatitis, 1994; 31: 31-36. Oral administration of amlexanox prior to sensitization resulted in complete non-responsiveness. It is proposed that a substantial reduction in the risk of sensitization from the use of an ophthalmic solution containing amlexanox may be achieved by the prior oral administration of tablets containing this drug.

Subacute Evaluations

1) Five Week Oral Toxicity Study of AA-673 In Rats (Report A-16-146; GLP)

Laboratory:

Number Of Animals: 10 males and 10 females per group

Animal Strain: Ta:Wistar

Dose Levels: 0, 40, 200 and 1000 mg/kg/day

Formulation: The compound was mixed with gum arabic and suspended in distilled water at concentrations of 0, 0.8, 4 and 10% (w/v) to correspond to the 0, 40, 200 and 1000 mg/kg doses-i.e. 10, 5, 5 and 10 ml/kg/ day respectively.

Route: Oral gavage- once a day.

Study Design: The rats were dosed 7 days a week for 5 weeks. The water intake and 24 hour urine volume were determined for 5/sex/group at the beginning and end of the study. Body weight and food consumption was determined weekly. A urinalysis was performed on 5/sex/group toward the end of the treatment period. Hematology and serum chemistry was evaluated on all animals (fasted) at the termination of treatment. A piece of liver was taken at necropsy from 5/sex/group for determination of enzymatic activity. At necropsy 16 organs/animal were weighed from 10/sex/group and 21 tissues/animal were processed for histology from 5/sex/group. Kidney and liver tissue from one male in the control group and two males in the 1000 mg/kg group was examined with an electron microscope.

RESULTS

Mortality: One male in the 200 mg/kg group died during the course of the evaluation due to a technical dosing error-i.e. not treatment related .

Clinical Observations, Body weight, Food Consumption, Urinalysis, Urine Chemistry, Water Intake, Urine Volume, Hematology, Hepatic Drug Metabolizing Activity: No treatment related findings.

Organ And Organ-to-Body Weights: A significant increase in the mean absolute and relative to body organ weight was noted for the cecum and stomach in the animals treated with 1000 mg/kg. This was considered to be treatment related.

Serum Chemistry: The alkaline phosphatase levels were significantly increased in the males and females given 1000 mg/kg as compared to the controls. This was a treatment related effect not noted in other groups.

Gross Necropsy: A treatment related white-yellowish mucous was observed on the surface of the gastric mucosa of almost all females and one male in the 1000 mg/kg group. This was not noted in the other groups.

Histopathology: Treatment related findings included the following in the 1000 mg/kg group:

Glandular stomach-

6 animals- thickening of mucosa with hypersecretion
5 animals- dilation of glandular lumen

Forestomach-

2 animals- hyperplasia of mucosa

Cecum-

4 animals- hypertrophy and desquamation of epithelium

Electron Microscopy: A slight dilation of the bile cuniculi in the liver was seen at a dose of 1000 mg/kg.

Summary: The no adverse affect level of AA-673 from this evaluation is 200 mg/kg. The target organs appear to be the cecum and the glandular stomach at a dose of 1000 mg/kg-i.e. pathological changes and weight increases. Electron microscopic changes were noted in the liver and a significant elevation in serum alkaline phosphatase was noted at this dose level. All of these changes were minimal in nature. The study is acceptable for its intended purpose.

2) 26 Week Oral Toxicity Study Of AA-673 In Rats (Report # A-16-185; GLP)

Laboratory:

Number Of Animals: 12 males and 12 females per group

Animal Strain: Jcl:Wistar Rats

Dose Levels: 0, 30, 100 and 300 mg/kg/day

Formulation: Dietary admix. Test diets were made up weekly.

Route: Oral

Study Design: Animals were fed diets containing the drug for 26 weeks. Clinical signs were monitored daily, food consumption 2 X week and body weight weekly. Five males and 5 females had a urinalysis done pretest and during weeks 6, 14 and 26. Hematology and serum chemistry evaluations were done on fasted animals at necropsy. All animals were necropsied and organ weights were obtained. Histopathological evaluation was done on 5 males and 5 females from each group. Liver from the control and the 100 and 300 mg/kg groups was examined under an electron microscope.

RESULTS

Mortality: No treatment related mortality occurred. There were two incidental deaths.

Diet Analysis: Concentrations of AA-673 were analyzed during weeks 5, 10, 15, 20 and 25 and found to be within 88 to 113% of theoretical. AA-673 was stable in the CE-2 rat chow for 2 weeks at room temperature. No homogeneity data were given.

Dietary Intake: The group mean dietary intakes were close to theoretical. Some of the ranges were outside of 10%.

Clinical Observations, Urinalysis, Hematology, Body Weight, Gross Necropsy Observations and Histopathological Analysis:
No treatment related effects were noted on any of these parameters.

Food Consumption: Males in the 300 mg/kg group consumed significantly more food than the control animals for most weekly periods up through 15 weeks. Females receiving the same dose did not.

Organ Weights: An increase in the cecum weight was noted only in the males receiving 100 and 300 mg/kg. No histopathological change was seen in the cecum or the other parts of the gastrointestinal tract indicating this effect was not treatment related.

Serum Chemistry: A significant increase was noted in the mean alkaline phosphatase levels only in the males given 300 mg/kg.

Electron Microscopy: A slight dilatation of the bile canaliculi in the centrolobular hepatocytes was seen in one male given 300 mg/kg and was considered to be treatment related.

Summary: The no effect level of AA-673 appears to be 100 mg/kg due to the elevated serum alkaline phosphatase and the dilated bile cuniculi in the males given 300 mg/kg. The study is acceptable for its intended purpose.

3) Five Week Oral Toxicity Study Of AA-673 In Beagle Dogs (Report A-16-136; GLP)

Laboratory:

Number Of Animals: 3 males and 3 females per group

Animal Strain: Canine, beagle;

Dose Levels: 0, 10, 30 and 100 mg/kg/day

Route: Orally in the morning by gelatin capsule containing the pure drug

Study Design: The dogs were dosed 7 days a week for 5 weeks. Food consumption was determined daily and body weight 2 x weekly. Clinical observations were done pre dose and 1 and 6 hours post dosing. Physicals, ophthalmic examinations (internal and external), hematology evaluations including clotting times, urinalysis and water intake were done pretest, during the midpoint and at the end of the study. Serum chemistry was done pretest and weekly. Blood for plasma drug levels was taken 2, 10 and 24 hours post dosing on drug day 36. Liver tissue from all dogs was assayed for drug metabolism (hydroxylase and N-demethylase). Organ weights were obtained at necropsy from all animals and 25 tissues/animal were prepared for histological examination. Selected liver samples were silver stained and selected liver and kidney tissues were prepared for enzyme histochemistry.

RESULTS

Mortality: No treatment related deaths occurred.

Body Weight, Clinical Signs, Food Consumption, Physical Examinations, Ophthalmological Examinations, Hematology and Prothrombin Times, Urinalysis, Water Intake, Hepatic Drug Metabolism, Organ Weights, Hepatic Silver Stains and Enzyme Histochemistry of Kidney:

No consistent or distinct treatment related effects were noted.

Serum Chemistry: Ornithine carbamyl transferase, alkaline phosphatase and glutamic pyruvic transaminase were increased in the 100 mg/kg group. This was treatment related.

Plasma Levels Of AA-673: Peak plasma concentrations were reached about 2 hours post dosing. The drug blood concentrations indicated that the increase in plasma levels was greater than the increase in dose.

Gross Necropsy: A slight discoloration of the liver in two males and two females given 100

mg/kg was noted.

Histopathology: Treatment related finding in the 100 mg/kg group included- Proliferation of the bile ducts accompanied by fibroplasia in the peripheral zone of the liver lobule; atrophy and degeneration of the hepatocytes in close proximity to this lesion; hypertrophy of the epithelium of the gallbladder.

Enzyme Histochemistry: An increase in alkaline phosphatase activity of the proliferated bile ducts was noted in animals given 100 mg/kg.

Summary: Hepatotoxicity was noted at the 100 mg/kg dose. The no effect level appears to be 30 mg/kg. This study is acceptable for its intended purpose.

4) Five Week Oral Toxicity Study Of AA-673 In Beagle Dogs Followed By 5 And 10 Week Recovery Periods (Report # A-16-486; GLP)

Laboratory:

Number Of Animals: 6 females in the control group and 9 females in the treatment group

Animal Strain: Canine, beagle;

Dose Level: 0 and 100 mg/kg

Route: Orally in the morning by gelatin capsule containing the pure drug

Study Design: The dogs were dosed 7 days a week for 5 weeks followed by a recovery period of 5 and 10 weeks. Food consumption and clinical observations were done daily. Serum chemistry was done pretest and at the end of the dosing and recovery periods. Two control and three treated animals were necropsied at the end of treatment and after 5 and 10 weeks of no dosing. Organ weights were obtained at the end of the AA-673 dosing period and the 5 week recovery period. Liver and gallbladder tissue were prepared for histological examination. Liver tissue was prepared for enzyme histochemistry and electron microscopic examination.

RESULTS

Mortality: No treatment related mortality occurred.

Clinical Signs: Most of the AA-673 dosed animals occasionally vomited undigested food throughout the treatment period.

Body Weight: Some animals showed a slight decrease during the dosing period which returned to expected values during the recovery period.

Serum Chemistry: Ornithine carbamyl transferase, alkaline phosphatase and glutamic pyruvic transaminase were increased in the treated animals at the end of the dosing period. The values were in the expected range 5 weeks after cessation of dosing.

Gross Necropsy: A slight discoloration of the liver surface was noted in 2 of the treated dogs after 5 weeks of dosing. This was not noted in any of the recovery dogs.

Histopathology: Hypertrophy of the bile duct epithelium, proliferation of peri-bile duct connective tissue and atrophy of hepatocytes around interlobular connective tissue was noted in all of the treated animals. After 5 weeks of recovery the only finding was a slight increase in the interlobular connective tissue in one dog. This change was not observed after 10 weeks of recovery.

Enzyme Histochemistry: A marked increase of alkaline phosphatase activity was noted in the bile cuniculi of the 3 treated dogs. This activity returned to expected values after the 5 week recovery period.

Electron Microscopy: A protrusion of hepatocytes into the bile cuniculi noted at the end of the dosing period was absent in the dogs after 5 weeks of recovery.

Summary: Hepatotoxicity noted after treatment with 100 mg/kg for 5 weeks was absent 10 weeks after no dosing, indicating complete recovery. The study is acceptable for its intended purpose.

5) 26 Week Oral Toxicity Study In Beagle Dogs (Report # A-16-187; GLP)

Laboratory:

Number Of Animals: 3/ sex/group

Animal Strain: Canine, beagle;

Dose Level: 0, 3, 10 and 30 mg/kg/day

Route: Orally in the morning by gelatin capsule containing the pure drug

Study Design: The dogs were dosed 7 days a week for 26 weeks. Food consumption was determined daily and body weight approximately weekly. Clinical observations were done pre dose and 1 and 6 hours post dosing. Physicals, ophthalmic examinations (internal and external), hematology, prothrombin times, serum chemistry, urinalysis, 24-hour water

intake and urine volume were done pretest and during weeks 5, 13 and 26. All animals were subjected to a complete necropsy and their organs were weighed. Tissues from all animals were examined histologically. Enzyme histochemistry was done on liver tissue from all treatment groups. Liver tissue from the control and 30 mg/kg group was examined with an electron microscope.

RESULTS

Mortality, Body Weight, Food Consumption, Clinical Signs, Physical Examinations, Ophthalmological Examinations, Hematology, Prothrombin Times, Serum Chemistry, Urinalysis, 24-Hour Water Intake and Urine Volume, Gross Necropsy, Organ Weight, Histopathology and Electron Microscopy:

No consistent or distinct treatment related changes were noted.

Enzyme Histochemistry: A slight increase in alkaline phosphatase in the bile cuniculi of the central part of the liver lobule of one of two males in the 30 mg/kg group was noted.

Summary: The maximum non-toxic dose level in this evaluation was 30 mg/kg. This study is acceptable for its intended purpose.

CHRONIC STUDIES

1) 18 Month Dietary Oncogenicity Study In Mice With AA-673 (Report # 295-060; GLP)

Laboratory:

Number Of Animals: 50/sex/group; 6 weeks old at study initiation

Animal Strain: mouse, $B_6C_3F_1$, Charles Rivers,

Dose Levels: 0, 3, 10, 30 and 100 mg/kg

Formulation: Dietary admix. Test diets were made up weekly. Homogeneity studies indicated a 20 minute mix resulted in preparations that assayed plus or minus 10% of theory for AA-673 consistently. Stability studies indicated the AA-673 was stable(plus or minus 5% of theory) in Purina Certified Chow #5002 under laboratory conditions over a period of 10 days. The two lots of AA-673 used for mixing the diets were assayed at the beginning of each use span and found to be 99.9% pure. The sponsor provided analytical data indicating that AA-673 was stable at room temperature for at least two years.

Pilot Study: A 17 week dietary dose range finding study in this strain of mouse was conducted

at using dose levels of 0, 25, 50, 100, 200, 500 and 1500 mg/kg (the latter two dosage levels from study week 14, and representing a change in the 25 and 50 mg/kg/day dose levels). A treatment related toxic nephrosis was noted beginning at a dose of 100 mg/kg . This effect increased in incidence and severity with increasing dose. No other treatment related effects were seen.

Study Design: Animals were fed the diets for 78 weeks. Food consumption and bodyweight were determined pretest, weekly during the first 14 weeks and thereafter every 2 weeks. Food efficiency was determined for the first 14 weeks. Clinical observations were done daily. Hematology evaluations were done at term and if possible on animals in extremis. All animals were subjected to a complete necropsy. A complete set of tissues was prepared for histopathological evaluation from the control and 100 mg/kg dose group, all animals that died or were sacrificed in extremis, plus all tissue masses with regional lymph nodes, gross lesions and the kidneys from the 3, 10 and 30 mg/kg groups.

RESULTS

Compound Consumption and diet analysis: The mean weekly compound consumption of all the AA-673 treated groups was within 10% of theory except for four instances during the 78 week treatment period. Diet assays every four weeks for AA-673 concentration in all groups indicated only six diet mixes that were greater or less than 10% of theory.

Mortality, Clinical Signs and Food Consumption: No treatment related effects were noted on these parameters.

Body Weight: No consistent treatment related effect was noted. In the males given 100 mg/kg there was a decrease in body weight in the last 6 months of treatment.

Hematology: A significant decrease in erythrocytes, hemoglobin and hematocrit were noted in the males given 100 mg/kg. This was not noted in the corresponding female group.

Gross Necropsy Observations: Males in the 100 mg/kg group had an incidence of 35/50 with granular kidneys. This treatment related effect was not noted in the females.

Histology: Toxic nephrosis of the kidney was noted in 50/50 males in the 100 mg/kg group.

Summary: The test material, AA-673, was determined to have no tumorigenic effect. The no effect level for toxicity to the kidney was 30 mg/kg. This study is acceptable for its intended purpose.

2) Two Year Dietary Oncogenicity Study In Rats With AA-673 (Report # 295-058; GLP)

Laboratory:

Number Of Animals: 50/sex/group; 5 weeks old at study initiation

Animal Strain: Charles Rivers Fisher 344 rats

Dose Levels: 0, 25, 80 and 250 mg/kg/day

Formulation: Dietary admix. Test diets were made up weekly. Homogeneity studies indicated a 10 minute mix resulted in preparations that assayed plus or minus 10% of theory for AA-673 consistently. Stability studies indicated the AA-673 was stable (plus or minus 5% of theory) in Purina Certified Chow #5002 under laboratory conditions over a period of 10 days. The three lots of AA-673 used for mixing the diets was assayed at the beginning of each treatment span and found to be 99.9% pure. The sponsor provided analytical data indicating that AA-673 was stable at room temperature for at least two years.

Pilot Study: A 13 week dietary ranging finding study in Fisher 344 rats was conducted at using dose levels of 0, 125, 250, 500 and 1000 mg/kg. Body weight was decreased at 1000 mg/kg. Serum levels of alkaline phosphatase, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase were increased in the males given 500 mg/kg and in both sexes at 1000 mg/kg. Histopathological evaluation of the liver indicated dilation of the extrahepatic and common bile ducts, bile duct hyperplasia, cholangitis, necrosis and pericholangitis. These were seen in both sexes at 1000 mg/kg and in the males at 500 mg/kg. Females at 500 mg/kg indicated only one trace instance of pericholangitis as did the males at 250 mg/kg. The dose of 125 mg/kg did not appear to produce any toxic effects.

Study Design: Animals were fed the diets for 104 weeks. Food consumption and body weight were determined pretest, weekly during the first 14 weeks and thereafter every 2 weeks. Food efficiency was determined for the first 14 weeks. Clinical observations were done daily. The animals were palpated for masses weekly. Hematology evaluations were performed on animals at term and on ones that were sacrificed in extremis. All animals were subjected to a complete necropsy. A complete set of tissues was prepared for histological evaluation from the control and 250 mg/kg dose group and all animals that died during the course of the study or were sacrificed in extremis. All tissue masses with regional lymph nodes, all gross lesions, liver and adrenals from all animals were also prepared for histopathological examination.

RESULTS

Compound Consumption And Diet Analysis: The mean compound consumption of all the

AA-673 treated groups was within 10% of theory except for three 2 week periods when it exceeded the 10% over the 104 weeks period. Diet assays every four weeks for AA-673 concentration in all groups indicated 14 values which were less than 10% of theory-i.e. 11 in the 80's and 3 in the high 70's.

Mortality, Hematology, Clinical Signs , Food Consumption And Food Efficiency: No treatment related effects were noted on these parameters.

Body Weight: There was a frequent significant decrease in body weight of the males given 250 mg/kg the second half of the study. The actual difference was small, 6%. This was occasionally noted in the high dose females.

Gross Necropsy Observations: Dilatation of the extrahepatic bile duct was noted in males given 250 mg/kg as well as an increase in eye lens discoloration.

Histology: Prominent biliary changes were noted in the males from the 250 mg/kg group. They included cystic dilatation, calculus formation and inflammation of the extrahepatic bile duct. Cholangitis and pericholangitis was noted in the liver. This effect was limited to a slight increase in pericholangitis in the females given 250 mg/kg.

Summary: The test material AA-673 was determined not to be carcinogenic. The no effect level for toxicity was determined to be 80 mg/kg. This study is acceptable for its intended purpose. See attached CAC forms for the rat and mouse.

SPECIAL TOXICITY STUDIES

1) Nasal Cavity Irritation Study Of AA-673 Nasal Solution After Forced Deterioration (Report # A-16-527). Only a summary report was available. The irritation potential of a deteriorated sample of AA-673 introduced into the nasal cavity of Jcl:Wistar rats 4 X/day for 14 days was evaluated. It was concluded that no irritation was produced by the deteriorated AA-673 applied to the nasal mucosa of rats under the test conditions.

2) Nasal Mucosal Irritation Study Of AA-673 Nasal Solution After Forced Deterioration In Rats (Report # A-16-585;GLP)

Laboratory:

Number Of Animals: 110/group

Animal Strain: Jcl:Sprague Dawley Rats

Duration Of Dosing: every 15 minutes for a total of nine times in one group
every 2 hours daily for 14 consecutive days

Dose Levels: 25 ul instilled in the left nostril per dose-AA-673 nasal solution or saline

Study Design: The animals were dosed and observed for clinical signs twice daily during the treastment period and once daily during the following observation period. They were weighed weekly. One and 7 days after the last instillation, 5 animals/group were sacrificed. The nasal area was prepared for histological examination.

RESULTS

No abnormalities were noted in clinical signs or at autopsy in either group of treated rats. Histopathological examination of the nasal tissues indicated that AA-673 did not cause irritation.

Summary: A deteriorated AA-673 nasal solution does not cause irritation to the nasal tissues. The study is acceptable for its intended purpose.

3) Five Week Toxicity Study Of AA-673 Delivered Into The Nasal Cavity In Rats (Report # A- 16-274; GLP)

Laboratory:

Number Of Animals: 5/sex/group

Animal Strain: Jcl:Sprague Dawley Rats

Duration Of Dosing: 5 Weeks, 7 days a week, 4 times a day. Each dose volume was 0.025 mL

Dose Levels: Saline control, 0.1 mL/rat/day
vehicle control, 0.1 mL/rat/day
AA-673 0.1 mg/rat/day; 0.1 mL/rat/day
AA-673 0.25 mg/rat/day; 0.1 mL/rat/day

Route: The solution was delivered 4 times a day to the left nasal cavity by means of a micropipette through the nostril.

Study Design: Animals were treated 4 times a day for 5 weeks. Clinical observations were noted daily. Body weights were taken on the 0, 1st, 3rd and 7th day and then twice weekly. A complete necropsy was conduced on each animal and the organs were weighed. The upper respiratory tract of each animal was prepared for histology and stained with three stains.

RESULTS

Mortality, Body Weight, Clinical Observations, Organ Weights and Gross Necropsy Observations:

No treatment related effects were note.

Histopathology: A very slight increase in the number of goblet cells in the respiratory region of the nose was noted in the animals treated with 0.25 mg/rat/day. However, there was no dose response relationship and this effect was also seen in the vehicle and saline controls. There were no changes indicative of degeneration of the cells.

Summary: The local irritative effect of AA-673 solution is very slight. The study is acceptable for its intended purpose.

4) Ocular Irritation Study Of AA-673 Ophthalmic Solution In Frequent Instillation In Rabbits (Report # AA-673/S-TX02)

Laboratory:

Number Of Animals: 9

Animal Strain: Japanese white aboriginal rabbits

Dose : several drops of the 1.0% AA-673 ophthalmic solution

Route: instillation in the conjunctival sac of the right eye

Study Design:

Group 1- 3 rabbits- 32 topical installations in the eye at 15 minute intervals for a day
Group 2- 3 rabbits- 16 topical installations in the eye at 30 minute intervals for a day
Group 3- 3 rabbits- not used

The eyes were examined before treatment and 30 minutes after the last treatment. The cornea was stained with fluorescein dye and examined at these times. The animals

behavior was also monitored.

RESULTS

Chemosis and redness of the conjunctivae and discharge were noted. No lesions were produced. The irritation cleared up 24 hours after the last instillation. The study is acceptable for its intended purpose

5) The External Ocular Toxicity Study Of Aged 0.25% AA-673 Ophthalmic Solution By 4 Week Repeated Instillation In Rabbits(Report # AA-673/S-TX03)

Laboratory:

Number Of Animals: 5 males

Animal Strain: Japanese white rabbits

Dose : Two drops of an aged (5 days) 0.25% AA-673 solution or physiological saline

Route: Instillation in the eye

Study Design: Animals had AA-673 (right eye) or saline (left eye) instilled onto the eye 9 times daily at 1 hour intervals for 28 days. The eyes were scored with the Draize procedure pretest and 30 minutes after the last instillation on days 1, 3, 7, 14, 21 and 28. Slit lamp examination with fluorescein staining followed the same schedule. Body weights were taken pretest and weekly and clinical observations were done daily.

RESULTS

The aged AA-673 0.25% solution had no effect on the rabbit eye or other parameters measured. This study is acceptable for its intended purpose.

6) Four Week Ocular Toxicity Study Of 0.5% AA-673 Ophthalmic Solution In Rabbits (Report # AA-673/S-TX01)

Laboratory:

Number Of Animals: 10

Animal Strain: Japanese white aboriginal rabbits

Dose Levels: 2 drops/dose (about 0.1 mL) ; 5 rabbits received AA-673 and 5 received saline

Formulation: 0.5% AA-673 ophthalmic solution or physiological saline

Route: conjunctival; AA-673 or physiological saline was put in the right eye; left eye was untreated

Study Design: The animals had either the drug or saline instilled onto the conjunctivae 9 times a day at 1 hour intervals for 29 days. The eye was scored using the Draize procedure and the cornea was examined using fluorescein and a slit lamp pretest and 1, 3, 7, 14, 21 and 28 days after study initiation. The pupil size and intraocular pressure was measured 2, 4 and 7 days prior to study termination Body weight and general condition were noted pretest and weekly thereafter.

RESULTS

No treatment related effects were noted on any of the parameters measures during the 29 day study. The study is acceptable for its intended purpose.

Reproductive Studies

1) Effect Of Amlexanox (AA-673) On Fertility And General Reproductive Performance Of The Rat (Report # A-16-473; GLP)

Laboratory:

Number Of Animals: 26 males and 26 females per group

Animal Strain: Jcl:Wistar,

Dose Level: 0, 30, 100 and 300 mg/kg

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 6%. It was further diluted with 5% gum arabic to make 2 and 0.6% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume to each group was 5 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 3 X during the study. All assays were well within plus or minus 10% of theory. Homogeneity and stability for 24 hours were determined and found to be within plus or minus 10% of theory.

Study Design: The males were treated daily for 9 weeks prior to mating. The females were treated daily for 2 weeks before mating and during the mating period. Dosing continued throughout the remainder of the study. Approximately one-half of the females were killed on day 13 of pregnancy, the remainder were allowed to rear their litters to day 22 after delivery. Food consumption, body weight, estrous cycle, copulation rate, conception rate, fertility index and various other reproductive indices were monitored.

RESULTS

Mortality, Body Weight, Food Consumption, Estrous Cycle, Conception Rate, Pre-Implantation Loss, Post- Implantation Loss, Number Of Corpora Lutea, Number Of Live Embryos, Morphological Observations, Development Of Maturational Landmarks, Gestation Period, Parturition, Suckling, Litter Size, Pup Mortality and Body Weight

No treatment-related effects were noted on any of these parameters- reproductive performance or pre and post natal development of the pups. The study is acceptable for its intended purpose.

2) Teratological Study of Amlexanox (AA-673) In The Rat (Report # A-16-472; GLP)

Laboratory:

Number Of Animals: Approximately 49 pregnant females per group

Animal Strain: Jcl:Wistar Rat,

Dose Levels: 0, 30, 100 and 300 mg/kg

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 6%. It was further diluted with 5% gum arabic to make 2 and 0.6% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume to each group was 5 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 1 X during the study. Assays were well within plus or minus 10% of theory. Homogeneity and stability for 24 hours were determined and found to be within plus or minus 10% of theory.

Study Design: The animals were mated at The rats were treated on days 6-17 of pregnancy. Twenty-one to 23 per group were necropsied on day 20 of gestation. Two-thirds of the fetuses were stained for skeletal examination. The remaining one-third were examined for visceral abnormalities using the freehand sectioning technique of Wilson. Various reproductive indices, food consumption, body weight, behavior and

mortality were calculated. The remaining 12 to 13 animals in each group were allowed to deliver. All dams were necropsied on day 22 or 23 postpartum- the number of implantation sites was counted and the main organs were examined histologically. The pups were sexed, weighed and their development assessed morphologically-pinna detatchment, incisor eruption and eye opening. Two males and two females from each litter in all dose groups were necropsied and examined for internal and skeletal (x-ray) abnormalities. One male and 1 female were examined microscopically for evidence of brain abnormalities. The remaining pups were reserved for behavioral and reproductive studies. The behavioral studies included- an open field test, water T-maze test and a wheel rotation activity test. The reproductive performance test involved - mating non-litter mates, allowing them to deliver. The pups were sacrificed on days 9 to 11. The main organs were examined histologically. An assessment of internal and skeletal development was made as well as a histological examination of the brain. The reproductive organs were examined thoroughly.

RESULTS

Mortality, Skeletal Development, Development Of The Internal Organs, Brain Development, Body Weight, Food Consumption, Litter Size, Pup Weight, Morphological Development, Number Of Implants, Number Of Resorptions, Maturational Landmarks and Behavior

No consistent or distinct treatment related effects were noted. The study is acceptable for its intended purpose.

3) Teratological Study Of Amlexanox (AA-673) In The Rabbit (Report # A-16-471; GLP)

Laboratory:

Number Of Animals: Approximately 12 to 14 pregnant females per group

Animal Strain: JW rabbit,

Dose Levels: 0, 30, 100 and 300 mg/kg

Pilot Study: A two week oral intubation in females of this strain of rabbit was conducted. All of the animals given 1000 mg/kg died. Two of 5 animals in the 300 mg/kg group showed a decrease in food consumption. On this basis the above doses were selected.

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 3%. It

was further diluted with 5% gum arabic to make 1 and 0.3% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume to each group was 10 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 2 X during the study. Assays were well within plus or minus 10% of theory. Homogeneity and stability of 0.6 and 6.0% (w/v) suspensions for 24 hours were determined previously and found to be within plus or minus 10% of theory.

Study Design: The animals were mated at Takeda Chemical Co. They were treated from day 6 through day 18 of pregnancy. Food consumption and body weights were obtained on days 0, 6, 13, 19, 23 and 28 of gestation. All animals were observed for signs of toxicity daily. The dams were necropsied on day 28 of gestation. Various reproductive indices were noted. The placenta, amnion and amniotic fluid were examined microscopically. The fetuses were examined for external and visceral abnormalities and variations. The heart and kidneys were freehand sectioned with a razor blade and examined for abnormalities. The fetuses were then stained for skeletal examination of potential abnormalities and variations. Prior to preparing the fetus for skeletal staining the head was freehand sectioned with a razor blade and the brain was examined for abnormalities.

RESULTS

Mortality, Skeletal Development, Development Of The Internal Organs, Brain Development, Body Weight, Food Consumption, Litter Size, Pup Weight, Number Of Implants, Number Of Resorptions And Histological Examination Of Organs

No consistent or distinct treatment related teratogenic or embryolethal effects were noted. A slight decrease in body weight gain and suppression of food consumption were noted in a few of the dams in the 300 mg/kg group the latter half of the treatment period. The study is acceptable for its intended purpose.

4) Effect Of Amlexanox (AA-673) On Peri- And Post-Natal Development Of The Rat (Report # A-16-474; GLP)

Laboratory:

Number Of Animals: 23 to 24 pregnant females per dose group

Animal Strain: Jcl:Wistar rat,

Dose Levels: 0, 30, 100 and 300 mg/kg/day

Pilot Studies: A 5 week oral toxicity study in rats indicated a no effect level of 200 mg/kg. An adverse effect was noted at 300 mg/kg in a 26 week oral rat study.

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 6%. It was further diluted with 5% gum arabic to make 2 and 0.6% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume for each group was 5 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 2 x during the study. Assays were well within plus or minus 10% of theory. Homogeneity and stability of 0.6 and 6.0% (w/v) suspensions for 24 hours were determined previously and found to be within plus or minus 10% of theory.

Study Design: The pregnant rats were dosed from day 15 of pregnancy through suckling to day 21 postpartum. All animals were allowed to deliver and the F1 pups were examined for morphological development and assessed in behavioral tests- negative geotaxis and grip strength.. The dams were necropsied on day 22-23 postpartum and the number of implantation sites counted. Two males and two females were necropsied at the same time and examined for external and internal abnormalities, skeletal and brain abnormalities. The remaining F1 pups after weaning were assessed for testes descent and vaginal opening and then a select few from each litter were used for behavioral and reproductive performance studies. Behavioral studies included pupillary reflex, pain response, rotarod performance, open field test, preyer's reflex, running wheel activity test and the water T-maze test. All F2 pups were necropsied on days 7 to 9 postpartum . Selected animals were examined for skeletal abnormalities and variations and brain abnormalities. The presence or absence of sperm in the epidimides and follicles and luteinization in the ovaries was determined.

RESULTS

Mortality, Motor Coordination, Grip Strength, Numbers Of Newborn per Litter, Number Of Implantation Sites, Number Of Resorptions, Sex Ratio, Reflexes, Pain Response, Auditory Response, Rotarod Performance, Clinical Signs, Body Weight, Copulation Rate, Gestation Period, Delivery, Nursing, Conception Rate, Skeletal Or Visceral Abnormalities and Brain Abnormalities

Summary: No treatment related changes were noted on any of the above mentioned parameters. This study is acceptable for its intended purpose.

Mutagenicity Studies

1) Mutagenicity Tests On Amlexanox Sodium Salt (1): Rec-assay And Reversion Test In Bacteria (report # A-16-541)

Laboratory:

Study Design: Two bacterial mutagenic assays were used to assess the drug- a repair test (modified rec assay) and a reverse mutation test (Ames test). Nine positive control agents were used and demonstrated to be active. The test strains for the repair test were B subtilis H17(rec+) and M45(rec-) and for the reverse mutation test were E. coli WP2uvrA and S. typhimurium TA100, TA98 and TA1537.

RESULTS

Negative results were obtained in the rec-assay at dosages of 125 and 1250 ug/disk. In the reverse mutation assay at dosages ranging from 100 to 5000 ug/plate negative results were obtained with and without metabolic activation (S9 fraction). It was concluded that the drug is not mutagenic or DNA damaging. The study is acceptable for its intended purpose.

2) Micronucleus Test On Amlexanox (AA-673) In Mice (Report # A-16-476; GLP)

Laboratory:

Number Of Animals: 5 males/group

Animal Strain: SPF (C3HxSWV)F1,

Dose Level: Single oral dose 0, 125, 500 and 2000 mg/kg
Single dose daily for four days 0 and 500 mg/kg

Formulation: Amlexanox was suspended in %5 gum arabic solution at 1.25, 5 and 20 %(w/v) such that all animals were given 10 mL/kg. Homogeneity and stability studies over 24 hours for this concentration range were acceptable-i.e. plus or minus 10% of theory.

Study Design: The drug was administered orally in a single dose at 0, 125, 500 and 2000 mg/kg or 0 and 500 mg/kg daily doses for 4 consecutive days. Mitomycin C, the positive control, was injected once intrapertioneally at a dose of 2 mg/5 mL/ kg. The animals were killed 30 hours after treatment and bone marrow was removed from the femur and processed into slides. The frequency of polychromatic erythrocytes and reticulocytes was determined.

RESULTS

No evidence of an increased frequency of bone marrow micronucleated erythrocytes in the drug treated groups was noted. This suggests that the compound is not mutagenic. This study is acceptable for its intended purpose.

Absorption, Distribution, Metabolism And Excretion Studies

1)This information was translated from the article published in Japanese, Metabolic Fate of Amlexanox (AA-673), A New Antiallergic Agent, In Rats, Mice, Guinea-Pigs And Dogs, Japanese Pharmacology & Therapeutics 13: 4933-4954.

Laboratory:

Animal Strain: male and female Jcl:Wistar rats
male Jcl:ICR mice
male Crj:Hartley guinea-pigs
male beagle dogs

Formulation: The drug was labelled with ^{14}C in the pyridine ring and had a radiochemical purity of greater than 99%. The 14C-AA-673 was appropriately diluted with nonlabelled drug and was suspended in 5% gum arabic solution for oral administration or was dissolved in a minimum volume of 1N NaOH and diluted with phosphate buffered saline for intravenous injection. The animals were dosed at the rate of 10 mg/kg.

Absorption and Kinetics

The ratio of radioactivity in urine was calculated following oral gavage and intravenous dosing to rats, mice, guinea-pigs and dogs (fasted or fed). Bioavailability was estimated to be 46, 61, 76 and 47% in rats, mice, guinea-pigs and dogs, respectively. The site of absorption was studied in pyloric-ligated rats after intragastric or intraduodenal administration of the drug. The plasma concentration was significantly higher after intraduodenal administration suggesting the drug was absorbed mainly from the small intestine. Further studies using a jejunal loop indicated absorption was mainly by the portal route in this area. The use of thoracic duct fistulated rats given the drug orally indicated absorption was unlikely by the lymphatic route.

The absorption of the drug after oral gavage was rapid in the rat, mouse and dog. It was delayed in the guinea-pig probably due to absorption from a wide range of the intestine.

The level of ^{14}C AA-673 and its metabolites in plasma were studied for at least 24 hours following oral gavage in rats, mice, guinea-pigs and dogs. The plasma concentration of the labelled drug and its metabolites were about equal in mice, guinea-pigs and dogs suggesting the metabolic characteristics are about the same. The rat had a substantial quantity of metabolite in the plasma which was identified as a conjugate that was not noted in the other species. The composition of the metabolites from the plasma of man resembles that found in mice, guinea-pigs and dogs but not rats.

In man a single oral application of 5mg from 5% paste resulted in an area under the curve(AUC, 0 to 24 hours) of 0.36 ug.hr/ml. Ten mg/kg given intraduodenally to the rat resulted in an AUC

(0 to infinity) of 4.23 ug.hr/ml. Ten mg/kg oral doses to the mouse and dog gave AUC (0 to infinity) values of 9.67 and 8.56 ug.hr/ml respectively.

Protein Binding And Erythrocyte Distribution

In vitro studies indicated radiolabelled drug was bound to plasma protein to the extent of 96 to 99% in mice, rats, guinea-pigs and dogs. The three concentrations of drug tested (0.5, 5.0 and 50 ug/ml were in the concentration range found in plasma from the oral gavage studies) indicated no dependence of binding on concentration. The binding was further studied and found to be reversible.

The percentage of drug bound or stuck to erythrocytes from these four species varied from 6 to 23% using the same drug concentration in another in vitro experiment. There did not appear to be a dependence of binding upon concentration.

Tissue Distribution And Accumulation Studies

Rats were dosed by oral gavage 1 x day for up to five days and their tissues examined for accumulation of radioactivity. No tissue accumulation of radioactivity was noted except in the organs responsible for the excretion of the drug and its metabolites. Rats were given the labelled drug intradudonally and killed at varying times up to 24 hours post dosing. Whole body autoradiography, also did not indicate any tissue accumulation other than those involved in the excretion of the drug over the 24 hour study period. These results agreed with those of the tissue distribution studies.

On day 20 of gestation rats were orally dosed with ^{14}C AA-673. Fetuses were removed from 15 minutes to 8 hours post dosing for analysis. Radioactivity was detected in the fetus and amniotic fluid indicating transfer or drug/metabolites across the placenta. There did not appear to be concentration of the drug or metabolites in the fetus since the concentration at each of the sampling times was lower than the concentration in the maternal plasma. Lacteal secretion was examined at the same times in females dosed orally with labelled drug on day 14/15 after parturition. Radioactivity was secreted in the milk. The predominant component was unchanged drug. The concentration in milk was higher than that in plasma as time progressed.

Enzyme Induction

The ability of AA-673 to cause enzyme induction was studied. Rats were orally dosed with 0, 10, 30 or 100 mg/kg/day for a total of 7 days and the activity of hepatic microsomal enzymes was studied 24 hours after the last dose. There was no increase in liver weight, microsomal protein per gram of liver, enzymatic activity per mg protein, and microsomal content of cytochromes p450 and b5 were the same for the AA-673 treated animals vs the controls. The positive control

material, phenobarbital, caused significant increases in weight of the liver, microsomal protein, all of the enzymatic activities and the microsomal content of both cytochromes. AA-673 did not cause hepatic microsomal enzyme induction in rats.

Metabolism

The metabolites in the urine and feces were identified after oral administration of the radiolabelled drug to rats, mice, guinea-pigs and dogs. In the plasma and excreta of all four species the drug was metabolized by hydroxylation and oxidation of the isopropyl moiety. The drug was metabolized by conjugation with glucuronic acid only in the rat (major) and guinea-pig (minor). Amlexanox (major fecal component) and the hydroxylated derivative (major urine metabolite) were present in the urine and feces from all four species. Unchanged amlexanox and the hydroxylated derivative have been found in the serum and urine of man after oral administration of the unlabelled drug. The urinary metabolic profiles were qualitatively similar for all species.

An in vitro study with rat tissue slices of brain, heart, lung, liver, kidney and duodenum was conducted with labelled drug to investigate the metabolism. It was determined that the conjugation was carried out mainly in the intestinal mucosa and the hydroxylation and oxidation of the isopropyl moiety were in the liver and kidney. Glucuronidation was only carried out in the rat.

Excretion

After oral administration of the labelled drug, almost all of the radioactivity was eliminated within 48 hours in rats, mice and dogs and within 120 hours in guinea-pigs. The bulk of the radioactivity appeared in the feces (75 to 91%) rather than the urine (5 to 23%).

Rats were given an oral dose of labelled drug 1 x day for 5 days and various pharmacokinetic parameters were determined. The results of this multiple dose study indicated no accumulation of either the parent drug or its metabolites during the five day study.

Summary: The drug is well absorbed from the intestine of rats, mice, guinea-pigs and dogs. It is distributed widely in tissues with no accumulation and is metabolized. The drug and its metabolites are preferentially eliminated from the body by fecal excretion and secondarily by the urinary route. AA-673 does not cause hepatic enzyme induction. These studies are acceptable for their intended purpose.

2) Pharmacokinetics And Metabolism of Amlexanox (AA-673), A New Antiallergic Agent, After Nasal Administration To Rats (Report # A-16-525; a two page report was provided)

Laboratory:

Study Design: Rats were given a single 0.25 mg/kg nasal dose of ^{14}C-AA-673 and sequential blood samples were obtained as well as feces and urine over the 24 hour study period. Animals were subjected to whole body autoradiography.

RESULTS

The ^{14}C-AA-673 was rapidly absorbed with a Tmax of 5 minutes followed by a biphasic decline. Whole body autoradiography indicated the radioactivity to be widely distributed in tissues. Excretion patterns indicated rapid elimination within 48 hours with 36 and 67% of the dose appearing in the urine and feces respectively. Analysis of the metabolites indicated that glucuronidation and oxidation of the isopropyl group occurred. This metabolic pattern is similar to the one after oral administration.

Summary: Absorption after nasal dosing is rapid. The drug does not appear to accumulate in tissues and is rapidly eliminated in the feces and urine. This study is acceptable for its intended use.

3) Intraocular Penetration of AA-673 Ophthalmic Solution, An Antiallergic Agent (Report # AA-673/S-DK02)

Laboratory:

Number of animals: total of 39 used in groups of 3 to 6

Animal Strain: Japan White Rabbit; males

Dose Level: 50 ul of a 0.25% ophthalmic solution of drug was instilled into both eyes

Route: Instillation into the conjunctival sac of the eye

Study Design: The animals were dosed and approximately 4 mL of blood was taken at the following times- 20 and 40 minutes and 1, 2, 4, 6, 8, 24 and 48 hours after instillation. Immediately after the collection of blood the animal was sacrificed. The eyeball together with the conjunctivae and extraocular muscle was removed. The conjunctivae was removed and a sample of anterior chamber aqueous was collected. The eyeball was quick frozen and cut into anterior and posterior segments. The lens, vitreous body, retina, choroid and iris and ciliary body were removed. All the tissues including blood were assayed using high pressure liquid chromatography after preparation.

RESULTS

The maximum concentration in the blood was reached in 20 minutes and then it declined thereafter. The concentration time course in each ocular tissue showed that after reaching their respective peaks, the concentrations declined exponentially and then slowly after 24 hours in the cornea and after 8 hours in the conjunctivae and anterior sclera. Only a low concentration was found in the retina and choroid up to 2 hours post instillation. After 8 hours the concentration was below the limit of detection in these tissues.

Summary: AA-673 penetrates into the cornea and conjunctivae rapidly after instillation and then disappears slowly. The drug would be expected to show sustained efficacy toward diseases of the external segment of the eye.

Summary:

Amlexanox was not a sensitizer and did not cause irritation of the mucous membrane of the mouth in a 7 day hamster cheek pouch irritatioin study. In a 6 month oral rat and dog evaluation the no effect level was 100 and 30 mg/kg respectively for hepatotoxicity which was considered to be the target organ. This was shown to be reversible in the dog in a recovery study. Life time studies giving the drug by the dietary route in the rat and mouse indicated the drug was not carcinogenic. This is indicated on the label. The no effect level in the mouse study was 30 mg/kg for toxic nephrosis and in the rat study was 80 mg/kg for biliary changes- cystic dilation, calculus formation, inflamation of the extrahepatic bile duct, cholangitis and pericholangitis. No adverse effect was noted in fertility and general reproductive performance studies in the rat, teratology studies in the rat and rabbit and peri and post-natal studies in the rat up to a 300 mg/kg dose given orally. Amlexanox was not mutagenic in the Ames or mouse micronucleus test.

The mean mg of Amlexanox per patient per day is approximately 0.2 mg/kg/day for a 60 kg person (see attachment from Chemex dated June 14, 1995). No adverse effect was noted on general reproductive performance and fertility in rat and rabbit studies up to 300 mg/kg amlexanox. This would give a no effect level of approximately 1500 times the projected human dose, which is indicated on the label.

Absorption studies in the rat, mouse, guinea-pig and dog indicated the oral bioavailability to be about 50%. The intestine was the major site of absorption. The metabolic characteristics of the drug in plasma were about the same in the rat, mouse, guinea-pig and dog as they were in man following an oral dose. The rat was the only species that conjugated the material. The drug was highly bound to plasma proteins and there was no dependence of binding on the drug concentration. ^{14}C studies demonstrated no specific tissue accumulation (following a single or multiple doses) except in the organs responsible for excretion of the compound and its metabolites. The drug crossed the placental barrier and resided in the milk of lactating dams.

Amlexanox was not a hepatic enzyme inducer. In the rat, mouse, guinea-pig, dog and man after oral dosing amlexanox was present in the feces (major component) and the urine(hydroxylated metabolite, minor component). After oral administration of the radiolabelled drug almost all of it was eliminated within 120 hours in rats, mice, guinea-pigs and dogs.

Conclusion:
The use of amlexanox for the treatment of aphthous ulcers on the oral mucosa as proposed would appear to be safe with respect to the results of the preclinical animals studies.

RECOMMENDATIONS

The question of projected human daily dose and the addition of wording to the package insert to instruct the patient as to what constitutes a dab-i.e. appropriate dose/ulcer was answered on June 14, 1995 by Dr. M. Charney. This NDA is approvable from the preclinical standpoint.

John Wedig, Ph.D.
Toxicologist

Original NDA
HFD-540
HFD-540/Pharm/JWedig
HFD-540/MO/EToombs
HFD-540/Chem/EPappas
HFD-540/CSO/JHolmes

Concurrence Only JW
HFD-540/DD/JWilkin 7/19/95
HFD-540/SPharm/AJacobs
7/10/95

Bio

NOV 16 1995

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NDA 20-511

Amlexanox Oral Paste 5%
(AA-673)

RESUBMISSION DATE: 04-17-95

Chemex Pharmaceuticals, Inc.
One Executive Drive
Fort Lee, New Jersey 07024

REVIEWER: Ene I. Ette, Ph.D., FCCP, FCP

BIOPHARMACEUTICS REVIEW

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Table of Contents

1. BACKGROUND:

This is an NDA filed for amlexanox 5% oral paste. Amlexanox is 2-amino-7-isopropyl-5-oxo-5H-[1]benzopyranol[2,3-b]pyridine-3-carboxylic acid. It has been shown *in vitro* to be an inhibitor of the formation and / or release of inflammatory mediators (histamine and leukotrines) from mast cells, neutrophils and mononuclear cells. Given orally to animals, amlexanox has been shown to be antiallergic and anti-inflammatory. It has been shown to suppress both immediate and delayed type hypersensitivity reactions. It has been marketed in Japān for the treatment of bronchial asthma and allergic rhinitis. The drug is metabolized by hydroxylation to form the M-1 metabolite (Fig. 1) and some unidentified conjugates. Amlexanox is reported to be practically insoluble in water,i.e, 1 part of amlexanox requires at least 10,000 parts of water per USP definition. This application is for the approval of amlexanox to used as a paste in the treatment of aphthous ulcers.

2. SYNOPSIS:

Topical Administration: From the studies reported in the NDA, serum levels of amlexanox were quite variable from patient to patient, probably reflecting variation in amount and rate of systemic absorption of amlexanox from the paste. C_{MAX}, T_{MAX}, and an elimination $t_{½}$ of 116.7 ± 70.4 ug/ml, 2.4 ± 0.9 h, and 3.5 ± 1.1 h, respectively, were obtained from a single dose study. The peak serum concentrations, AUC values or individual T_{MAX} did not correlate with size of active ulcer. Also, the data indicate that the drug was not immediately absorbed in all subjects.

Amlexanox is metabolized to the metabolite, M-1 which is inactive. Amlexanox, M-1, and their conjugates were eliminated in the urine, accounting for 17% of the applied dose.

Eighteen patients who had 1 to 3 minor aphthous ulcers participated in an open-label, single-center study. 5% amlexanox paste was applied 4 times per day for 7 days regardless of when their ulcers healed for up to a maximum of 29 applications per ulcer. The drug was found to be safe and non-irritating to normal healthy patients when applied directly to oral mucosa. Serum levels of amlexanox were relatively low and quite variable with an apparent dependency on the variable amount of drug applied by each subject.

Another open-label, multi-center, multiple dose, long term safety study in 100 patients with aphthous ulcer for 28 days was conducted to provide additional information on the safety of 5% amlexanox paste. Irritation was evaluated in terms of the severity of erythema on an erythema grading scale. The results indicate that 5% amlexanox oral paste has little or no irritation potential when applied four times a day for 28 days. It appeared to be well tolerated by patients. Patients did not demonstrate any systemic adverse effects as measured by clinical chemistry values. All laboratory parameters (hematology, clinical chemistries and urinalysis) were either within normal laboratory limits or considered by investigators not to be of any clinical significance. Ten patients had liver enzyme values more than 50% above normal ranges. However, all of these values were either sporadic and returned to normal values by Week 4 while still on treatment or were consistent with baseline entry values.

Oral Administration: who have marketed this drug in Japan for bronchial asthma, allergic rhinitis among other uses carried out a study with orally administered amlexanox tablets which has been included as part of this submission. It was an open, single-dose and multiple-dose pharmacokinetic study using 25 healthy adult male as volunteers. Tablets

1 Page deleted

containing either 12.5 mg or 50 mg of amlexanox were used. To groups of three subjects each, single doses of 12.5 mg, 25 mg and 100 mg were administered after an overnight fast. In a cross-over design, a group of four subjects received two doses of 50 mg amlexanox one week apart; one dose was given while fasting and the other dose was given postprandial. Four groups of three subjects each participated in multiple-dose studies. Amlexanox was rapidly absorbed after oral administration of tablets. The serum levels of the metabolite, M-1, are approximately 10% of the levels of amlexanox. The serum levels of amlexanox appear to be proportional to dose up to the 50 mg. Food may decrease the bioavailability of amlexanox. There was evidence of slight accumulation (10%) of amlexanox on multiple dosing.

Release Rate: In a release rate study using FP-vericel membrane in Franz diffusion cells, the overall mean release rate of amlexanox from amlexanox 5% paste was 153.1 $ng/cm^2min^{1/2}$ with a range of $ng/cm^2min^{1/2}$.

Metabolism and Protein Binding in Animals: The only protein binding studies and mass balance studies carried out were done in animals (rats, mice and guinea pigs). The results show that the drug was highly distributed to the gut, liver, and kidney. In the rat it was also distributed into the lungs, and it is 96% rat plasma protein bound.

3. FORMULATION: amlexanox is an odorless, white to yellowish white crystalline powder. The composition of the product used in the studies is shown below..

Study Material	5% Amlexanox
Amlexanox	5.0% (w/w)
Mineral Oil, USP	% (w/w)
Gelatin, NF	% (w/w)
Pectin, USP	% (w/w)
Carboxymethylcellulose sodium, USP	% (w/w)
Carboxymethylcellulose sodium, USP	% (w/w)
Glyceryl Monostearate, NF	%(w/w)
White Petrolatum, USP	% (w/w)
Benzyl Alcohol, NF	% (w/w)

4. COMMENTS:

1. There was control on the amount of amlexanox applied/administration/patient in the multiple dose studies, therefore the extent of absorption could not be characterized. In subsequent

submissions involving this type of therapeutic agent well controlled multiple dose studies should be done.

2. Individual data were not provided in the oral administration study. Thus, no conclusion could be arrived at regarding the linearity or nonlinearity of amlexanox pharmacokinetics following the route of administration.

3. Also, the type of food used in the food effect study was not stated.

4. The statement on elimination half-life in the Pharmacokinetic and Metabolism section of the label should read: *The half-life for elimination was 3.5 ± 1.1 h in healthy volunteers.*

5. RECOMMENDATION:

The Div. of Pharmaceutical Evaluation III recommends that the pharmacokinetic section of the NDA is acceptable provided there are no safety concerns.

Convey the above comments to the Sponsor.

11/14/95

Ene I. Ette, Ph.D., FCCP, FCP
Pharmacometric staff

FT initialed by F. Pelsor, Pharm.D....

Biopharm Day Attendees on 11/3/95: N. Fleischer, M. Mehta, M. L. Chen, F. Pelsor

cc: NDA 20-511, HFD-540, HFD-855 (Ette), HFD-880 (Pelsor, Fleischer), HFD-340 (Vishwanathan), Chron, Division, Drug, Reviewer's Files, HFD-19 (FOI)

6. SUMMARY OF STUDIES

6.1 ASSAY METHOD: A sensitive, specific, precise, accurate, and reproducible HPLC method was used for the quantification of amlexanox and its metabolites.

6.2 TOPICAL ADMINISTRATION:

6.2.1 SINGLE DOSE STUDY (Study No.

This open-label safety study in 12 male patients (age: 29.5 ± 7.7 years, 8 Caucasians and 4 Hispanics) having 1 to 3 minor aphthous ulcers (average size: 5.1 ± 4.28 mm^2) was designed to determine the pharmacokinetics of amlexanox after a single topical administration of 100 mg of 5% Amlexanox Paste applied directly to an aphthous ulcer. All patients had normal laboratory values of prothrombin and partial prothrombin times as well hemoglobin and hematocrit. All patients were kept under constant medical supervision in a clinic throughout the study. A target dose of 100 mg of 5% Amlexanox Paste was applied topically to an aphthous ulcer at least 2 hours after a meal and the patients were not allowed to eat until 2 hours post dosing. The drug was applied to a clean preweighed applicator which was then reweighed after application to determine the exact amount of drug applied. Patients were not allowed to drink fluids for 1 hour post dosing and were allowed only limited water through a straw for the next hour. Blood was collected at the following times in relation to dosing: Baseline, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 Hours. Urine was collected at the following times in relation to dosing: Baseline, 0-6, 6-12, 12-24 hours. Serum was analyzed for amlexanox and urine was analyzed for the amlexanox, its major metabolite M-1 and conjugates. All samples were analyzed with HPLC procedures.

The 5% Amlexanox Paste was well tolerated; there were no reported adverse events. All baseline clinical laboratory parameters were within normal clinical laboratory ranges or did not deviate from normal ranges in any clinically significant manner.

Serum concentrations of amlexanox were relatively low but measurable in 11 of 12 patients. All serum levels for one patient were below the limits of quantitation. The serum levels of amlexanox were quite variable from patient to patient (Table 1). This variability probably reflects variation in amount and rate of systemic absorption of amlexanox from the paste. The C_{MAX} was found to be 12 ± 70.4 ug/ml, while the T_{MAX} and elimination $t_{½}$ were 2.4 ± 0.9 h, and 3.5 ± 1.1 h, respectively. Tables 2 and 3 summarizes the results of the pharmacokinetics parameter values for amlexanox. The peak serum concentrations, AUC values or individual T_{MAX} did not correlate with size of active ulcer (Table 4). Also, the data indicate that the drug was not immediately absorbed in all subjects. Amlexanox was metabolized to the metabolite, M-1. Amlexanox, M-1, and their conjugates were eliminated into the urine, accounting for 17% of the applied dose (Table 3).

TABLE 1: URINARY EXCRETION OF AMLEXANOX AND METABOLITES; STUDY NO. 110

Patient No.	Amlexanox + Conjugates (mg)				M-1 only (mg)				M-1 + Conjugates (mg)			
	0-6 hr	6-12 hr	12-24 hr	Total	0-6 hr	6-12 hr	12-24 hr	Total	0-6 hr	6-12 hr	12-24 hr	Total
	0.39	0.16	0.08	0.63	0.79	0.33	0.19	1.30	1.37	0.51	0.32	2.21
	-	-	-	-	-	-	-	-	-	-	-	-
	0.23	0.08	0.05	0.37	0	0	0	0	0	0	0	0
	0.07	0.24	0.01	0.31	0.05	0.49	0.05	0.60	0.11	0.72	0.06	0.90
	0.09	0.26	0.05	0.40	0.10	0.30	0.03	0.43	0.16	0.41	0.03	0.60
	0.10	0.10	0.04	0.23	0.04	0.04	0	0.08	0.10	0.04	0	0.14
	0.06	0.03	0.04	0.12	0.10	0.07	0.04	0.21	0.11	0.08	0	0.19
	0.30	0.21	0.14	0.65	0.15	0.11	0.06	0.31	0.19	0.12	0.06	0.37
	0.34	0.12	0.11	0.56	0.14	0.07	0	0.21	0.14	0.08	0.10	0.32
	0.37	0.10	0.10	0.58	0.23	0.04	0.08	0.34	0.20	0.04	0.08	0.31
	0.17	0.11	0.06	0.34	0	0.04	0	0.04	0.07	0.04	0.17	0.28
	0.14	0.16	0.04	0.33	0.16	0.06	0	0.22	0.15	0.06	0	0.21

NOTE: Urine levels of amlexanox and conjugates from patient were low but detectable. Amount excreted could not be calculated since urine volumes were not recorded. M-1 and its conjugates were not detectable in the urine from Patient

TABLE 2: PHARMACOKINETIC PARAMETERS CALCULATED FOR EACH PATIENT

Patient No.	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-24} (ng·hr/ml)	$t_{1/2}$ (hr)	Urinary Excretion (% Dose)			
					Amlexanox + Conjugates	M-1 only	M-1 + Conjugates	Total†
	168.3	2	506	3.2	10.4	21.7	36.8	47.2
	5.0	1	30	*				
	109.9	2	241	1.6	6.8	0	0	6.8
	145.0	3	379	4.3	6.2	11.7	17.6	23.8
	58.0	4	238	**	7.5	8.0	11.2	18.8
	114.9	2	384	**	4.6	1.5	2.7	7.3
	41.3	3	167	*	1.9	3.3	2.9	4.8
	246.2	1	973	3.4	14.4	6.8	8.3	22.7
	205.2	3	539	3.1	11.0	4.0	6.2	17.3
	107.2	3	308	3.4	11.1	6.5	5.9	17.0
	54.1	3	174	5.3	7.2	0.9	6.0	13.2
	145.1	2	350	**	5.0	3.3	3.1	8.1

† Total is the sum of Amlexanox + Conjugates and M-1 + Conjugates. * Serum levels low or not detectable. ** Terminal portions of curves appeared biphasic; single half-life could not be calculated.

Table 3: Summary of Pharmacokinetic Parameters; Study No. 110

	Serum Pharmacokinetic Parameters			
	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-24} (ng · hr/ml)	$t_{1/2}$ (hr)
Mean	116.7	2.4	357	3.5
SD	70.4	0.9	242	1.1
	Urinary Excretion (% Dose)			
	Amlexanox + Conjugates	M-1 only	M-1 + Conjugates	Total†
Mean	7.8	6.2	9.2	17.0
SD	3.6	6.2	10.3	12.0

† *Total is the sum of Amlexanox + Conjugates and M-1 + Conjugates.*

TABLE 4: COMPARISON OF STUDY MATERIAL USE, ULCER SIZE, AND PHARMACOKINETIC PARAMETERS

PATIENT NUMBER	NET WEIGHT OF MATERIAL APPLIED [MG]		ULCER SIZE (SQ MM)	PHARMACOKINETIC PARAMETERS		
	PASTE	AMLEXANOX		MAXIMUM SERUM CONC. (NG/ML)†	TIME OF MAX. SERUM LEVEL (HRS)	AUC (NG·HR/ML
	120	6.0	1	202.0	2	506
	100	5.0	4	< 10	-	30
	107	5.4	2.25	117.6	2	241
	102	5.1	15	147.9	3	379
	107	5.4	6	62.1	4	238
	102	5.1	10	117.2	2	384
	128	6.4	4	52.8	3	167
	90	4.5	4	199.3	2	973
	102	5.1	1	209.3	3	539
	104	5.2	9	111.5	3	308
	94	4.7	1	50.9	3	174
	134	6.7	4	194.5	2	350

† *dose- normalized to 100 mg of paste*

6.2.2 MULTIPLE DOSE STUDIES

6.2.3.1 Study 109

This an open-label, single-center study with 18 patients (age: 29.6 ± 3.3 yr, 5 males and 13 females) who had 1 to 3 minor aphthous ulcers at study entry was conducted to measure Amlexanox serum levels after a single dose and at steady state conditions under anticipated clinical use of 5% Amlexanox Paste. All patients applied 5% Amlexanox Paste 4 times per day for 7 days of treatment regardless of when their ulcers healed for up to a maximum of 29 applications per ulcer. The patients were arbitrarily divided into 3 groups of 6 patients per group. One group applied 5% Amlexanox Paste to 1 ulcer. The second group applied 5% Amlexanox Paste to 2 areas (2 ulcers or 1 ulcer plus another approximately equal area on the contralateral side of their mouth). The third group applied 5% Amlexanox Paste to 3 areas (1-3 ulcers plus other approximately equal areas in the contralateral side of their mouth to equal 3 areas total). All patients were evaluated for signs of local irritation. Serum was collected prior to and 2 hours after both the first dose and the last dose of 5% Amlexanox Paste as well as 24 hours after the last dose. Serum was analyzed for the presence of Amlexanox by a validated HPLC procedure. Duplicate serum samples were stored under two different conditions, one more rigorous than the other, to determine the need for rigorous storage conditions in future studies.

The 5% Amlexanox Paste was well tolerated. All 18 patients completed the protocol and were evaluable for safety. There were no reported adverse events and there were absolutely no signs of any irritation at any evaluation time in any of the patients. All clinical laboratory parameters were within normal clinical laboratory ranges or did not deviate from normal ranges in any clinically significant manner.

Serum concentrations of Amlexanox (as summarized in Table 5) were: (a) relatively low but measurable in most patients using 5% Amlexanox Paste, (b) quite variable, probably reflecting variations in amount applied; c) apparently dependent on dose since the protocol was silent about exact amount of drug to be applied by the patient. The Sponsor stated that similar blood levels were obtained 2 h after a single dose and after 7 days of the drug. The data does not seem to support this assertion because of the wide variability in concentrations (Fig. 2), and probably dose applied.

The levels measured two hours after dosing with 5% Amlexanox paste are consistent with oral dosing of about 1 mg of Amlexanox. Thus, four times a day dosing would expose patients to about 4-5 mg per day which is about 20-40 times less than the recommended dose of 75-150 mg a day used for asthma in Japan.

Figure 2. Amlexanox in Serum
Study 109

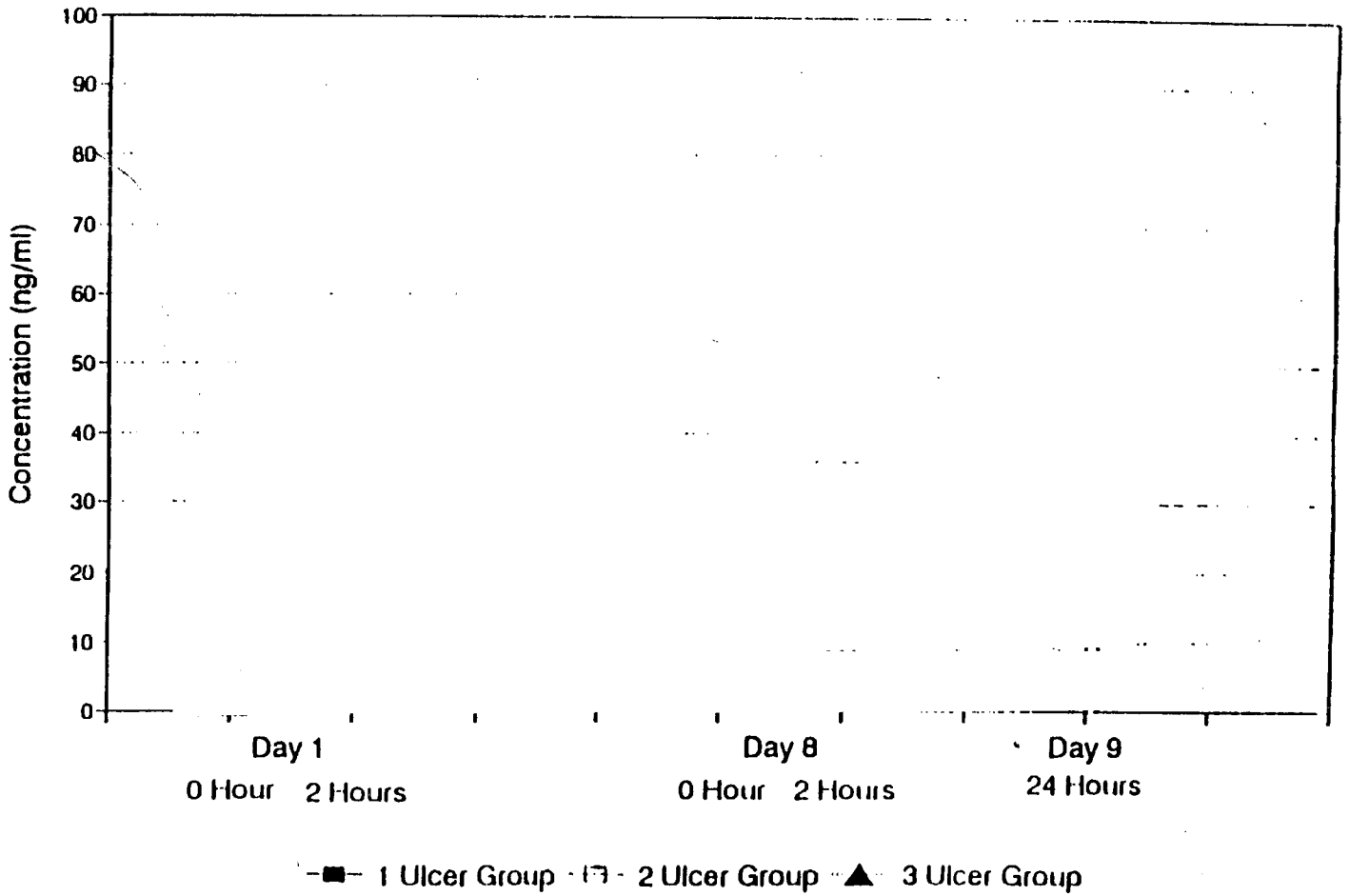


Table 5: Summary of Serum Concentrations of Amlexanox Study 109

Group		Concentration of Amlexanox (ng/ml)				
		Day 1		Day 8		Day 9
		0 hr	2 hr	0 hr	2 hr	24 hr
1	Mean	1.5	19.5	6.8	15.3	3.0
	Std Dev	*3.6*	*11.7*	*11.0*	*10.6*	*3.4*
	Range					
2	Mean	0.0	12.3	12.4	42.7	3.8
	Std Dev	*0.0*	*7.3*	*22.5*	*53.1*	*6.4*
	Range					
3	Mean	0.0	50.1	17.8	27.7	5.2
	Std Dev	*0.0*	*48.1*	*14.2*	*26.7*	*10.8*
	Range					

N = 6 except for Group 3, Day 1, 2 hours when N = 5

6.2.3.2 Study 111: This was an open-label, multi-center, long term safety study in 100 patients conducted to provide additional information as to the safety of 5% Amlexanox paste. Patients enrolled with an aphthous ulcer and then applied 5% Amlexanox paste four times a day for 28 days. At each of the weekly visits during the treatment period and again one week following study completion or discontinuation, patients were evaluated for local irritation effects as well as clinical laboratory parameters. Irritation was evaluated in terms of the severity of erythema on an erythema grading scale shown in Table 6. If erythema was present, investigators were asked to determine whether the erythema was related to the application of test medication or simply a symptom of the aphthous ulcer present.

Patients were monitored weekly throughout the study for changes in clinical laboratory parameters. Evaluations for weeks 1, 2, 3, and 4 were obtained under non-fasting conditions. Baseline evaluations were done after fasting.

For determination of peak and trough serum levels of amlexanox, serum samples were collected pre-dose and 2 hrs post-dose on Day 1, pre-dose after 1, 2 and 3 weeks of dosing, pre-dose and 2 hrs post-dose for the last dose at Week 4, and one week follow-up. The serum concentrations were determined by HPLC.

The average severity of erythema at baseline was mild to moderate (1.3 Score with 1 = Mild). The data in the Table 6 show that the average severity of erythema decreased at each visit, and is consistent with the healing of aphthous ulcers. In all cases except one, the observations of erythema were associated with aphthous ulcers and not attributed to the application of 5% amlexanox oral paste (Table 6).

One patient developed contact mucositis on Day 27-28 of the study. The patient indicated on the diary card that new aphthous ulcers developed on Day 26. Since this mucositis occurred at the very end of the study, the use of 5% Amlexanox paste was stopped as indicated in the protocol at the end of the study and all symptoms were noted to have resolved at the one week follow-up visit.

Table 6: Severity of Erythema Present

	Baseline	Week 1	Week 2	Week 3	Week 4	One week Follow-up
Ave. Erythema Score	1.3	0.3	0.2	0.1	0.06	0.02
No. of Patients with						
Erythema =0	7	52	76	88	91	96
Erythema=0.5	15	26	13	6	4	1
Erythema =1.0	32	13	8	3	4	1
Erythema = 1.5	12	2	1	0	0	0
Erythema = 2.0	21	5	1	2	0	0
Erythema = 2.5	13	1	0	0	0	0
No. of Patients with Erythema Potentially Related to Amlexanox	0	0	0	0	1	0

None of the values for the hematological tests or urinalysis which were reported to be outside the normal range were considered to be clinically significant.

Particular attention was paid to the results of the liver enzyme tests, including ALT, AST, alkaline phosphatase and total bilirubin, since asymptomatic increases in these some liver enzymes were seen in a small percent of patients in the Japanese clinical studies of orally administered amlexanox. Eighteen patients demonstrated levels of one or more of these tests that were outside the normal laboratory range. Most of these values occurred sporadically in one or the other enzyme throughout the dosing period. Most of these values were less than 50% out of range.

The results of the serum amlexanox measurements are summarized in Table 7. Two hours after the first dose, the mean serum level of amlexanox was 25.7 ± 37.2 ng/ml. During Weeks 2-4 the mean trough levels of amlexanox were 30-40 ng/ml indicating that steady state conditions were reached by the end of one week of dosing. The mean serum level 2 hours post dosing at Week 4 was 74.1 ± 115.7 ng/ml which is a similar increase as that observed after the first dose. At the 1 week follow-up, the mean serum level had decreased to 0.6 ± 3.5 ng/ml. There was a relatively large variability in the measured serum levels. About 50% of the trough serum levels were below the limits of quantitation (10 ng/ml), whereas about 10% had trough levels of >100 ng/ml. None of the levels at any time were >800 ng/ml. The reason for this variability probably reflects variations in amount of paste applied and amount absorbed. The formulation of this paste was designed for adherence to the oral mucosa; reproducible oral bioavailability was not a factor in the design.

Some of the subjects had predose drug levels which were suggested to be due to error in sample handling.

Table 7: Serum Concentrations of Amlexanox by Study Site

Sampling Time	Serum Amlexanox Concentration (ng/ml)	
	Mean ± Std Dev	Range
Day 1, Pre-dose	0.3 ± 1.6	
Day 1, 2-hr	25.7 ± 37.2	
Week 1, Pre-dose	27.4 ± 68.6	
Week 2, Pre-dose	33.2 ± 66.4	
Week 3, Pre-dose	38.9 ± 93.6	
Week 4, Pre-dose	37.5 ± 82.5	
Week 4, 2-hr	74.1 ± 115.7	
Follow-up	0.6 ± 3.5	

6.3 ORAL ADMINISTRATION:

Report No. AA-673/X-108: Preliminary Report of Phase I Clinical Study of AA-673, an Antiallergic Drug

The study was an open, single-dose and multiple-dose pharmacokinetic study using 25 healthy adult men as volunteers. Tablets containing either 12.5 mg or 50 mg of amlexanox were used. To groups of three subjects each, single doses of 12.5 mg, 25 mg and 100 mg were administered after an overnight fast. In a cross-over design, a group of four subjects received two doses of 50 mg amlexanox one week apart; one dose was given while fasting and the other dose was given postprandial.

Four groups of three subjects each participated in multiple-dose studies of sequentially longer duration. Amlexanox was administered 2.5 hours after meals. The first group received two 100-mg doses in one day, morning and evening. The second group received three 100-mg doses on the first day and one 100-mg dose on the second day for a total of four doses. The third group received three 100-mg doses on each of the first two days and a 200-mg on the morning of the third day for a total of seven doses (six 100-mg and qne 200-mg). The fourth group received one 100-mg dose on the first day, three 100-mg doses on the second through fifth days, and a 100-mg dose on the morning of the sixth day for a total of 14 doses.

Blood samples were collected, serum was prepared and the concentrations of amlexanox and its metabolite, M-1, were determined by HPLC. Urine samples were also collected and analyzed for amlexanox and M-1. The urine samples were incubated with ß-glucuronidase and sulfatase to hydrolyze conjugates before analysis.

Table 8 shows the pharmacokinetic parameters for amlexanox and M-1 and compares them to values obtained with 5% Amlexanox Paste (Study 110). Amlexanox was rapidly absorbed with maximal serum levels generally occurring within two hours after dosing. The serum levels of M-1 were approximately 10% of the amlexanox levels. $AUC_{0\text{-}24}$ and C_{max} generally increased linearly with increasing dose up to 50 mg fasting dose (Figs. 3). However, the Sponsor did not provide individual data for a determination of dose linearity or nonlinearity to be carried out. Multiple dosing with 100 mg 2.5 h after food tends to suggest minimal accumulation (10% from AUC ratios) after the 14th dose. Thus, the kinetics of amlexanox appeared to be dose proportional up to the 50 mg dose. Linearity of amlexanox pharmacokinetics beyond this point is questionable.

Postprandial, the C_{max} and $AUC_{0\text{-}24}$ values for a 50-mg dose were lower than for a dose administered to fasted subjects. This would indicate an effect of food on bioavailability. However, the percentages of the dose excreted in the urine as amlexanox and M-1 were the same with and without food.

One subject had a mild stomach ache of 10 minutes duration after a single dose of 100 mg amlexanox. No other adverse events were reported. There were no abnormal physical examination findings or laboratory test results attributable to amlexanox administration.

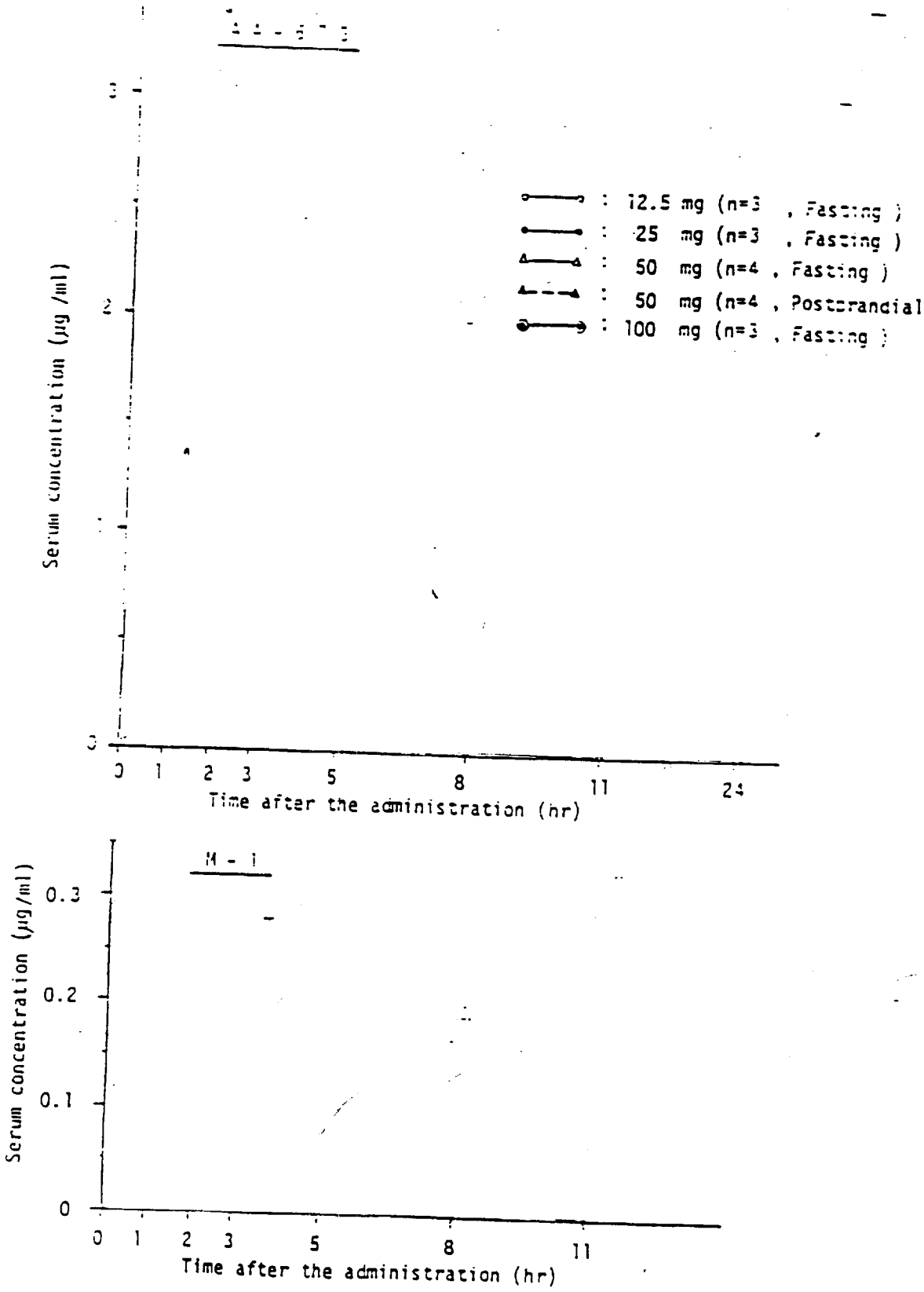


Fig. 3 Serum concentration of AA-673 and its metabolite after single oral administration

Table 8: Pharmacokinetic Parameters for Amlexanox Oral Tablets

Dose (mg)	Amlexanox					Metabolite, M-1				
	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-24} (μg · hr/ml)	$t_{1/2}$ (hr)	Urine excretion (% dose)	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-24} (μg · hr/ml)	$t_{1/2}$ (hr)	Urine excretion (% dose)
Single Dose Administration of 5% Paste (Chemex Study)										
5 mg	0.12	2.4	0.36	3.5	7.8	-	-	-	-	9.2
Single Dose Administrations of Tablets Study)										
12.5 mg fasting	0.49*	1.16*	1.19	n.r.	5.3	0.08*	1.67*	0.17	n.r.	26.7
25 mg fasting	1.14	1.61	4.08	3.59	9.7	0.13*	2.67*	0.55	n.r.	38.5
50 mg fasting	4.78	0.98	13.4	5.59	8.9	0.20*	2.00*	0.73	n.r.	27.8
50 mg fed	1.87	1.75	7.54	7.61	9.7	0.16*	2.50*	0.67	n.r.	26.4
100 mg fasting	2.84	1.86	14.8	9.04	7.1	0.22*	3.00*	1.18	n.r.	26.2
**Multiple Dosing with Tablets Study)*										
100 mg, 1st dose	2.75	2.49	12.9	5.38	-	0.33*	3.33*	1.26*	n.r.	-
100 mg, 14th dose	5.40	1.60	14.2	5.13	9.7	0.36*	2.67*	1.86*	n.r.	25.9

* Calculated by from data for individual subjects.
n.r. - not reported, too few data points for reliable estimate.
** - Drug administered 2.5 h after food.

6.4 *IN VITRO* RELEASE TESTING OF AMLEXANOX FROM AMLEXANOX 5% ORAL PASTE: Solubility determinations carried out during assay development showed that 500,000 ng/ml (0.5 mg/ml) of amlexanox, can be dissolved in the pH 7.4 phosphate buffer. Therefore, to provide sink condition, a pH of 7.4 phosphate buffer of the following composition was selected: 6.8 g potassium phosphate, 1.3 g monobasic sodium hydroxide, qs to 1 L with deionized HPLC grade water, and pH adjusted to 7.4 with 10% NaOH solution. With this buffer a membrane selection study was carried out, and amlexanox content was determined by HPLC and plotted against the square root of time. The suitability of three different synthetic membranes (cellulose acetate: pore size 1.2 μm, diameter 47 mm, FP-vericel (FP-450), polyvinyledene difluoride: pore size 0.45 μm, diameter 25 mm, vinyl metricel (VM-1), polyvinyl chloride: pore size 5.0 μm, diameter 25 mm) for the characterization of amlexanox release rate was investigated. Approximately 1 g of the 5% amlexanox oral paste (lot 1093-0003 used in Phase III clinical studies) was applied to each membrane. Three Franz cells (i.e., 3 runs) were used for each membrane type. The receptor phase was 0.5 M phosphate buffer (pH 7.4). In each run after product application, the receptor phase was (maintained at 37 $\pm$ 2^{0}C) samples were drawn at 0, 30, 60, 120, 240, 360, and 480 min.

The release rate of the drug was determined by calculating the slope of the linear regression obtained by plotting the amount of drug released versus the square root of time of the last four sampling times. The Sponsor based the calculations on the following assumptions: (1) the last four sampling times represent the steady state diffusion process through the membrane, and (2) the surface area of membrane (1.767 cm^2) in contact with the product and the receptor volume of in each Franz cell (7 ml) were similar for all Franz cells used in the study.

Table 9 shows the mean $\pm$ SD release rate of three runs for each membrane. FP-vericel was selected because (1) chromatograms of the 0 min samples of the cells fitted with vinyl metricel (VM-1) and cellulose acetate membranes showed a peak at the expected retention time of amlexanox, therefore the potential for errors in assaying drug concentrations were recognized; (2) the relatively large size (diameter: 47 mm) of the cellulose acetate membrane posed more handling problems during the experiment and therefore was considered unsuitable.

The release rate profile of amlexanox from lot 1093-0003 was determined using approximately 750 mg of the paste placed on FP-vericel membrane contained in each of 9 Franz diffusion cells. The experimental conditions (except the temperature which was 30^{0}C $\pm$ 1^{0}C) and sampling times and calculation of release rate were as for membrane selection. The experiment was run for 2 days to determine the reproducibility of the data. The results are summarized in Table 10 and Figs. 4 & 5. The overall mean release rate was 153.1 ng/cm^{2}min^{½} with a range of ng/cm^{2}min^{½}.

Table 9

In Vitro Diffusion of Amlexanox Through Synthetic Membranes

Test Product: 5% Amlexanox Oral Paste (CHX 3673-5N4) Lot 1093-0003
Receptor Phase: 0.05M Phosphate Buffer (pH 7.4) Temperature: 37°C

Sampling Time	FP-Vericel (FP-450)		Cellulose Acetate		Vinyl Metricel (VM-1)	
	Amlexanox Mean (ng/ml)	Std Dev	Amlexanox Mean (ng/ml)	Std Dev	Amlexanox Mean (ng/ml)	Std Dev
Initial	0	0	3.36	1.61	3.60	2.02
min	2.98	1.34	15.65	2.25	8.11	3.31
min	9.04	4.59	18.07	11.44	16.98	8.09
min*	69.85	49.87	105.89	54.08	50.31	20.89
min*	112.91	109.33	244.43	146.01	120.71	72.23
min*	334.27	209.73	338.98	194.58	259.52	127.22
min*	459.50	283.66	469.01	270.32	361.91	199.51

Corr. Coeff. *	0.9528	0.9953	0.9804
Y-inter.*	-383.02	-254.44	-290.05
Rate * (slope), ng/ml. $min^{\frac{1}{2}}$	37.26	32.32	29.01

*: The corr. coeff. (r^2), Y-intercept (A), and Rate (slope, B) are calculated from data related to the sampling times marked with * only.

Table 10

InVitro Release of Amlexanox From Oral Paste Lot # 1093-0003 @ 30°C

Sampling Time	Sq.Rt.Time ($min^{\frac{1}{2}}$)	Amlexanox Mean (Std.Dev.) (ng/cm^2)	Amlexanox Mean (Std.Dev.) (ng/cm^2)
		DAY 1	DAY 2
Initial	0.00	0.00 (0.00)	0.00 (0.00)
___ min	5.48	0.00 (0.00)	21.22 (6.88)
___ min	7.75	22.74 (10.93)	79.21 (28.82)
___ min*	10.95	268.39 (71.81)	236.29 (72.47)
___ min*	15.49	1039.3 (205.64)	569.93 (157.62)
___ min*	18.97	1786.1 (276.76)	930.82 (226.94)
min*	21.91	2619.9 (354.93)	1289.4 (259.06)
Corr. Coeff. *		0.9933	0.9915
Y-inter.*		-2141.6	-819.5
Rate (slope) * $ng/cm^2min^{\frac{1}{2}}$		212.1	94.0

Mean Release Rate ($ng/cm^2min^{\frac{1}{2}}$) = 153.1 of the last four sampling time data points marked with *.

FIGURE 4: IN VITRO AMLEXANOX DIFFUSION STUDY

CONC. IN RECEPTOR FLUID AT 30° C (Day 1)

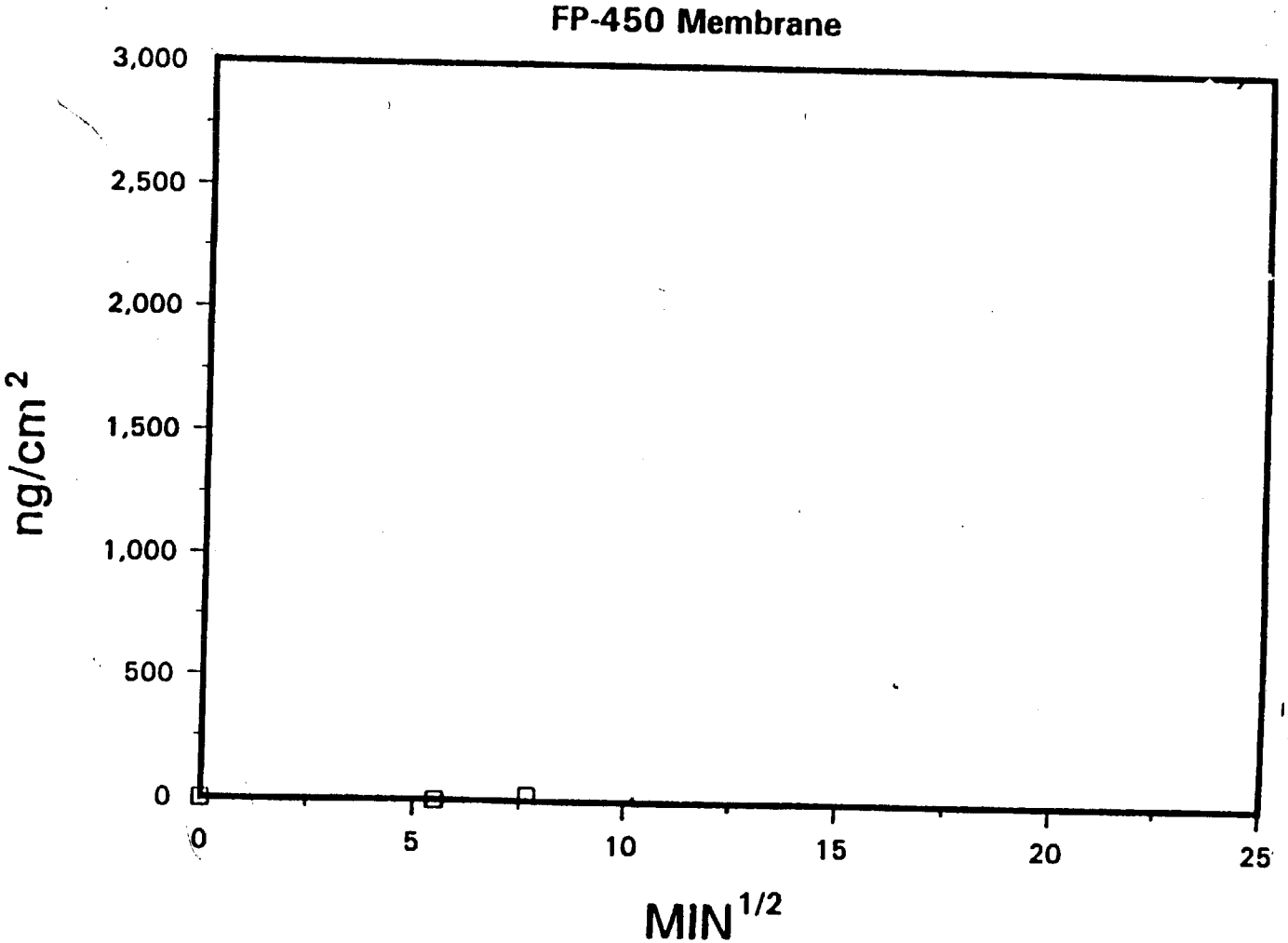
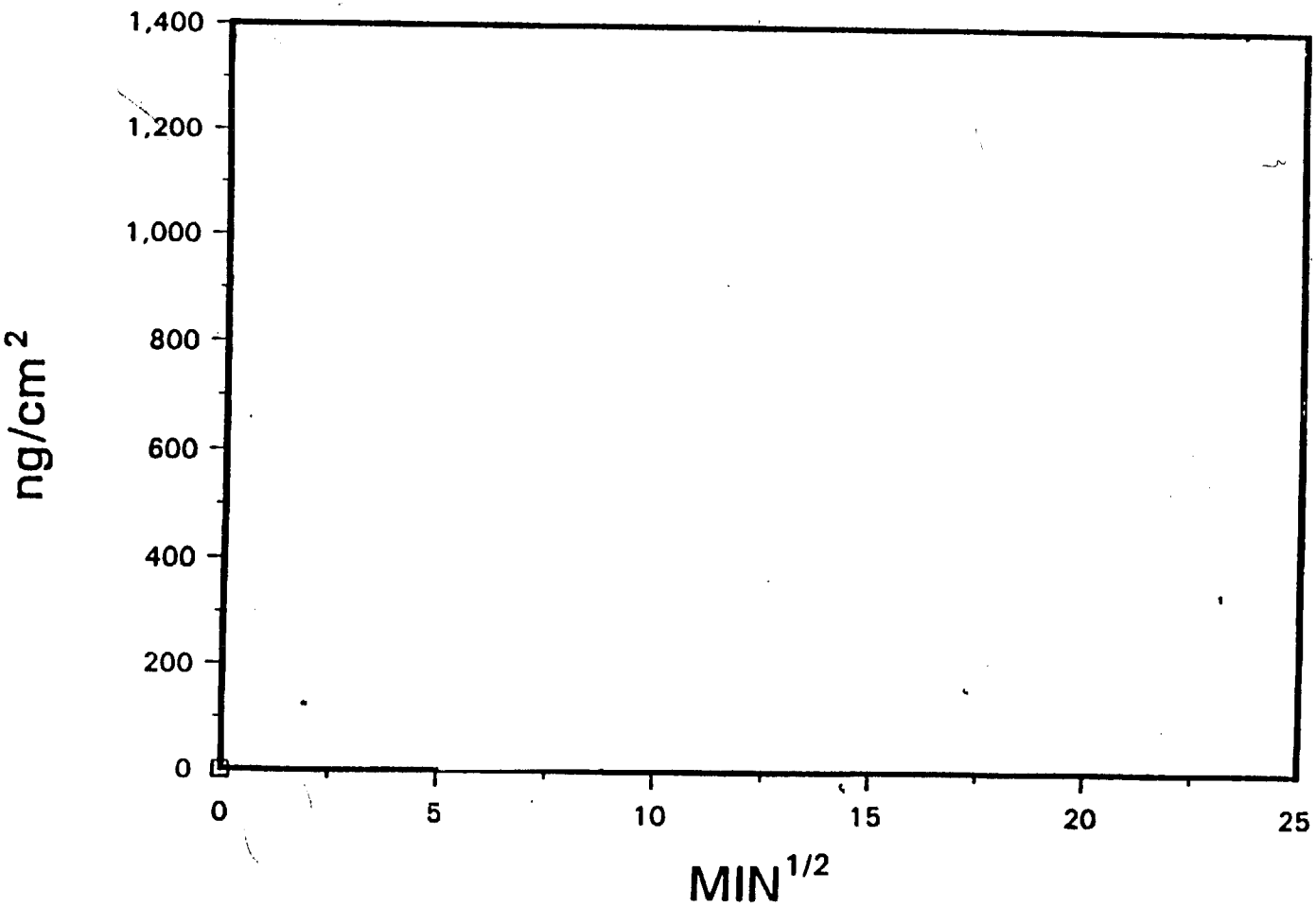


FIGURE 5: IN VITRO AMLEXANOX DIFFUSION STUDY

CONC. IN RECEPTOR FLUID AT 30° C (Day 2)

Lot # 1093-0003

FP-450 Membrane



Stat

Statistical Review and Evaluation

NDA: 20-511 Date: JUL - 7 1995

Applicant: Chemex Pharmaceuticals, Inc.
One Executive Drive, Ft. Lee, NJ 07024

Name of Drug: Amlexanox Oral Paste (5%)

Documents Reviewed: Original NDA volumes 1.14-1.19 of 59, dated August 31, 1988.
Re-Submission date April 19, 1995

I. Background: In this NDA submission a carcinogenicity study in rats was included. This study was intended to assess the carcinogenicity potential of Amlexanox Oral Paste in rats when administered orally in dietary mixture at some selected dose levels. The lengths of the study was 729 days. The reviewing toxicologist Dr. John Wedig, HFD-540, requested the Division of Biometrics to perform the statistical review and evaluation of this study. The results of the review have been discussed with Dr. Wedig.

II. Design: Two separate experiments, one in male and one in female rats were conducted. In each of these experiments there were three treated groups, known as low, medium, and high dose groups and a control group. Two hundred male and two hundred female Fischer 344 rats were randomly divided into equal size of 50 animals to form the four treatment groups. The dose levels for the treated groups were 25, 80, and 250 mg/kg/day for low, medium, and high dose groups, respectively. The animals in control group remained untreated.

The animals were checked twice daily for mortality and morbidity. A complete histopathological examination was performed on all animals in the control and high dose group. In low and medium dose groups only livers and adrenal glands of the animals and any abnormal tissues found in the gross examination were microscopically examined.

III. Sponsor's analysis

Survival data analysis: The sponsor analyzed the survival data using the methods described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965). These methods include the tests for linear trend in the mortality with the increased drug level, and the pairwise comparisons of the treated groups with the control. The plots of Kaplan-Meier estimates of the survival distributions of the treatment groups were presented for each sex. The tests did not show any statistically significant positive linear trend or increased mortality in the treated groups.

Tumor data analysis: The sponsor used the similar methods to analyze the tumor data as they used in the mortality data analysis. The event in this case was the time of detection of tumor. The animals which did not develop a tumor were considered as censored. The actual dose levels used in each treated groups were used as the score in the sponsor's analysis.

The tests showed statistically significant positive linear trend in the incidence of pheochromocytoma in adrenal medula, and follicular adenoma in thyroid in female rats.

IIIc. Reviewer's analysis

The reviewer independently performed analyses on the submitted data. Since the sponsor's analysis of survival data was found to be quite satisfactory, the reviewer did not repeat the survival data analysis. Tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980). Data used in the reviewer's analysis were taken from the hard copy submission from the sponsor.

Tumor data analysis: Since, only livers and adrenal glands of all animals in each group were microscopically examined the reviewer performed the positive linear trend tests on liver and adrenal gland tumor data and pairwise comparisons of the high dose group with the control in some other selected tumor types. Since the selected tumor types were not labeled as malignant the reviewer assumed them as 'not cause of death'. With this assumption and following Peto et al. (1980), the reviewer applied the 'prevalence method', to test for positive linear trend. The exact permutation trend test was used to calculate the p-values of all tests. The scores used for the trend test were 0, 25, 80, and 250 for control, low, medium, and high dose groups, respectively. Since, the original data were not available and also no statistically significant difference in mortality among the treated groups were detected, no mortality adjustment was done in the reviewer's analysis. Among the tested tumor types adrenal medula/ pheochromocytoma in female rats showed p-value less than .05 ($p=.0036$) for the positive linear trend test.

Multiple testing adjustment: The rule proposed by Haseman (A re-examination of false positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339, 1983) for pairwise comparisons and the rule proposed by the Division of Biometrics (Lin K. and Rahman M., False Positive Rates in Tests for Linear Trends in Tumor incidence in Animal Carcinogenicity Studies of New Drug, unpublished report, Division of Biometrics, CDER, FDA, 1995) for trend tests were used to adjust the effect of multiple testings. The two rules state that in order to keep the over all false positive rate at nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level for pairwise comparisons and at 0.025 level for positive linear trend tests and for tumor

types with spontaneous tumor rate greater than one percent the level should be set at 0.01 for pairwise comparisons and 0.005 for the positive linear trend tests.

On the basis of the rule described above the positive linear trend in pheochromocytoma in adrenal medula in female rats is considered to be statistically significant. No pariwise comparison was found to be statistically significant. The incidence rates and p-values of tumor types tested for positive linear trends and pairwise comparisons are given in Table 1.

V. Summary

No statistically significant (at .05 level) linear trend or difference in the mortality among treatment groups was found in either sex.

Incidence of pheochromocytoma in adrenal medula in female rats showed a statistically significant positive linear trend.

Mohammad Ataur Rahman

Mohammad A. Rahman, Ph.D.
Mathematical Statistician

Karl K. Lin 7/7/95

Concur: Karl K. Lin, Ph.D., Group Leader

cc: Original NDA 20-511
HFD-540/Dr. Wilkin
HFD-540/Dr. Wedig
HFD-710/Chron
HFD-715/Dr. K. Lin
HFD-715/Dr. Rahman
HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-511 Amlexanox Oral Paste (5%)
Rat carcinogenicity studies
HFD-715/Diskette Rahman-2/AMLEXANO.CAR
HFD-400/Dr. Contrera

Table 1

Tumor rates and p-values of the tested tumor types
for positive linear trend

Sex	Organ/Tumor	Tumor rate C 50	L 50	M 50	H 50	P-value Trend	Pair (C,H)
Male	Adrenal medula/Pheochromocytoma	6	9	9	2	.9731	.9703
	Thyroid/Parafollicular Cell Adenoma	1	2	3	5	-	.1022
	Thyroid/Follicular Adenoma	1	1	0	0	-	1.0000
Female	Adrenal medula/Pheochromocytoma	1	1	3	7	.0036	.0297
	Thyroid/Follicular Adenoma	0	0	0	2	-	.2475
	Thyroid/Parafollicular Cell Adenoma	6	0	0	4	-	.8411

NOV 0 1 1996

Statistical Review and Evaluation
(NDA Consult)

NDA#: 20-511

Applicant: Block Drug Company, Inc.

Name of Drug: Aphthasol (amlexanox oral paste) 5%

Documents Reviewed: Amendment to approvable letter Vol 8.1 dated August 2, 1996; final proposed label

Indication: Aphthous ulcers

Medical Input: Dr. Phyllis Huene, HFD-540

A. INTRODUCTION

The purpose of this consult is to review certain statistical issues submitted by the sponsor in an amendment as their response to the approvable letter dated April 16. 1996. This augments the statistical review performed on Aphthasol dated January 4, 1996.

The sponsor met with the Division of Dermatologic and Dental Products on July 8, 1996 to discuss final labeling. Statistical input was provided by Dr. Ralph Harkins, Director, Division of Biometrics IV at this meeting. The statistical reviewer completely concurs with his statistical comments as reflected in the meeting minutes.

The review is based on the report as submitted by the sponsor on their database. No modifications to the database or further reanalysis on it were attempted.

B. EFFICACY EVALUATION

Four clinical trials were conducted by the sponsor (Studies 102, 106, 107 and 108) of which Studies 107 and 108 were deemed pivotal. Studies 102 and 106 were considered supportive studies. They are summarized as follows:

Study	Treatment arms
Study 102	amlexanox 5%, amlexanox 1% and vehicle
Study 106	amlexanox 5%, vehicle and no treatment
Study 107	amlexanox 5% and vehicle
Study 108	amlexanox 5%, vehicle and no treatment

1) To compare the treatments in the Clinical Studies section in the label, Studies 106, 107 and 108 were combined for comparison of amlexanox to vehicle; Studies 106 and 108 were combined for comparing amlexanox to no treatment. This is acceptable as a means to combine results for labeling purposes.

2) The graph of cumulative percentage of patients with healed ulcers has been extended to 100%, the number of days (x-axis) originate at Day 0 and error bars have been included for each data point. This is in accordance to the statistical input given by FDA.

3) Kaplan-Meier estimates of the cumulative percentages of patients healed and their standard errors were obtained. The Der-Simonian and Laird approach was applied to obtain a combined estimate of the difference, its standard error and the corresponding z-statistic. Since two estimates for amlexanox were obtained (one from comparison with vehicle and the other from comparison with no treatment), the lower of the two estimates was used. This is reasonable.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

To compare the treatments in the Clinical Studies section in the label, Studies 106, 107 and 108 were combined for comparison of amlexanox to vehicle; Studies 106 and 108 were combined for comparing amlexanox to no treatment. This is acceptable as a means to combine results for labeling purposes.

The graph of cumulative percentage of patients with healed ulcers has been extended to 100%, the number of days (x-axis) originate at Day 0 and error bars have been included for each data point. This is in accordance to the statistical input given by FDA.

Kaplan-Meier estimates of the cumulative percentages of patients healed and their standard errors were obtained. The Der-Simonian and Laird approach was applied to obtain a combined estimate of the difference, its standard error and the corresponding z-statistic. Since two estimates for amlexanox were obtained (one from comparison with vehicle and the other from comparison with no treatment), the lower of the two estimates was used. This is reasonable.

Overall, the statistical approach used by the sponsor in the final proposed label is reasonable and is in accordance to the input given by the FDA.

Alaka Chakravarty
11/1/96

Alaka G. Chakravarty, Ph.D.
Biomedical Statistician,
Division of Biometrics IV

11/01/'96

Concur: Rajagopalan Srinivasan, Ph.D.
Acting Team Leader,
Division of Biometrics IV

cc:

Orig. NDA 20-511
HFD-540
HFD-540/Dr. Blay
HFD-540/Dr. Wilkin
HFD-540/Dr. Katz
HFD-540/Dr. Huene
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Dr. Chakravarty
Chron.

This review contains 3 pages (C:\WPFILES\NDAREVS\AMLEX1.CON)

Statistical Review and Evaluation JAN 4 1996

NDA#: 20-511

Applicant: Chemex Pharmaceuticals Inc., Fort Lee, NJ 07024

Name of Drug: Aphthasol (Amlexanox Oral paste 5%)

Documents Reviewed: Volumes 1.47, 1.58 - 1.56, 4.6 - 4.16, 4.18, 2.1, Amendment dated July 31, 1995

Indication: Apthous ulcers

Review Type: Clinical / Statistical

Medical Input: Dr. Phyllis Huene, HFD-540

Table of Contents:

A. INTRODUCTION

The sponsor submitted results to determine the efficacy and safety profile of Amlexanox 5% Oral paste for treatment of aphthous ulcers. Reports of four clinical trials were submitted by the sponsor, all of which were conducted in U.S. These pivotal studies were multi-center, double blinded, randomized, parallel group efficacy trials on patients having aphthous ulcers. A summary table is provided in Table 1 for comparison. It is noted that protocols 107 and 108 are pivotal efficacy trials. Protocol 102 was developed as a dose-ranging study and is submitted along with protocol 106 to serve as a supporting study in a pooled fashion. In discussion with the Medical Officer and the Reviewing Statistician during development, Ms. Beth Turney, protocols 107 and 108 will be reviewed separately as pivotal studies, along with statistical review of the justification for poolability of studies 102 and 106.

Table 1: Summary of pivotal Efficacy Studies

Study	102			106			107		108		
Study Design	Double-Blind, Vehicle-Controlled, Multi-Center, Randomized, Parallel Groups										
Group	5% A	1% A	V	5% A	V	NT	5% A	V	5% A	V	NT
# of Patients	81	79	42	60	59	62	211	213	197	198	133
Males/Females	38/43	42/37	12/30	31/29	26/33	23/39	98/113	103/110	85/113	101/97	74/59
Age (Range)	18-70	13-61	20-68	18-52	19-65	18-52	18-64	18-64	18-68	18-66	18-55
No. of Centers	10			6			12		12		
Dosing	Same Formulation for All Studies Applied Topically to Ulcers Four Times a Day *(q.i.d.)* by Patients										
Duration (# of Doses)†	4 Days (16)			10 Days (40)			6.5 Days (26)		7.5 Days (30)		
Evaluation	Days 1; 2, 3 or 4; & 5			Daily			Daily (except Day 2)				
Efficacy Parameters	Ulcer Size, Pain, Erythema & Physician's Score *(All Scales Defined Complete Resolution)*						Ulcer Size & Pain *(Both Scales Defined Complete Resolution)*				
Entry Criteria	Identical for All Four Studies *(Patients with One to Three Ulcers of Less Than 48 Hours Duration)*										

† = Maximum Number of Doses Applied; ulcers treated until healed or maximum number whichever occurs first.

5% A = 5% Amlexanox; 1% A = 1% Amlexanox; V = Vehicle; NT = No Treatment

Baseline Consistency:

Baseline parameters for Protocols 107 and 108 are summarized in Tables 2 and 3.

Table 2: Baseline characteristics in Protocol 107

	5% AMLEXANOX		VEHICLE	
	MALE	FEMALE	MALE	FEMALE
SAMPLE SIZE	99 (47%)	112 (53%)	102 (48%)	111 (52%)
AGE: (Mean ± Std)	26.2 (± 5.0)	29.4 (± 9.0)	26.7 (± 6.7)	27.7 (± 7.4)
RACE				
CAUCASIAN	90 (42%)	97 (46%)	86 (40%)	89 (42%)
BLACK	1 (0.5%)	6 (2.8%)	3 (1.4%)	6 (2.8%)
HISPANIC	3 (1.4%)	4 (1.9%)	0 (0%)	4 (1.9%)
ASIAN	5 (2.4%)	5 (2.4%)	12 (5.6%)	10 (4.7%)
OTHER	0 (0%)	0 (0%)	1 (0.5%)	2 (0.9%)

Table 3: Baseline characteristics in Protocol 108

	5% AMLEXANOX		VEHICLE		NO TREATMENT	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
SAMPLE SIZE	85 (43%)	112 (57%)	101 (51%)	97 (49%)	74 (56%)	59 (44%)
AGE: (Mean±Std)	28.0 (±8.6)	27.8 (± 9.1)	26.4 (± 4.9)	28.3 (± 8.7)	28.2 (± 7.1)	27.7 (± 8.6)
RACE						
CAUCASIAN	77(39%)	98(50%)	89(45%)	82(41%)	65(49%)	51(38%)
BLACK	1(0.5%)	2(1.0%)	0(0%)	5(2.5%)	0(0%)	1(0.8%)
HISPANIC	2(1.0%)	3(1.5%)	3(1.5%)	6(3.0%)	3(2.20%)	1(0.8%)
ASIAN	5(2.5%)	9(4.6%)	9(4.5%)	4(2.0%)	6(4.5%)	6(4.5%)

It is noted that there are no significant differences between treatment arms with respect to age, gender, race at baseline. The p-values obtained from Cochran-Mantel-Haenszel test for gender and race information and from ANOVA for age were above 0.15 in each case.

B. EFFICACY EVALUATION

The primary efficacy variables are healing of aphthous ulcers and acceleration of pain relief. Ulcer cure is defined as 100% resolution of ulcers. The sponsor has submitted information on cure rates as mean reduction in ulcer size as well as median time to first resolution of ulcers and pain relief.

Reviewer Comments: Since aphthous ulcers are self-limiting, it is considered that the median time to complete resolution of the ulcer and pain relief is of primary clinical relevance. The sponsor submitted results from Wilcoxon test as well as log rank statistic, and often statistical significance is obtained in one but not the other. In an effort to justify usage of one nonparametric test over another, the following reference is made (Statistical Methodology in the Pharmaceutical Sciences, edited by D. Berry, pp. 329-331):

"The log-rank statistic is an example of what is often termed a censored data rank test. This test is fully efficient against alternatives in which the hazard rates between samples are proportional across time". On the other hand, Prentice generalization of Wilcoxon test (used in SAS software package as a default) "place more emphasis on earlier times".

It is thus deemed prudent to utilize log-rank statistic for median time to complete resolution of ulcer, but use Wilcoxon for testing median time to pain relief.

The analyses presented here are based on the sponsor's database.

Reviewer's comment on the database:

Subsequent to the submission, an inconsistency in the database was noticed. Eight patients in site 2 were assigned wrong treatment codes. The sponsor provided re-analyses of the database as well as a rewritten statistical report. The analyses reported in this review reflect the change in the database.

In an answer to a query by the Medical Officer, the sponsor responded to the issue that the sample size, N, varies from table to table. It was stated that for direct summarization tables, actual number of patients from whom data was collected at the evaluation time are represented in the table, with information on successes carried forward. A patient not healed will have ulcer size information. Any discrepancy can

therefore occur only from missing data. For tables based on derived calculation and for determining the time to first occurrence of healing, similar algorithm was followed. This was considered acceptable by the statistical reviewer.

Aphthous Ulcer Healing:

TABLE 4: PERCENT OF PATIENTS HEALED BASED ON ULCER SIZE (PROTOCOL 107)

TREATMENT GROUP GROUP SIZE	% of Patients Healed (Size = 0 x 0 mm)		**p-Value** Comparison of Treatment Groups
	5% AMLEXANOX	**VEHICLE**	
Day 3	3.4%	2.4%	ns
Day 4	13.9%	15.3%	ns
Day 5	36.5%	24.5%	**0.008**
Day 6	49.8%	41.2%	0.077
Day 7	68.8%	54.1%	**0.002**
MEDIAN TIME TO HEAL (Treatment Days)	5.0	5.6 Wilcoxon p-value = **0.010** Log-Rank p-value = **0.012**	

It is noted that there is a significant difference in percent of patients having healed ulcer at days 5 and 7, as well as in median time to heal. The percentage of patients healed by Amlexanox is consistently higher than the vehicle numerically from Day 5 onwards. However, the difference in median time to heal is 0.6 days. It is to be determined by the clinical reviewer if this difference, even though statistically significant by both tests, is clinically meaningful.

TABLE 5: PERCENT OF PATIENTS HEALED BASED ON ULCER SIZE (PROTOCOL 108)

TREATMENT GROUP GROUP SIZE [N]	% HEALED (SIZE = 0 X 0 MM)			p-Values	
	5% AMLEXANOX *[N=197]*	VEHICLE *[N=198]*	NO TREATMENT *[N=133]*	Amlex vs Vehicle	Amlex vs No Treat.
Day 3	5.61%	4.04%	0.75%	*ns*	*0.024*
Day 4	19.07%	12.69%	7.63%	*0.032*	*0.004*
Day 5	34.87%	25.76%	19.55%	*0.047*	*0.003*
Day 6	50.26%	39.90%	31.58%	*0.033*	*0.001*
Day 7	62.05%	52.33%	46.97%	*0.050*	*0.008*
Day 8	70.92%	59.60%	50.38%	*0.018*	*0.000*
Median Time to Heal (Days)	5.0	5.8	6.6	*Wilcoxon p-value =0.015 Log-rank p-value = 0.053*	*Wilcoxon p-value= 0.000 Log-rank p-value = 0.001*

It is noted that there is a significant difference in rate of ulcers healed between Amlexanox and vehicle from day 5 onwards, as well as in median time to ulcer healing. The difference is statistically significant by Wilcoxon test but not by log-rank statistic. Since the primary interest is in the overall profile of ulcer healing, log-rank statistic is more appropriate in this instance. The difference in median time to heal between treatment and vehicle arm is 0.8 days. It is to be determined by the clinical reviewer if these differences, even though statistically significant by both tests, are clinically meaningful. Amlexanox is statistically superior to no treatment on all evaluation timepoints and in median time to ulcer healing by both Wilcoxon and log-rank statistics.

An analysis was done to see if there is a difference in ulcer healing rates between the treatment arms between days 4 to 6. A patient is considered a cure in this analysis if all the treated ulcers get healed in 4-6 days. A comparison of cure rates in two protocols are summarized in Table 6.

Table 6: Ulcer healing rate summary in Protocols 107 and 108

Protocol	Cure rates			Confidence Interval
	Amlex (%)	Vehicle (%)	No treatment	
107	90/198 (45.4%)	78/195 (40.0%)	----------	$_{198,\ 195}$ (-0.0482, 0.1573) $_{45.4\%,\ 40.0\%}$
108	82/188 (43.6%)	68/185 (36.7%)	40/130 (30.7%)	Amlex vs vehicle: $_{188,\ 185}$ (-0.0360, 0.1732) $_{43.6\%,\ 36.7\%}$ Amlex vs no treatment: $_{188,\ 130}$ (0.0158, 0.2414) $_{43.6\%,\ 30.7\%}$

It is seen that in both protocols, there is no statistically significant difference between the treatment arm and the vehicle with regard to the ulcer healing rate between days 4 and 6. Amlexanox is statistically superior to no treatment in Protocol 108. Note that multiple comparison correction was not applied to the construction of the confidence intervals.

Pain relief:

Patients were instructed to mark their perception of pain on a Visual Analog Scale (VAS). A score of ≤ 0.5 cm on the VAS was considered to be complete resolution of pain. If patients had more than one ulcer, they were not considered as having complete resolution of pain unless pain had resolved from all of their treated ulcers.

TABLE 7: PERCENT OF PATIENTS WITH COMPLETE RESOLUTION OF PAIN (Protocol 107)

	% of Patients with Pain Resolved (VAS score ≤0.5 cm)		p-Value Comparison of Treatment Groups
	5% AMLEXANOX	VEHICLE	
Day 3	19.7%	12.4%	**0.041**
Day 4	38.5%	33.0%	ns
Day 5	56.3%	47.9%	0.086
Day 6	70.7%	60.3%	**0.022**
Day 7	79.3%	72.7%	0.107
MEDIAN TIME TO HEAL (TREATMENT DAYS)	3.5	4.0 Wilcoxon p-value = **0.022** Log-rank p-value = **0.062**	

There is a statistically significant difference between treatments on Day 3 and Day 6. The median time to pain relief is statistically significant by Wilcoxon test, but fails to establish significance over vehicle in log-rank test. It is to be noted that since early pain relief is desirable, Wilcoxon test is more appropriate here. However, whether a reduction of 0.5 days in pain relief in a self-limiting disease is clinically meaningful needs to be determined by the Medical Officer.

The pain relief for patients in Protocol 108 is discussed in Table 8. It was seen that there was a statistically significant difference between Amlexanox and vehicle from Day 5 for each evaluation timepoints, and between Amlexanox and no treatment arm for all timelines. The median time to pain relief fails to establish statistical significance between Amlexanox and vehicle by Wilcoxon test (more appropriate in this context) but is marginally significant by log-rank test. There is a statistically significant difference between Amlexanox and no treatment with regard to median time to heal by both tests. However, it is to be noted that the reduction in pain relief is 0.6 days between the treatment arm and vehicle and 1.4 days between treatment arm and no treatment group. It is to be determined by the Medical Officer whether this difference, though statistically significant, is clinically meaningful.

TABLE 8: PERCENT PATIENTS WITH COMPLETE RESOLUTION OF PAIN (PROTOCOL 108)

TREATMENT GROUP GROUP SIZE [N] [a]	% WITH COMPLETE RESOLUTION OF PAIN (± *Std Err*)			P-VALUE COMPARISONS BETWEEN GROUPS	
	5% AMLEXANOX *[N=197]*	VEHICLE *[N=198]*	NO TREATMENT *[N=133]*	Amlex vs Vehicle	Amlex vs No Treat.
Day 3	14.87% *(2.55)*	15.15% *(2.55)*	6.77% *(2.18)*	*ns*	*0.026*
Day 4	38.46% *(3.48)*	33.33% *(3.35)*	16.54% *(3.22)*	*ns*	*0.000*
Day 5	54.87% *(3.56)*	43.43% *(3.52)*	35.34% *(4.14)*	*0.022*	*0.001*
Day 6	71.28% *(3.24)*	56.06% *(3.53)*	46.62% *(4.33)*	*0.001*	*0.000*
Day 7	80.0% *(2.86)*	65.15% *(3.39)*	57.14% *(4.29)*	*0.001*	*0.000*
Day 8	84.10% *(2.62)*	75.76% *(3.05)*	69.92% *(3.98)*	*0.039*	*0.002*
Median Time for Pain Resolution (Days)	3.6	4.3	5.0	*0.042*	*0.000*
	Wilcoxon p-values: Amlex vs vehicle = 0.057 Amlex vs no treatment < 0.001 Log-rank p-values: Amlex vs vehicle = 0.047 Amlex vs no treatment < 0.001				

Further analyses to see if there is a difference in pain relief rates between the treatment arms between days 3 and 5 were done. A patient is considered a cure in this analysis if complete pain relief is reached between days 3 and 5. A comparison of cure rates in two protocols are summarized in Table 9.

Table 9: Pain relief summary in Protocols 107 and 108

Protocol	Cure rates Amlex (%)	Vehicle (%)	No treatment	Confidence Interval
107	84/198 (42.4%)	97/195 (49.7%)	----------	$_{199,\ 195}$ (-0.1766, 0.0302) $_{42.4\%,\ 49.7\%}$
108	83/188 (44.1%)	83/185 (44.8%)	46/130 (35.3%)	Amlex vs vehicle: $_{188,\ 185}$ (-0.1134, 0.0991) $_{44.1\%,\ 44.8\%}$ Amlex vs no treatment: $_{188,\ 130}$ (-0.0274, 0.2027) $_{44.1\%,\ 35.3\%}$

It is seen that in both protocols, there is no statistically significant difference between the treatment arm and the vehicle with regard to the pain relief rate between days 3 and 5. Amlexanox is statistically equivalent to no treatment in Protocol 108. Note that multiple comparison correction was not applied to the construction of the confidence intervals.

Additional Efficacy evaluations:

The Medical Division wondered if the data might show a temporal effect of the drug by analyzing ulcer healing and pain relief in three time periods over the treatment regimen. For Protocol 107, the time is subdivided into days 1-3, 4-5 and 6-7. In Protocol 108, the timepoints considered are days 1-3, 4-6 and 7-8. A patient is considered a cure if he/she is got complete healing of the ulcers or resolution of pain in that timepoint. Fisher's exact χ^2 test was performed to determine if there is a significant difference between the treatment arms, summarized in tables 10 and 11.

Table 10: Ulcer Healing and Pain Relief Progression over Time (Protocol 107)

Criteria	Days	Amlexanox 5% paste Cure	Fail	Total	Vehicle Cure	Fail	Total	χ^2 p-value
Ulcer Healing	Days 1-3	7	191	198	4	191	195	0.5431
	Days 4-5	64	134	198	45	150	195	0.0406
	Days 6-7	64	133	197	55	140	195	0.3566
Pain Relief	Days 1-3	39	159	198	23	172	195	0.0317
	Days 4-5	45	153	198	74	120	194	0.0009
	Days 6-7	78	120	198	49	145	194	0.0028

It is seen that there is a significant difference between the treatment arm and the vehicle only at days 4-5 on ulcer healing. For pain relief, there is a statistically significant difference between Amlexanox and the vehicle for each of the time periods considered. However for days 4-5, Amlexanox is statistically inferior to its vehicle with resspect to pain relief.

Table 11: Ulcer Healing and Pain Relief Progression over Time (Protocol 108)

Criteria / Days	Amlexanox Cure	Amlexanox Fail	Vehicle Cure	Vehicle Fail	No treatment Cure	No treatment Fail	p-value (Amlex vs veh)	p-value (Amlex vs no trt)
Ulcer Healing								
Days 1-3	11	178	8	177	1	129	0.5101	0.0198
Days 4-6	82	106	68	117	40	90	0.1767	0.0205
Days 7-8	41	148	36	149	23	107	0.5933	0.3806
Pain Relief								
Days 1-3	27	162	30	155	9	121	0.6035	0.0411
Days 4-6	113	76	79	106	52	78	0.0009	0.0005
Days 7-8	25	162	68	116	32	95	< 0.001	0.0076

It is noted that for ulcer healing, there is no statistical difference between Amlexanox and vehicle. However, Amlexanox is statistically superior to no treatment upto Day 5. For pain relief, Amlexanox is statistically superior to vehicle for days 4-6. A reversal is noted at Days 7-8 when Amlexanox is statistically inferior to both vehicle and no treatment.

Pooled Results from Protocols 102 and 106:

Study 102 was a Phase II dose-ranging study with 5% Amlexanox, 1% Amlexanox and vehicle on a 4 day dosage regimen. Study 106 was a Phase III study with 5% Amlexanox, vehicle and no treatment on a 10 day dosage regimen. These two studies were pooled by the sponsor on the basis of Day 5 results to provide supportive evidence for ulcer healing and pain relief profile of Amlexanox over its vehicle.

The reason for pooling two studies were provided by the sponsor as having the same formulation, study design, dosing regimen, inclusion/exclusion criteria, baseline consistency and similar data collection and management.

Table 12 summarizes the results from the pooled study.

TABLE 12: COMPARISON OF RESULTS FROM CLINICAL STUDIES 102 AND 106

Study No.	% OF PATIENTS WITH RESOLUTION OF SYMPTOMS ON DAY 5							
	SIZE		ERYTHEMA		PAIN		Physician's Assessment	
	Veh	5% Amlex	Veh	5% Amlex	Veh	5% Amlex	Veh	5% Amlex
102	30%	43%	35%	39%	55%	70%	30%	33%
106	35%	53%	45%	57%	57%	77%	36%	53%
102 & 106	33%	47%	41%	46%	56%	73%	33%	41%
CMH p-value at Day 5	**0.023**		NS		**0.01**		**0.13**	

If two studies are pooled by DerSimonian and Laird approach, the p-values reflecting poolability are 0.8183 and 0.8367 for ulcer healing and pain relief respectively. Since Since the p-values are not significant ($p > 0.15$), we proceed to obtain the combined cure rates and the associated confidence interval.

The confidence intervals for combined cure rates are as follows:

Ulcer healing: $_{135,\ 93}$ (0.0171, 0.2730) $_{45.9\%,\ 32.2\%}$

Pain Relief: $_{133,\ 87}$ (0.0672, 0.3279) $_{72.9\%,\ 52.8\%}$

This indicates that, based on the combined cure rates, Amlexanox is statistically superior to its vehicle with respect to ulcer healing and pain relief. The sponsor's analysis, replicated here for completeness in Table 13, corroborates this analysis.

Table 13: DerSimonian and Laird Method of Analysis of Efficacy Evaluable Patients from Combined Database for Studies 102 and 106

	Difference in % Patients Cured Between 5% Amlexanox and Vehicle on Day 5							
	Study 102		Study 106		Chi-Sq.	Combined		p-Value
	Diff.	SE	Diff.	SE		Diff.	SE	
% Healed (Size = 0 mm^2)	13.0	9.1	17.5	9.6	0.12	15.2	6.6	**0.022**
% With No Pain	14.6	9.4	20.1	9.1	0.17	17.4	6.5	**0.008**
No Erythema	3.5	9.3	11.5	9.7	0.36	7.3	6.7	**ns**
PI Score	3.3	9.0	16.8	9.6	1.05	9.6	6.7	**ns**

The p value is based on the ratio of the combined difference and its standard error. ns - denotes p > 0.15.
DerSimonian, R., Laird, N. (1986): Controlled Clinical Trials, 7:177

Reviewer Comments on Poolability of Protocols 102 and 106:

It is the statistical reviewer's concern that the pooling seems artificial. Day 5 on Protocol 102 denotes the end of treatment timepoint, whereas it represents during treatment timepoint for Protocol 106 (in fact it is exactly midpoint of the treatment regimen). However, determination needs to be made if this is of any clinical meaningfulness by the Medical Officer.

An additional confounding factor is that 22 patients participated in both studies, thus compromising independence of the two studies. These patients were counted as two individual patients in the combined database. They are summarized in Table 14.

TABLE 14: LISTING OF PATIENTS THAT PARTICIPATED IN BOTH STUDIES

Left to right alignment of numbers are listings of the same patient in both studies; for example, patient in Study 102 was patient in Study 106.

DATA FROM STUDY 34,787-102		DATA FROM STUDY 34,787-106	
Group	**Patient No.**	**Group**	**Patient No.**
1% Amlex		NONE	
5% Amlex		NONE	
1% Amlex		Vehicle	
5% Amlex		Vehicle	
Vehicle		Vehicle	
Vehicle		5% Amlex	
1% Amlex		5% Amlex	
5% Amlex		5% Amlex	

C. SAFETY EVALUATION

Table 15 summarizes the adverse clinical effects related to the NDA formulation.

TABLE 15: SEVERITY OF ADVERSE EVENTS RELATED TO NDA FORMULATION

NDA Formula, Oral Topical Application

BODY SYSTEM	EVENT	VEHICLE [N = 512]			1% AMLEXANOX [N = 79]			5% AMLEXANOX [N = 679]		
		Mild (%)	Mod. (%)	Severe (%)	Mild (%)	Mod. (%)	Severe (%)	Mild (%)	Mod. (%)	Severe (%)
Gastrointestinal	Nausea	1† (0.2)	1 (0.2)	-	-	-	-	3 (0.4)	1 (0.1)	-
	Diarrhea	-	-	-	-	-	-	-	1(0.1)	-
Neurological	Facial Flushing	-	-	-	-	-	-	1 (0.1)	-	-
Dermatological	Rash on Hands	-	1† (0.2)	-	-	-	-	-	-	-
Local Application Site Reactions	Pain/Stinging/Burning	3 (0.6)	2 (0.4)	1† (0.2)	1 (1.3)	-	-	8 (1.2)	1 (0.1)	-
	Dryness	-	-	-	1 (1.3)	-	-	2 (0.3)	-	-
	Foul Taste	1 (0.2)	-	-	-	-	-	-	-	-
	White Plaque	1 (0.2)	-	-	-	-	-	-	-	-
	Superficial Mucocele	1 (0.2)	-	-	-	-	-	-	-	-
	Bumps on Lip	-	-	-	-	-	-	1 (0.1)	-	-
	Mucositis	-	-	-	-	-	-	1 (0.1)		
Total # of Adverse Events		7 (1.4)	4 (0.8)	1 (0.2)	2 (2.5)	0 (0.0)	0 (0.0)	16 (2.4)	3 (0.4)	0 (0.0)
# of Patients Reporting Adverse Events		11 (2.1)			2 (2.5)			16 (2.4)		

It was noted that local application site reactions are most common, with pain/stinging/burning reported in 1.2% of the patients. The duration of adverse events were usually less than a day, with pain/stinging/burning reported in one instance for 6 days for a patient on 5% Amlexanox. Another patient on treatment arm reported bumps on lip to be lasting > 9 days. Overall, the drug seems to be clinically well-tolerated.

To elicit long-term safety and tolerance profile, 100 patients with aphthous ulcers were enrolled in an open-label, multicenter trial to apply 5% Amlexanox qid for 28 days. Patients were monitored weekly for changes in clinical laboratory parameters (CBC, hematology and urine analysis). None of the hematologic or serum chemistry values were reported outside of normal laboratory range. Ten patients had at least one value at some point in the study of ALT, AST, alkaline phosphatase or total bilirubin that was more than 50% out of range. Six of them were enrolled with elevated values. These values remained high and/or returned to normal during the study; none of these values increased significantly during treatment. However, the combined normal range was defined as the lowest and highest laboratory normal values from the 4 laboratories, this rendered interpretation of these abnormalities virtually impossible. Overall, the drug seems to be well-tolerated with respect to laboratory parameters.

No deaths were reported on the protocols.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

There was no baseline inconsistency in the demographic characteristic of the patient population enrolled in Studies 107 and 108 (Tables 2 and 3).

Aphthous ulcer healing:

On Protocol 107, there is a significant difference in percent of patients having healed ulcers at days 5 and 7, as well as in median time to heal (Table 4). In Protocol 108, there is a significant difference in rate of ulcers healed between Amlexanox and vehicle from day 5 onwards, as well as in median time to ulcer healing. The difference is statistically significant by Wilcoxon test but not by log-rank statistic. Amlexanox is statistically superior to no treatment on all evaluation timepoints and in median time to ulcer healing by both Wilcoxon and log-rank statistics (Table 5). It is to be determined by the clinical reviewer if a median reduction of 0.6 days in Protocol 107 and 0.8 days on Protocol 108 is clinically meaningful.

There is no statistically significant difference between the treatment arm and the vehicle with regard to the **ulcer healing rate** between days 4 and 6 on either protocol. Amlexanox is statistically superior to no treatment in Protocol 108 (Table 6). If time periods of Days 1-3, 4-5 and 6-7 are considered, it is seen that there is a significant

difference in first time healing rate between the treatment arm and the vehicle only at days 4-5 on ulcer healing on Protocol 107 and no statistical difference on Protocol 108 (Tables 10 and 11).

Pain Relief:

On Protocol 107, there is a statistically significant difference between treatments on Day 3 and Day 6. The median time to pain relief is statistically significant by Wilcoxon test (Table 7).

On Protocol 108, there is a statistically significant difference between Amlexanox and vehicle from Day 5 onwards for each evaluation timepoints, and between Amlexanox and no treatment arm for all timelines. The median time to pain relief fails to establish statistical significance between Amlexanox and vehicle by Wilcoxon test. There is a statistically significant difference between Amlexanox and no treatment with regard to median time to heal by both tests. It needs to be determined by the Medical Officer whether a median reduction of 0.5 days on Protocol 107 and 0.6 days on Protocol 108 is clinically meaningful (Table 8).

It is seen that in protocol 108, there is no statistically significant difference between the treatment arm and the vehicle with regard to the pain relief rate between days 3 and 5. Amlexanox is statistically superior to vehicle in Protocol 107 and no treatment in Protocol 108 (Table 9). There is a statistically significant difference in first time pain relief rates between Amlexanox and the vehicle for days 6-7 on Protocol 107 and days 4-6 on Protocol 108. However, Amlexanox is seen to be statistically inferior to its vehicle on days 4-5 on Protocol 107 and days 7-8 on Protocol 108 (Tables 10 and 11).

Pooled efficacy from Protocols 102 and 106:

Based on the combined cure rates, Amlexanox is statistically superior to its vehicle with respect to ulcer healing and pain relief. The sponsor's analysis is in corroboration with this analysis.

It is the statistical reviewer's concern that the pooling seems artificial. Day 5 on Protocol 102 denotes an end of treatment time point, whereas it represents during treatment time point for Protocol 106 (in fact it is exactly the midpoint of the treatment regimen). However, determination needs to be made if this is of any clinical meaningfulness by the Medical Officer. An additional confounding factor is that 22 patients participated in both studies, thus compromising independence of the two studies. These patients were counted as two individual patients in the combined database (Table 14).

Safety Profile:

The drug seems to be well-tolerated clinically and with respect to laboratory parameters (Table 15).

In conclusion, Aphthasol has failed to establish accelerated ulcer healing and faster pain relief over vehicle in the treatment of aphthous ulcers.

Alaka Chakravarty 1/3/96

Alaka G. Chakravarty, Ph.D.
Biomedical Statistician, Biometrics IV

1/3/96

Concur: Rajagopalan Srinivasan, Ph.D.
Acting Team Leader

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Ralph Harkins, Ph.D.
Acting Division Director

cc:
Archival NDA 20-511
HFD-540
HFD-540/Ms. Holmes
HFD-540/Dr. Katz
HFD-540/Dr. Wilkins
HFD-540/Dr. Huene
HFD-701/Dr. Anello
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Dr. Chakravarty
HFD-344/Dr. Pierce
Chron.

This review contains 18 pages.

Chem

CAC Executive Meeting
July 25, 1995

Attendees: Joseph DeGeorge (HFD-150); Joseph Contrera (HFD-400); Anwar Goheer (HFD-007); William Fairweather (HFD-715); Mohammad Rahman (HFD-715); Abby Jacobs (HFD-540); John Wedig (HFD-540); Amy Nostrandt (HFD-540); David Shriver (HFD-540); Margaret Brower (HFD-150); Albert DeFelice (HFD-110); Tom Papoian (HFD-110); D.G. Patel (HFD-110); Ernest Belair (HFD-110); and Sharon Olmstead (HFD-001)

The following information reflects a brief summary of the committee discussion and its recommendations. For detailed study information, reference should be made to the individual reviews submitted to the committee.

NDA 20-511 (Wedig; Jacobs)
Amlexanox
The sponsor submitted data from the 104 week carcinogenicity studies in rats and mice. Using a pairwise comparison for the thyroid adenomas in male rats and pheochromocytomas in female rats neither neoplasm was found to be statistically significant. The pheochromocytomas were found to be statistically significant with the trend test analysis.

The committee agreed that the statistically significant finding for pheochromocytoma in female rats using the trend test analysis is not biologically significant. Therefore, the committee does not recommend including this information in the labeling. The committee also agreed with the conclusion that the neoplasms seen in the mouse treated groups were comparable to the controls.

Joseph DeGeorge, Ph.D.
Acting Chair, CAC

cc: NDA 20-511
HFD-540/AJacobs/JWedig
CAC files

concurrence: JDeGeorge/AGoheer/AJacobs/7/31/95

FDA CDER CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC)
RODENT CARCINOGENICITY FACT SHEET

NDA:# 20-511 IND· DRUG CODE#:AA-673;CHX- 3673
CAS#:68302-57-8 DATE:July 5,1995

Other NDA's #89-066 and #19-940

DIVISION(s):Topical Drug Products

DRUG NAME(s):Amlexanox

SPONSOR:Chemex Pharmaceuticals, Ft. Lee, NJ

LABORATORY:

P/T REVIEWER(s):John Wedig, Ph.D. Sandra Morseth, Ph. D.

P/T REVIEW DATE: 1995 1990

CARCINOGENICITY STUDY REPORT DATE: April and August 1988

THERAPEUTIC CATEGORY:Treatment of aphthous ulcers on the oral mucosa.

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION:Anti-allergic and anti-inflammatory; the mechasnism of action for accelerating the healing of aphthous ulcers is unknown.

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date):NO

MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay):NO: Ames test; micronucleus test in the mouse.

RAT CARCINOGENICITY STUDY (multiple studies? Std1;Std2 etc.):STD1

RAT STUDY DURATION (weeks):104

STUDY STARTING DATE:Protocol signed January 17, 1985; animals initially dosed March 13, 1985

STUDY ENDING DATE:Last animal killed on March 17, 1987; final report August 31, 1988.

RAT STRAIN: Charles Rivers Fisher 344

ROUTE:Dietary admix

DIETARY RESTRICTIONS (Y/N):None

FDA CDER CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC)
RODENT CARCINOGENICITY FACT SHEET

DOSING COMMENTS:The mean compound consumption of all the AA-673 tyreated groups was within 10% of theory except for three 2 week periods when it exceeded the 10% over the 104 week dosing period. Diet assays every four weeks for AA-673 concentrations in all groups indicated 14 values which were less than 10% of theory-i.e. 11 in the 80's and three in the high 70's.

No. Rats in Control (C1) Group:50\sex
Low Dose (LD)Group:50\sex
Middle Dose (MD)Group:50\sex
High Dose (HD)Group:50\sex

RAT DOSE LEVELS (mg/kg/day)

Rat Low Dose: 25
Rat Middle Dose:80
Rat High Dose: 250

Dose adjusted during study:No

Basis for Doses Selected (MTD; AUC ratio; saturation; maximum feasible): A 13 week dietary dose range finding study tested dose levels of 0, 125, 250, 500 and 1000 mg/kg. Body weight was decreased at 1000 mg/kg. Serum levels of alkaline phosphatase, SGOT and SGPT were increased in the males given 500 mg/kg and in both sexes given 1000 mg/kg.
Histopathological evaluation of the liver indicated dilation of the extrahepatic and common bile ducts, bile duct hyperplasia, cholangitis, necrosis and pericholangitis. These effects were seen in both sexes at 1000 mg/kg and in the males at 500 mg/kg. Females at 500 mg/kg indicated only one trace instance of pericholangitis as did the males at 250 mg/kg. The dose of 125 mg/kg did not appear to produce any toxic effects.

RAT CARCINOGENICITY (negative;positive;MF;M;F):

Negative for carcinogenicity

RAT TUMOR FINDINGS:

There were no increased incidences of tumors except for the following:

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RODENT CARCINOGENICITY FACT SHEET

Incidence of pheochromocytoma

Dose mg/kg/day	0	25	80	250
Males	(49)	(50)	(50)	(50)
No. animals with tumor	6	9	9	2
% incidence	12	18	18	4
Females	(50)	(50)	(50)	(50)
No. animals with tumor	1	1	3	7
% incidence	2	2	6	14

()= number of animals examined

Range of % incidence in historic control animals at IRDC, 24 month studies:
males 1.7 to 11.4; females 0 to 6.0:incidence was 0 to 16% in females from the analysis of 200 2 year studies with 1940 animals, Boorman, et.al.1990, NTP data, see attached.

The number of thyroid parafollicular cell adenoma's was increased in the male high dose vs the control but was within the percent incidence for the historical control.

RAT STUDY COMMENTS:

A biostatistical consult was requested from Mohammad A. Rahman, Ph.D. (HFD-715) for analysis of the relevance of the number of pheochromocytoma's and the thyroid adenoma's in the treated groups vs the control (see attached evaluation). With respect to the thyroid adenoma the pairwise comparison was not found to be statistically significant.

The incidence of pheochromocytoma in female rats showed a statistically significant positive linear trend. The pairwise comparison was found not to be statistically significant.

Since the increased incidence of pheochromocytoma was not statistically significant in a pairwise comparison and was

only noted in the high dose group where evidence of serious toxicity was apparent, the compound was considered not to be carcinogenic. The exposure to 250 mg/kg of amlexanox in the rat is greatly in excess of the intended human exposure-i.e.1250X.

COMMENDATIONS:None

MOUSE CARCINOGENICITY STUDY (multiple studies? Std1;Std2 etc.): One study

MOUSE STUDY DURATION (weeks): 78

STUDY STARTING DATE:June 17, 1985 (protocol signed);July 12, 1985 (in life started).

STUDY ENDING DATE:January 19, 1987 (in life); April 6, 1988 (report completed)

MOUSE STRAIN:$B_6C_3F_1$

ROUTE:Dietary admix

DIETARY RESTRICTIONS (Y/N):None

DOSING COMMENTS:Mean compound consumption of all treated groups was plus or minus 10% of theory. Only 6 diet mixes (analysis monthly) varied more than plus or minus 10% of theory.

No. Mice in Control Group:50/sex
Low Dose Group:50/sex
Mid Dose Group:50/sex
Mid-High Dose Group:50/sex
High Dose Group:50/sex

MOUSE DOSE LEVELS (mg/kg/day)

Mouse Low Dose:3
Mouse Mid Dose:10

FDA CDER CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC)
RODENT CARCINOGENICITY FACT SHEET

Mouse Mid-High Dose:30
Mouse High Dose:100

Dose adjusted during study? NO

Basis for Doses Selected (MTD; AUC ratio; saturation; maximum feasible):Maximum Tolerated Dose. A 17 week dietary dose range finding study in this strain of mouse was conducted using dose levels of 0, 25, 50, 100, 200, 500 and 1500 mg/kg (the latter two dosage levels from study week 14, and representing a change in the 25 and 50 mg/kg/day dose levels). A treatment related toxic nephrosis was noted beginning at a dose of 100 mg/kg. This effect increased in incidence and severity with increasing dose. No other treatment related effects were seen.

Prior FDA Concurrence (Div/CAC)? (y/n;Date):NO

MOUSE CARCINOGENICITY (negative;positive;MF;M;F):Negative

MOUSE TUMOR FINDINGS:The prevelance and types of neoplasms were similar for both the control and treated group

Mouse Study Comments: In the 100 mg/kg group 35/50 males had granular kidneys noted at gross necropsy (11 mild, 20 moderate and 4 severe). Microscopic examinatioin of the kidney from the males in the 100 mg/kg group indicated 50/50 had toxic nephrosis (10 trace, 28 mild and 12 moderate severity). No toxic nephrosis was noted at the lower doses.

Pathology of the Fischer Rat

Reference and Atlas

EDITED BY

Gary A. Boorman, Scot L. Eustis, and Michael R. Elwell
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RESEARCH TRIANGLE PARK, NORTH CAROLINA

ACADEMIC PRESS, INC.
HARCOURT BRACE JOVANOVICH, PUBLISHERS
San Diego New York Boston London Sydney Tokyo Toronto

Table 1 (*continued*)

	Male Rats						Female Rats					
	Untreated			Corn Oil Gavage			Untreated			Corn Oil Gavage		
	Animals with Tumors[a]	Rate[b] %	Range %	Animals with Tumors[a]	Rate[b] %	Range %	Animals with Tumors[a]	Rate[b] %	Range %	Animals with Tumors[a]	Rate[b] %	Range %
Tooth	(1936)			(1949)			(1983)			(1950)		
Odontoma	2	0.1		0	0.0		0	0.0		0	0.0	
Salivary Gland	(1895)			(1914)			(1939)			(1934)		
Adenoma	0	0.0		1	0.1		0	0.0		3	0.2	
Adenocarcinoma	1	0.1		0	0.0		0	0.0		0	0.0	
Fibrosarcoma	2	0.1		1	0.1		0	0.0		0	0.0	
Sarcoma	2	0.1		0	0.0		0	0.0		0	0.0	
Liver	(1928)			(1946)			(1979)			(1945)		
Neoplastic Nodule	80	4.1		52	2.7		45	2.3		33	1.7	
Hepatocellular Carcinoma	20	1.0		12	0.6		3	0.2		0	0.0	
Cholangiocarcinoma	0	0.0		1	0.1		0	0.0		2	0.1	
Cholangioma	1	0.1		2	0.1		0	0.0		0	0.0	
Lipoma	1	0.1		0	0.0		0	0.0		0	0.0	
Esophagus	(1851)			(1850)			(1909)			(1836)		
Squamous Cell Carcinoma	0	0.0		1	0.1		0	0.0		1	0.1	
Forestomach	(1912)			(1924)			(1955)			(1936)		
Squamous Cell Papilloma	3	0.2		6	0.3		5	0.3		8	0.4	
Squamous Cell Carcinoma	2	0.1		1	0.1		1	0.1		1	0.1	
Leiomyosarcoma	1	0.1		1	0.1		0	0.0		0	0.0	
Glandular Stomach	(1912)			(1924)			(1955)			(1936)		
Adenocarcinoma	1	0.1		0	0.0		0	0.0		0	0.0	
Fibrosarcoma	0	0.0		1	0.1		0	0.0		0	0.0	
Neurofibrosarcoma	1	0.1		0	0.0		0	0.0		0	0.0	
Sarcoma	0	0.0		0	0.0		1	0.1		0	0.0	
Small Intestine	(1865)			(1887)			(1939)			(1914)		
Adenomatous Polyp	0	0.0		1	0.1		0	0.0		0	0.0	
Adenocarcinoma	7	0.4		2	0.1		0	0.0		0	0.0	
Fibrosarcoma	1	0.1		0	0.0		1	0.1		0	0.0	
Sarcoma	1	0.1		1	0.1		1	0.1		0	0.0	
Malignant Schwannoma	0	0.0		0	0.0		0	0.0		1	0.1	
Leiomyoma	1	0.1		1	0.1		0	0.0		0	0.0	
Leiomyosarcoma	3	0.2		1	0.1		2	0.1		1	0.1	
Large Intestine/Rectum	(1936)			(1949)			(1983)			(1950)		
Adenomatous Polyp	0	0.0		2	0.1		0	0.0		0	0.0	
Adenocarcinoma	2	0.1		1	0.1		0	0.0		0	0.0	

Fibroma	1	0.1	0	0.0	0	0.0	0	0.0
Fibrosarcoma	0	0.0	1	0.1	0	0.0	0	0.0
Lipoma	0	0.0	0	0.0	0	0.0	1	0.1
Malignant Schwannoma	1	0.1	0	0.0	0	0.0	0	0.0
Pancreas	(1868)		(1865)		(1934)		(1875)	
Acinar Cell Adenoma	5	0.3	100	5.4	3	0.2	7	0.4
Acinar Cell Carcinoma	0	0.0	5	0.3	0	0.0	0	0.0
Benign Mixed Tumor	0	0.0	1	0.1	0	0.0	0	0.0
Malignant Mixed Tumor	1	0.1	0	0.0	0	0.0	0	0.0
Pancreatic Duct	(1868)		(1865)		(1934)		(1875)	
Adenoma	1	0.1	0	0.0	0	0.0	0	0.0
Endocrine System								
Pancreatic Islets	(1868)		(1865)		(1934)		(1875)	
Islet Cell Adenoma	59	3.2	93	5.0	19	1.0	13	0.7
Islet Cell Carcinoma	39	2.1	31	1.7	5	0.3	3	0.2
Pituitary, Pars Distalis	(1868)		(1898)		(1934)		(1901)	
Adenoma	417	22.8	519	27.3	869	45.2	760	40.0
Carcinoma	42	2.3	38	2.0	72	3.7	53	2.8
Pituitary, Pars Intermedia	(1868)		(1898)		(1934)		(1901)	
Adenoma	3	0.2	6	0.3	2	0.1	3	0.2
Craniopharyngioma	0	0.0	1	0.1	0	0.0	0	0.0
Pituitary, Pars Nervosa	(1868)		(1898)		(1934)		(1901)	
Glioma	0	0.0	0	0.0	2	0.1	0	0.0
Adrenal Cortex	(1915)		(1937)		(1968)		(1940)	
Adenoma	23	1.2	25	1.3	56	2.8	50	2.6
Carcinoma	2	0.1	3	0.2	4	0.2	5	0.3
Adrenal Medulla	(1915)		(1937)		(1968)		(1940)	
Pheochromocytoma	489	25.5	543	28.0	99	5.0	122	6.3
Ganglioneuroma	5	0.3	4	0.2	3	0.2	3	0.2
Thyroid	(1904)		(1909)		(1938)		(1913)	
Follicular Cell Adenoma	13	0.7	18	0.9	12	0.6	17	0.9
Follicular Cell Carcinoma	10	0.5	28	1.5	7	0.4	13	0.7
C–Cell Adenoma	147	7.7	168	8.8	156	8.0	155	8.1
C–Cell Carcinoma	73	3.8	78	4.1	66	3.4	63	3.3
Parathyroid	(1303)		(1405)		(1328)		(1422)	
Adenoma	6	0.5	3	0.2	2	0.2	4	0.3
Hematopoietic System								
All Sites	(1936)		(1949)		(1983)		(1950)	
Mononuclear Cell Leukemia	651	33.6	335	17.1	401	20.2	377	19.3

(continues)

540 PAPPAS

OCT 25 1996

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-511 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 10/6/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4/17/95	4/19/95	4/21/95 (CR1)
AMENDMENT/~~AC~~ AZ	7/31/95	8/2/95	8/8/95 (CR1)
AMENDMENT/BC	8/15/95	8/16/95	8/18/95 (CR1)
AMENDMENT/~~BC~~ NC	2/7/96	2/8/96	2/8/96 (CR2)
AMENDMENT/BC	3/7/96	3/8/96	3/8/96 (CR2)
AMENDMENT/BC	4/2/96	4/3/96	4/3/96 (CR3)
AMENDMENT/~~BC~~ AZ	8/2/96	8/5/96	8/5/96 (CR3)
AMENDMENT/NC	9/6/96	9/12/96	9/18/96 (CR3)
AMENDMENT/BC	9/24/96	9/27/96	10/4/95 (CR3)
AMENDMENT/BC	10/8/96	10/10/96	10/10/96 (CR3)
AMENDMENT/BC	10/18/96	10/21/96	10/21/96 (CR3)

NAME & ADDRESS OF APPLICANT: Chemex Pharmaceuticals, Inc.
One Executive Drive
Fort Lee, NJ 07024

DRUG PRODUCT NAME

Proprietary:	Aphthasol
Nonproprietary/USAN:	amlexanox
Code Names/#'s:	AA-673 & CHX 3673
Chem.Type/Ther.Class:	1 P

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL. CATEGORY/INDICATION: Aphthous ulcers

DOSAGE FORM: Paste

STRENGTHS: 5%

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:
2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano-[2,3-b]-pyridine-3-carboxylic acid; mol. wt. 298.30; empirical formula: 298.30.

see Chemist's Review #1 for structural formula

SUPPORTING DOCUMENTS:
DMF

RELATED DOCUMENTS:
IND IND

Phillip Vincent, HFD-357. This information was also sent to Dr. Vincent on 10/18/96 for review.

3. Phase 4 Commitment: Acceptable

Block Drug Company, Inc. commits to the following information:

* To lower the upper viscosity limits (4,500,000 cps) in the Regulatory Finished Product Specification when more experience has been obtained on the optimum limit from stability studies on full term scale production batches.

* To submit a description of the composition of the laminate sealant used in the Glaminate tube.

In addition, the applicant responded with the following submissions:

Amendment dated 9/24/96:

Methods Validation:

A revised methods validation package was submitted on 9/24/96. These methods were revised per FDA methods guideline information faxed to the firm on 7/30/96. This submission incorporates information originally submitted in Volumes 4.3 and 7.1 to provide a complete, current methods validation package which supersedes Volume 4.3, the original methods validation package. Note: The methods submitted on 9/24/96 supersedes the revised methods submitted on 4/2/96.

AMENDMENT/NC 9/6/96

Labeling:

The applicant submitted a specimen of the carton label for Aphthasol. This labeling was revised to reflect changes to the "Usual Dosage" section of the carton to correspond to the dosage recommendation of the package insert; e.g., "within 10 days". They indicated that the expiration date and lot number will appear on the carton and on the crimp of the tube. From a technical standpoint, nothing has changed; the labeling remains the same.

NDA 20-511
Chemex Pharmaceuticals, Inc.
Amlexanox Oral Paste, 5%

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approved from a manufacturing standpoint. Deficiencies that were part of the approvable letter dated 4/16/96 have been corrected.

Establishment Inspection: The original EER (ID # 8053) for the facilities was found acceptable for CGMPs on 8/14/95. A FUR (ID # 9669) dated 3/11/96 for these facilities remains acceptable (see memo dated 3/12/96 from HFD-324).

Environmental Assessment: Status is pending.

Labeling: Acceptable from a technical standpoint.

Methods Validation: Pending methods validation request; to be initiated.

Ernest G. Pappas 10/22/96
Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-511
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Alam
HFD-160/Hussong
HFD-540/Blay
HFD-540/DeCamp WJ 10/21/96
HFD-830/Sheinin

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: 10/22/96

Between: Sandra M. Wells, Ph.D.
Block Drug Co.

And: Ernest G. Pappas
FDA

Initiated by: FDA

Subject: Amlexanox Oral Paste, 5% (NDA 20-511)

I called Block Drug Co and spoke with Dr. Wells regarding their amendment of 10/8/96. I indicated that numerical designation for Amlexanox Raw Material Specifications (100-703A) was incorrectly stated. I indicated that it does not correspond with the specification sheet number 100N-703B.

Dr. Wells said that specification number 100-703A was not correct and should be 100N-703B. It was their old specification number for Amlexanox. It was changed to 100N-703B when the revised particle size specification implemented. She asked if they needed to submit a new amendment. I said that this will not be necessary because I will cover this with a memo.

Ernest G. Pappas
Reviewing Chemist (HFD-540)

cc: Orig:
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Alum
HFD-540/Blay
HFD-540/De Camp

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: 3/28/96

Between: Richard Bourne, Ph.D.
Block Drug Co.

And: Ernest G. Pappas
Wilson H. De Camp, Ph.D. Wilson H. De Camp, Ph.D. 4/1/96

Initiated by: FDA

Subject: Amlexanox Oral Paste, 5% (NDA 20-511)

We called Block Drug Co and spoke with Dr. Bourne regarding their Methods Validation Package which was submitted in the original application. In this regard, we referred them to items 3 A1- 3 B6 of the table of context. We also requested that they include the MSDS information for the impurities.

This telecon was concluded with the applicant agreeing to submit this information ASAP.

4/1/96 Telecon - We received a call from Dr. Bourne regarding the MSDS information that was requested on 3/28/96. He said that did not have any information on MSDS for these impurities.

We indicated that they needed to provide this information for the safe use by the analyst. The applicant said that we clarified what information that should submitted.

EGP 4/1/96

Ernest G. Pappas
Reviewing Chemist (HFD-540)

cc: Orig:
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Alum
HFD-540/Blay
HFD-540/De Camp

gw 4/2/96

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: 3/22/96

Between: Richard Bourne, Ph.D.
Block Drug Co.

And: Ernest G. Pappas
Roy Blay

Initiated by: FDA

Subject: Amlexanox Oral Paste, 5% (NDA 20-511)

I called Block Drug Co and spoke with Dr. Bourne regarding the upper viscosity limit cps) as reported in the Finished Product Specification as being too high. I indicated that this limit should be lowered as more experience is obtained on the optimum limit from stability studies, on full scale production batches. This is a Phase 4 request and should be submitted via a supplement.

The applicant agreed that these specifications were set high based on preliminary development work. However, they gave the commitment that they will lower the upper viscosity limit cps) as more experience is obtained from stability studies on viscosity measurements on full scale production batches. When they have obtained the optimum upper viscosity limit, they will revise their Regulatory Finished Product Specification accordingly.

This telecon was concluded with the applicant agreeing to submit a supplement post-approval for the above request.

Ernest G. Pappas
Reviewing Chemist (HFD-540)

cc: Orig:
HFD-540/Division File
HFD-540/Pappas EGP 3/22/96
HFD-540/Huene
HFD-540/Alum
HFD-540/Blay
HFD-540/De Camp WDJ 3/24/96
RJB 3/31/96

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-511 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 3/14/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4/17/95	4/19/95	4/21/95
AMENDMENT/AC	7/31/95	8/2/95	8/8/95
AMENDMENT/BC	8/15/95	8/16/95	8/18/95
AMENDMENT/BC	2/7/96	2/8/96	2/8/96
AMENDMENT/BC	3/7/96	3/8/96	3/8/96

NAME & ADDRESS OF APPLICANT: Chemex Pharmaceuticals, Inc.
One Executive Drive
Fort Lee, NJ 07024

DRUG PRODUCT NAME

Proprietary:	Aphthasol
Nonproprietary/USAN:	amlexanox
Code Names/#'s:	AA-673 & CHX 3673
Chem.Type/Ther.Class:	**1 P**

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL. CATEGORY/INDICATION: Aphthous ulcers

DOSAGE FORM: Paste

STRENGTHS: 5%

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:
2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano-[2,3-b]-pyridine-3-carboxylic acid; mol. wt. 298.30; empirical formula: 298.30.

see Chemist's Review #1 for structural formula

SUPPORTING DOCUMENTS:
DMF

RELATED DOCUMENTS:
IND IND

REMARKS/COMMENTS:

The applicant responded on 3/7/96 to the Chemistry deficiencies as conveyed to them on 12/7/95 per facsimile. This response is the result of a informal response submitted by the applicant on 12/21/95 and further discussed with us by telecon on 2/1/96. These chemistry deficiencies, in the areas of Physico-Chemical Characteristics, Drug Substance Specifications, Components and Composition, Manufacturing and Packaging, Drug Product Specifications and Methods, and Stability, were reviewed and found acceptable (see Chemist Review Notes; pg. 4). However, there are some minor deficiencies in the CMCs, most of which can be corrected post approval during Phase 4. The applicant agreed to correct them at that time (see memo of telecon).

Environmental Assessment: The original EA consult was sent to Phil Vincent, Ph.D., (HFD-004) on 6/2/95. This EA consult was completed and returned to HFD-540 with deficiencies (see EA Review from HFD-357 dated 3/12/96).

Labeling: The labeling is approvable from a technical standpoint; FPL should be requested.

Trade Name consult was received from the Labeling and Nomenclature Committee on 10/30/95. The committee found the trade name "Aphthasol" acceptable (see memo dated 10/30/95).

Note: The Committee indicated that "the correct established name is 'Amlexanox Dental Paste' and recommends that the Division (HFD-540) work with the USP regarding this matter".

This reviewer finds the recommendation unacceptable because the intended indication of this product is for treatment of aphthous ulcers. The revision of the established name as recommended by the Committee suggests that the product is a dental paste, which it is not. Therefore, this reviewer's recommendation is Amlexanox Oral Paste. The use of the word "Dental" by the Committee is incorrect. By definition, dental implies "pertaining to a tooth or teeth". It is not applied to gums.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approvable from a manufacturing standpoint. Deficiencies which must be resolved are the submission of an acceptable revision of the EA by the applicant and the correction of inconsistent particle size specifications for the bulk and finished drug. The CSO should request certain

phase IV commitments from the applicant (see Chemist Review Notes; pg. 19).

Establishment Inspection: The original EER (ID # 8053) for the facilities was found acceptable for CGMPs on 8/14/95. A FUR (ID # 9669) dated 3/11/96 for these facilities remains acceptable (see memo dated 3/12/96 from HFD-324); see attached EERs.

Environmental Assessment: The EA was completed and returned to HFD-540 with deficiencies (see attached EA Review from HFD-357 dated 3/12/96). CSO should include these deficiencies in the approvable letter to the applicant.

Labeling: The labeling is approvable; FPL should be requested. The Labeling and Nomenclature Committee found the trade name "Aphthasol" acceptable (see memo dated 10/30/95).

Methods Validation: Methods validation has been deferred. Upon receipt of three copies of sections 3.A.1 through 3.B.6 of the March 7, 1996, submission, plus safety information (MSDS's) for related substances I-IV, the m.v. package will be complete and can be sent to the home district office for assignment.

Ernest G. Pappas 3/27/96
Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-511
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Alam
HFD-160/Hussong
HFD-540/Blay
HFD-540/DeCamp WB 3/27/96
HFD-830/Sheinin

RJW 3/31/96

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-511 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6/7/95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4/17/95	4/19/95	4/21/95
AMENDMENT/AC	7/31/95	8/2/95	8/8/95
	8/15/95	8/16/95	8/18/95

NAME & ADDRESS OF APPLICANT: Chemex Pharmaceuticals, Inc.
One Executive Drive
Fort Lee, NJ 07024

DRUG PRODUCT NAME

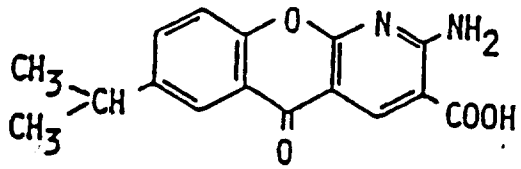
Proprietary:	Aphthasol
Nonproprietary/USAN:	amlexanox
Code Names/#'s:	AA-673 & CHX 3673
Chem.Type/Ther.Class:	1 P

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL.CATEGORY/INDICATION: Aphthous ulcers

DOSAGE FORM: Paste
STRENGTHS: 5%
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano-[2,3-b]-pyridine -3-carboxylic acid; mol. wt. 298.30; empirical formula: 298.30.



$C_{16}H_{14}N_2O_4$

SUPPORTING DOCUMENTS:
DMF

RELATED DOCUMENTS (if applicable):
IND IND

REMARKS/COMMENTS:

The applicant has provided a New Drug Application for Aphthasol (amlexanox) Oral Paste, 5%. for the topical treatment of aphthous ulcers. Amlexanox has been a marketed in Japan as tablets, nasal and ophthalmic solutions for the treatment of bronchial asthma, allergic rhinitis and allergic and vernal conjunctivitis, respectively. This NDA contains a 1P classification. In support of this NDA, the applicant has provided comprehensive information on the chemistry, manufacturing and controls of this drug product. The application also contained draft labeling.

However, even though the CME information was very comprehensive and appeared thorough on its face value, deficiencies were observed in the areas of Physico-Chemical Characteristics, Drug Substance Specifications, Components and Composition, Manufacturing and Packaging, Drug Product Specifications and Methods, Stability and Environmental Assessment. The labeling was reviewed and found acceptable from a technical standpoint.

The applicant responded on 7/11/95 to our telecon (see 6/8/95 memo) with additional information regarding CMC. This information is reviewed in the chemist review. Also, the applicant's amendment of 8/15/95 refers to a meeting held at the San Juan District Office on 8/10/95. This amendment contained additional stability data which corrects data submitted on table 8 for Lot No. H3003. Instead of 4.67% (amlexanox assay) at the 18 month storage station, the data is now reported at 4.97%. This data are found to fall within specifications and does not affect the status of the stability data.

A deficiency was observed in the stability protocol from a microbiological standpoint. This deficiency should be referred to the microbiologist for review (see pg. 50).

Methods validation have not been implemented because of analytical deficiencies. They will be sent to the District Laboratories as soon as the analytical methods are corrected.

Establishment evaluation review was requested 5/5/95 via Cirts. Memo dated 8/14/95 from the Office of Compliance found the firms in compliance with CGMPS (see chemist review (item G, pg. 51). The environmental assessment was sent on 6/1/95 to Dr. Phillip Vincent for review.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 (b)(1) of the Act

CSO should take the appropriate action.

Ernest G. Pappas 9/11/95
Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-511

HFD-540/Division File
HFD-540/Pappas/EGP
HFD-540/Huene
HFD-540/Wedig
HFD-160/Hussong
HFD-540/Holmes
HFD-540/De Camp WL 9/11/95

9/19/95

(486)
Boring

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr Dan Boring, Chair, (HFD-530)

From: Division of Topical Drug Products (HFD-540)

Attention: Ernie Pappas Phone: 827-0880 9/5/95

Date: 9/5/95

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Aphthasol NDA # 20-511
Company Name: Chemex Pharmaceuticals, Inc.

Established name, including dosage form: Amlexanox Oral Paste, 5%*

Other trademarks by the same firm for companion products:
N.A.

Indications for Use (may be a summary if proposed statement is lengthly): Treatment of amphthous ulcers (canker sores)

Initial comments from the submitter (concerns, observations, etc.):

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Sept.95

Subject: consult #486

Consult #486 (HFD-540)
Consult #486 (HFD-540)

HASOL Amlexanox Oral Paste 0.5%

A review revealed no names which sound like or look like the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

D L Boring, Chair

NOTE: The Committee believes the correct established name is "Amlexanox Dental Paste" and recommends that the Division reviewers work with USP regarding this matter.

micro

CONSULTATIVE REVIEW TO HFD-540 SEP 25 1995

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
25 September 1995

A. 1. NDA (20-511)

SPONSOR Chemex Pharmaceuticals, Inc.
Fort Lee Executive Park 1
One Executive Drive
Fort Lee, NJ 07024

2. PRODUCT NAMES: Amlexanox Oral Paste, 5%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A laminated LDPE/aluminum tube with a plastic screw cap closure containing 5 grams of adhesive oral paste for topical application QID directly to aphthous ulcers. Application is to continue for at least 10 days.

4. METHOD(S) OF STERILIZATION: This product is not sterile but is preserved with benzyl alcohol.

5. PHARMACOLOGICAL CATEGORY: Anti-inflammatory and antiallergic agent to promote healing

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: 6 September 1994 (subject of this review)

2. DATE OF AMENDMENTS: 17 April 1995 (RS), 31 July 1995 (AZ) and 15 August 1995 (BC). These are subjects of this review.

3. RELATED DOCUMENTS: E-mail memorandum from Ernest Pappas (21 August 1995) discussing microbiological attributes results which were missing in a Certificate of Analysis, but described in the product specifications.

4. ASSIGNED FOR REVIEW: 26 April 1995

C. REMARKS: This is a non-sterile gel for topical administration. It is preserved with benzyl alcohol.

D. CONCLUSIONS: The application is recommended for approval from the standpoint of microbiological quality.

David Hussong, Ph.D.

PNC 9/25/95

cc:

Original NDA 20-511
HFD-160/Consult File
HFD-5400/CSO/J. Holmes
HFD-540/Chemist/E. Pappas
drafted by: D. Hussong, 09/25/95
R/D initialed by: P. Cooney, 09/25/95

HFD-540

CONSULTATIVE REVIEW TO HFD-540
DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Comments for Filing Meeting
31 May 1995

A. 1. NDA 20-511

SPONSOR Chemex Pharmaceuticals

2. PRODUCT NAMES: Amlexanox Oral Paste (5%)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: An adhesive oral paste provided in 5 gram tubes for topical application QID directly to aphthous ulcers. Application is to continue for at least 10 days.

4. METHOD(S) OF STERILIZATION: None. The product is not sterile.

5. PHARMACOLOGICAL CATEGORY: Anti-inflammatory and antihistamine.

6. DRUG PRIORITY CLASSIFICATION: NA

B. 1. DATE OF INITIAL SUBMISSION: 6 September 1994

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 26 April 1995

C. REMARKS: The date of the filing meeting is 1 June 1995. The product is not sterile. Microbial proliferation is controlled by preservatives % benzyl alcohol). Bioburden specifications include absence of USP defined pathogens, absence of objectionable microorganisms and no more than 500 CFU per gram of product Volume 1.5, page 157). Antimicrobial preservatives effectiveness testing was described in volume 1.5, page 221).

Stability of marketed product will be assessed by a protocol described in volume 1.4, page 269. The methods include benzyl alcohol, preservatives effectiveness, and container and closure integrity. Microbial limits assessments were not noted in the proposed stability protocol. Shelf life of the product is proposed to be 60 months (volume 1.4, pages 266 to 269).

D. CONCLUSIONS: The application is fileable. Minor deficiencies are forthcoming.

5/31/95

David Hussong, Ph.D.

5/31/95

cc:

Original NDA 20-511
HFD-160/Consult File
HFD-540/CSO/J. Holmes
drafted by: D. Hussong, 05/31/95
R/D initialed by: P. Cooney, 05/31/95

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS. —

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Chemex Pharmaceuticals, Inc.	April 17, 1995
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
One Executive Drive Fort Lee, NJ 07024	(201) 944-1449
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	20-511

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Amlexanox Oral Paste, 5%	AphthasolTM

CODE NAME *(If any)*	CHEMICAL NAME
AA-673 CHX 3673	2-amino-7-isopropyl-5-oxo-5H[1]benzopyrano-[2,3-b]-pyridine-3-carboxylic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Oral paste	Topical	5%

PROPOSED INDICATIONS FOR USE

Aphthous ulcers

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 19 1995
HFD-520

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND
IND

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☒ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Martha R. Charney, Ph.D. Vice President, Regulatory Affairs	M. Charney /A. Richardson	4/17/95

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
1 Executive Drive Fort Lee, NJ 07024	Phone (201)944-1449 Fax: (201)944-9474

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

FORM FDA 356h (10/93)

EA + Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-511

APHTHASOL™

(amlexanox)

ORAL PASTE, 5%

Division of Dermatologic and Dental Drug Products

(HFD-540)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

APHTHASOL™

(amlexanox)

Oral Paste, 5%

NDA 20-511

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for APHTHASOL™ Oral Paste, 5%, Block Drug has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Amlexanox is a chemically synthesized drug which is administered as an oral paste in the treatment of aphthous ulcers in immunocompetent individuals. The drug substance is manufactured by Takeda Chemical Industries, Ltd., Hikari, Japan. The drug product is produced and packaged at Reedco, Inc., Humacao, Puerto Rico. The finished drug product will be used in residences throughout the United States.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Rejected or returned drug product will be disposed of at a licensed landfill or to a permitted incinerator for destruction. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are

expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

10.25.96
DATE

Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

10/28/96
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

HFD-540/R. Blay copy to NDA 20-511
HFD-357/FONSI File 20511
HFD-357/Docket File
HFD-205/FOI COPY

FOIA COPY OF EA FOR NDA 20-511 AS AMENDED 10/25/96

ENVIRONMENTAL ASSESSMENT

AMLEXANOX

Amlexanox Environmental Assessment Summary

1. Date: August 1, 1996

2. Name of Applicant: Block Drug Company, Inc.

3. Address: 257 Cornelison Avenue, Jersey City, NJ, 07302

4. Description of Proposed Action

   a. Requested Approval: Chemex Pharmaceuticals, Inc. has filed an NDA (20-511) pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for an oral paste formulation containing 5% amlexanox, packaged in 5 gram glaminate tubes. An Abbreviated Environmental Assessment (AEA) has been submitted pursuant to 21 CFR 25.31a(b)(3) on the basis that 5% amlexanox oral paste is intended for topical application.

   b. Need for Action: Amlexanox oral paste, 5%, is intended to be used for the treatment of aphthous ulcers in immunocompetent individuals.

   c. Production Locations: Proprietary intermediates are not used in the production of the drug substance. Amlexanox will be synthesized by
   The drug product, 5% amlexanox will be produced and packaged at Reedco, Inc. (a subsidiary of Block Drug Company, Inc.) in Humacao, Puerto Rico. See Confidential Appendices A for the complete addresses of manufacturing facilities and a description of the type of environment at and near these production locations.

   d. Locations of Use: Product distribution will be throughout the United States. Product use will be in residences throughout the United States.

   e. Disposal Sites: Amlexanox product returns will be managed at:

   Block Drug Company, Inc.
   2149 Harbor Avenue
   Memphis, TN 38113

   Block Drug Company, Inc.
   131 Docks Corner Road
   Dayton, NJ 08810

   Products returns will be disposed of through the Memphis, TN site.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

   a. Nomenclature

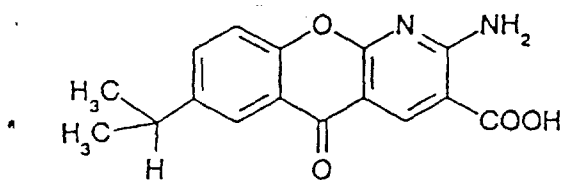
i. Established Name: Amlexanox
ii. Brand/Proprietary Name: Amlexanox
iii. Chemical Name: 2-Amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-*b*]-pyridine-3-carboxylic acid

b. Chemical Abstracts Service (CAS) registration number: CAS: 68302-57-8

c. Molecular Formula: $C_{16}H_{14}N_2O_4$

d. Molecular Weight: 298.30

e. Structural (graphic) Formula:



Amlexanox

f. Physical Description: White crystalline powder

g. Solubility: Freely soluble in dimethyl sulfoxide. Soluble in N,N-dimethylformamide. Slightly soluble in tetrahydrofuran or dioxane. Very slightly soluble in methanol, ethanol, acetone, ethyl acetate, ethyl ether or chloroform. Practically insoluble in water, acetonitrile or hexane.

h. Melting Point: No definite melting or decomposition observed at temperatures up to 320°C.

i. Drug Product: -

Active Ingredient: Amlexanox 5%

Inactive Ingredients: Mineral Oil, USP
Gelatin, NF
Pectin, USP
Glyceryl monostearate, NF
White petrolatum, USP
Carboxymethylcellulose sodium,
Carboxymethylcellulose sodium,
Benzyl alcohol, NF

j. Impurities: No impurities are found in the drug substance at a level greater than 1%.

k. See Non-Confidential Appendices for Amlexanox MSDS

6. Introduction of Substances into the Environment

a. Substances Expected to be Emitted:

Filtrates and washings as well as spent activated charcoal are generated during synthesis.

Reedco, Inc.

Amlexanox will be made by mixing together the ingredients listed above. No chemical reactions occur, and the mixing vessel is not vented to the outdoors. Therefore, no adverse impact to air quality from Amlexanox manufacturing activities is anticipated, and no air permit is required for this process.

Washwaters from periodic cleaning of the weighing, mixing, sieving, conveying and filling equipment may contain sanitizer, detergent and small amounts of Amlexanox.

All Amlexanox paste raw material storage, manufacturing activities and finished goods storage will take place indoors, with no discharges to the storm sewer. Therefore, no adverse impact to storm water quality from Amlexanox manufacturing activities is anticipated. Stormwater discharges are permitted under EPA "Chemical Specialties Manufacturers Association" group permit #619. As a delegated state, Puerto Rico has recently promulgated permitting requirements and pollution prevention regulations for stormwater discharges under the jurisdiction of the Environmental Quality Board. The facility submitted a Notice of Intent in accordance with the requirements on March 29, 1996 and will continue with the permitting process as required.

Returned goods, discarded packing, and small amounts of product will comprise the solid waste generated from this operation. Returned goods then will be sent to a fully permitted landfill or to a fully permitted incinerator for destruction, thereby reducing the volume of waste.

b. Controls Exercised

Filtrates and washings generated during synthesis are collected, neutralized, and the ethanol is recovered by distillation. The residue from distillation is transferred to a pit for treatment of materials with high chemical oxygen demand (COD). Throughout the plant, factory effluent is thoroughly checked by every manufacturing department. The effluent from each area is gathered in the environmental protection facilities and treated scrupulously in compliance with environmental regulations.

Spent activated charcoal is incinerated in a special incinerator which removes sulfur oxides and nitrogen oxides.

Reedco, Inc.

Amlexanox will be made by mixing together the ingredients listed above. No chemical reactions occur, and the mixing vessel is not vented to the outdoors. A dust collector dedicated to the mixing vessel will be utilized to control dust when raw materials are added. Air from the dust collector is filtered and returned to the processing room via the supply air plenum. Therefore, no adverse impact to air quality from Amlexanox manufacturing activities is anticipated, and no air permit is required for the production of Amlexanox. However, the facility is covered by permit PFE-LC-36-0295-D193-I-II-0, issued on February 16, 1995 with an expiration date of February 16, 2000.

The only wastewater that will be generated is washwater from the cleaning and sanitizing of the mixing vessel and the associated equipment. Washwaters will drain to the wastewater sewer, where they will combine with other manufacturing wastewaters. Wastewaters are discharged to the Puerto Rico Aqueduct and Sewerage Authority (PRASA), in accordance with PRASA permit no. GDA-91-607-062 which was issued on March 1, 1996 and has no expiration date. At low concentrations, Amlexanox is expected to be fully biodegraded in the PRASA wastewater treatment plant.

Rejected, expired, or waste drug product will be returned to Block Drug Company, Inc. facilities in Memphis, TN and Dayton, NJ. Returned drug product will then be sent to a fully permitted landfill or to a fully permitted incinerator for destruction, thereby reducing the volume of waste. The Company currently utilizes Laidlaw Environmental Services to incinerate returned goods. Waste materials from our Memphis location generally are sent to the Laidlaw facility in Clive, Utah (EPA ID # USD982595795). However, the Company must have the flexibility to utilize other incineration facilities should the need arise. Circumstances such as the Laidlaw incinerator being down for maintenance or even simply our perception that Laidlaw's environmental performance standards are not high enough are reasons to utilize other facilities. Therefore, Block Drug

Company, Inc. will utilize other incineration facilities that have been audited and approved by the Corporate Environmental, Health and Safety Group.

Any discarded Amlexanox and/or packaging are non-hazardous industrial waste, and will be disposed of from Reedco by landfilling with other plant non-hazardous industrial waste. No change in environmental impact is expected.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Emission standards that apply to operation: Japanese local and national regulations would apply to the plant.

Statement of compliance: See attached statement in Document a-16-566.

Reedco, Inc.

Federal, state and local emission standards expected to apply to the operation:

Air - Puerto Rico Environmental Quality Board,"Regulation for the Control of Atmospheric Pollution."

Water - 40 CFR Parts 122 and 403 general Pretreatment and National Pollutant Discharge Elimination System

OSHA - 29 CFR Part 1910

Waste - 40 CFR Chapter I, Subchapter I and Puerto Rico Environmental Quality Board, "Regulations for the Control of Hazardous and Non-Hazardous Solid Wastes."

Statement of compliance: This operation will comply with all applicable federal, state, and local environmental, safety, and industrial hygiene regulations.

d. Effect of Proposed Action

See Confidential Appendices for Effect of Proposed Action

7-11. Pursuant to 21 CFR 25.31a(b)(3)(ii), documentation for items 7 through 11 are not required. Item 14 (References) of 21 CFR 25.31a is not applicable. Item 15 of 21 CFR 25.31a is also not required.

12. List of Preparers:

Christian S. Berry
Director Environmental and Safety Engineering
Block Drug Company, Inc.

8-1-96
Date

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist
Block Drug Company, Inc.

8/1/96
Date

Angela M. Licata, M.S.
R&D Toxicologist
Block Drug Company, Inc.

8/1/96
Date

13. Certification

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of Block Drug Company, Inc.

Richard K. Bourne, Ph.D.
Vice President, Regulatory Affairs
Block Drug Company, Inc.

August 1, 1996
Date

14. References

None

15. Appendices

Non-Confidential Appendices
Amlexanox drug substance MSDS

Confidential Appendices

Addresses of manufacturing facilities

Document No. A-16-566, Statement of Environmental Protection,

Solubilities and Partition coefficients of Amlexanox

Effect of Proposed Action

Non-Confidential Appendices

Pharmaceutical Production Division
TAKEDA CHEMICAL INDUSTRIES, LTD

NO. A-16-611

DOCUMENT DATA SHEET

Title : Material Safety Data Sheet of AA-673

Document No. : A-16-611

☑ Original ☐ Revision

Supersedes : N / A (not applicable)

Use : Information for drug handling

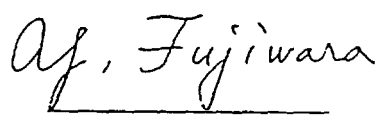
Reason for Revision : N / A

Pharmaceutical Production Division
TAKEDA CHEMICAL INDUSTRIES, LTD.

NO. A-16-611

Material Safety Data Sheet of

AA-673



Yoshitaka Fujiwara

Senior Research Head

Chemical Development Laboratories

Pharmaceutical Production Division

April, 1996

Pharmaceutical Production Division
TAKEDA CHEMICAL INDUSTRIES, LTD.

NO. A-16-611

Material Safety Data Sheet

product : AA-673
Internal ID : AA-673
Date : April, 1996

Section Ⅰ... Material Identification

Trade / Material Name : Amlexanox
Description :
Other Designation :
CAS : [68302-57-8]
Chemical name : 2-Amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b]-pyridine-3-carboxylic acid
Manufacturer :
Name : Pharmaceutical Production Division, Takeda Chemical Industries, Ltd.
Address : 17-85, Juso-honmachi 2-chome, Yodogawa-Ku Osaka, 532, Japan

Section Ⅱ... Ingredient and Hazards

Ingredient Name : AA-673
Percent : 100 %
Exposure Limits : ———

Section Ⅲ... Physical Data

Appearance and Odor : White crystalline powder and Odorless
Boiling Point : ———
Water Solubility : 0.005 mg / ml at 25°C
pH : ———
Evaporation Rate : ———

Specific Gravity : ———
Melting Point : >320°C
% Volatile by Volume : ———
Molecular Weight : 298.30

Section Ⅳ... Fire and Explosion Data

Flash Point : ———
Extinguish Media : Water Spray, Dry Chemical, CO_2
Autoignition Temperature : no data
Unusual fire or explosion hazard : This material, like most organic materials, in powder form is capable of creating a dust explosion.
Specific fire-fighting procedures : Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.

Section Ⅴ... Reactivity Data

Chemical Incompatibilities : Strong bases, Strong acids
Conditions to avoid : High temperature, Light
Hazardous Decomposition Products : As with any other organic material, combustion will produce carbon dioxide and probably carbon monooxide.

Section Ⅵ... Health Hazard Information

Summary of Risks : Sensitization potential
Delayed contact hypersensitivity assey ; Positive
- Prevent direct contact with skin and eyes.
- Equipment to be used when handling : Gloves, Dust mask, Goggles. Use appropriate air-line suit at large scale handling where dusting occurs.

Medical conditions which may be aggravated by contact : Skin rash
Target organs : Liver, Stomach, Cecum

Primary entry Route(s) : Oral
Acute Effects : No specific change
Subacute and chronic changes : Increase in plasma ALP level, inflammation of bile duct, thickening of mucosa and dilatation of gland in glandular stomach, hypertrophy and desquamation of epithelium in cecum (rat). Increases in plasma ALP, GOT, GPT, OCT and total cholesterol level, proliferation of bile ductule, atrophy or degeneration of hepatocyte (dog).
Reproduction : No abnormality
Mutagenicity : None
Carcinogenicity : None

Signs and symptoms of overexposure

Eye contact : May be cause irritation.
Skin contact : May be cause irritation.
Inhalation : May be harmful.
Ingestion : May be harmful.

First aid

Eye contact : Immediately flush with plenty of water for at least 15 min and get medical attention.
Skin contact : Immediately wash skin with soap and plenty of water.
Inhalation : Asymptomatic therapy. Artificial respiration if necessary.
Ingestion : Same as above

Section Ⅶ... Spill, Leak and Disposal Procedures

Spill / Leak Procedures : Thoroughly collect the material, wash the area with water and detergent and collect the washing solution.

Waste management / Disposal :

- Small quantities : Incineration
- Large quantities : Chemical recycling or incineration

NDA 20-511

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.
One Executive Drive
Fort Lee, NJ 07024

SEP 28 [illegible]

Dear Dr. Charney:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug or Product: amlexanox oral paste, 5%

Date of Application: September 6, 1994

Date of Receipt: September 7, 1994

Our Reference Number: NDA 20-511

Unless we find the application not acceptable for filing, the filing date will be November 6, 1994.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact:

Joanne M. Holmes
Project Manager
(301) 594-4877

Sincerely yours,

Maria Rossana R. Cook
Supervisor, Project Management Staff
Division of Topical Drug Products
Office of Drug Evaluation and Research II
Center for Drug Evaluation and Research

cc:
ORIG. NDA 20-511
HFD-82
HFD-540

HFD-540/SMO/Chambers
HFD-540/MO/Toombs
HFD-540/SChem/DeCamp
HFD-540/SPharm/Alam
HFD-540/Pharm/Mainigi
HFD-520/SMicro/Sheldon
HFD-426/SBiopharm/Pelsor
HFD-713/SBiostat/Harkins
HFD-713/Biostat/Turney
HFD-540/SPMS/Cook
HFD-540/PMS/Holmes
Acknowledgement

NDA 20-511

Martha R. Charney, Ph. D.
Vice-President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.
One Executive Drive
Fort Lee, NJ 07024

NOV 3 1994

Dear Dr. Charney:

Please refer to your September 6, 1994 new drug application (NDA) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for amlexanox oral paste, 5%.

We have given your NDA a preliminary review, and we find it is not sufficiently complete to merit a critical medical and technical review. Thus, it will not be filed as a new drug application within the meaning of section 505 (b) of the Act.

We are refusing to file this NDA under 21 CFR 314.101 (d) (3) for the following reason:

> It does not on its face contain information required under section 505 (b) (1) (d) of the Act, that is, because the facility identified in the application as the site for production of the drug substance is not ready for inspection by FDA investigators for compliance with current good manufacturing practice regulations.
>
> This application is designated to be of a priority therapeutic benefit. Therefore, facilities for manufacture of the drug product and drug substance must be ready for inspection at the time of the resubmission of the NDA.

Although not required for the initiation of a substantive review, the following should be submitted:

1. A statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR.

2. The required Fraud Policy notice.

3. Copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing with all non-English package inserts been translated.

4. A statement that the integrated summary of safety includes all safety data for this product of which the applicant is aware, from all sources, domestic and foreign, including the cut-off date for the preparation of the ISS.

5. A statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical. If they are not identical, a letter to the archival NDA that specifies distinctly all of the differences in the two submissions.

6. A separate methods validation package should be submitted, as per CDER guidelines.

7. Demographic, baseline disease, and efficacy analysis tables by center.

8. Since the formulation to be marketed differs from the formulation used in the toxicology studies, the applicant should reconsider repeating the studies using the to-be-marketed product. If the studies will not be repeated, it is necessary to provide justification as to why such repetition should not be required.

9. The proposed labeling sections relative to pharmacology must be appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 21 CFR 201.57.

10. A statement that the pharmacology/toxocology studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference. If you have any questions please call:

Joanne Holmes
Project Manager
(301) 594-6627

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101 (c). If you do so, the application shall be filed over protest under 21 CFR 314.101 (b). The filing date will be 60 days after the date you requested the informal conference.

Under the Prescription Drug User Fee Act of 1992, FDA will refund one-half of the fee submitted with the application (25% of the total fee due). If you decide to file the application over protest, the filing of the application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original IND
HFD-540
HFD-540/CHEM/Pappas 11/3/94
HFD-520/MICRO/Utrup 11/3/94
HFD-540/PHARM/Mainigi
HFD-540/MO/Toombs
HFD-540/DIV DIR/Wilkin 11/3/94
HFD-540/PROJ MGR/Holmes

REFUSE TO FILE

HFD-713/Stat/Turney
HFD-496/Biopharm/Lee

Concurrence:
HFD-540/CHEM SUPV/DeCamp 11/3/94
HFD-520/MICRO SUPV/Sheldon 11/3/94
HFD-540/PHARM SUPV/Alam 11/3/94
HFD-540/MO SUPV/Chambers
HFD-540/PROJ MGT SUPV/Cook

HFD-713/Supv Stat/Hankins 11-3-94
HFD-496/Biopharm Supv/Pelsor

RECORD OF A TELEPHONE CONVERSATION

DATE: November 4, 1994

TO: Dr. Van Inwegen
Dr. Khandwala
Chemex Pharmaceuticals, Inc.

SUBJECT: Refuse to File

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

Dr. Van Inwegen was informed that this NDA was Refused to File and that a copy of the letter would be transmitted by telefacsimile to Chemex possibly on November 7, 1994. When he requested the reason for the Refuse to File, he was told that the issue was that the facility for the manufacture of the bulk drug substance was not ready for inspection. He then informed the project manager that Chemex had discussed this particular issue with members of FDA and conflicting advice was given. Allegedly, a senior member of FDA management had informed Chemex that submitting the NDA with manufacturing facilities that were not yet ready for inspection was acceptable.

The project manager asked Dr Van Inwegen if it were possible to learn which individual at FDA gave Chemex the information regarding the readiness of manufacturing facilities. He responded that he would look into the matter and call the project manager back later in the day.

Dr. Van Inwegen expressed the following two concerns:

1. If the application is resubmitted, will Chemex have to start at the very beginning of the process and pay another user fee.

The project manager responded by informing him that regarding fees, information would be provided in the letter.

2. If it is possible to make some changes such that the facility could be ready for inspection earlier, at what point must it be ready relative to the date of submission.

The project manager responded by informing him that it has been a policy that applications considered to be of a priority therapeutic benefit must have all facilities ready for inspection at the time of submission.

This conversation ended amicably.

Subsequent to the above conversation, the project manager was called by Dr. Khandwala, who reiterated concern over the user fee and that he felt the manufacturing facility was a GMP issue and not a fileablility issue.

The project manager informed him that the purpose of the original call was simply to inform the applicant of the Refuse to File status, and that Chemex may initiate their response after receipt of the Refuse to File letter.

Dr. Khandwala requested permission to speak with the Division Director before the letter is sent by telefacsimile. He was informed that while the project manager was unsure whether that was possible, she would look into the matter.

He then asked what was meant by standard and priority therapeutic benefit and was told that the definition is based on important therapeutic characteristics. The project manager then repeated what had been told to Dr. Van Inwegen regarding when facilities should be ready for these types of drugs.

This conversation also ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-540/CHEM SUPV/DeCamp
HFD-520/MICRO/Utrup
HFD-520/MICRO SUPV/Sheldon
HFD-540/PHARM/Mainigi
HFD-540/PHARM SUPV/Alam
HFD-713/BIOSTAT/Turney
HFD-713/BIOSTAT SUPV/Harkins
HFD-426/BIOPHARM/Ette
HFD-426/BIOPHARM SUPV/Pelsor
HFD-540/MO/Toombs
HFD-540/MO SUPV/Chambers
HFD-540/DIV DIR/Wilkin
HFD-54/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes

11/7/94

Cook

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

November 7, 1994

Food and Drug Administration
Rockville MD 20857

Atul Khandwala, Ph.D.
Executive Vice President
Chemex Pharmaceuticals, Inc.
One Executive Drive
Ft. Lee, New Jersey 07024

SENT BY FACSIMILE AND BY POST

Dear Dr. Khandwala,

In her absence, I am responding to your November 4, 1994 facsimile to Dr. Woodcock. As you are aware, under the performance goals associated with the Prescription Drugs User Fee Act of 1992 (PDUFA), the Center for Drugs must perform complete reviews and act upon applications within specific time frames. At the present time, a complete action includes having completed the required inspections of the facilities used in the manufacture of the proposed product.

In order to be able to meet the time frames to which the Agency has committed under PDUFA, the Center requires: (1) that the facilities used in the manufacture of the product that is the subject of a priority review application be ready for inspection at the time of submission of the application and (2) that the facilities used in the manufacture of the product that is the subject of a standard review application be ready for inspection by month four (4) of the 12 month original review cycle. Without such readiness on the part of sponsors for inspections, the chances of the Center meeting its performance goal on an application become quite slim.

In the case of NDA 20-511, it is my understanding that at the time of submission of this priority application that your bulk drug facilities were not going to be ready for inspection until seven months later (filed in September 1994 and ready for inspection in April 1995). This is a facial omission from the application that would clearly keep us from meeting either a priority or a standard review performance goal. Because of this facial omission, the application was refused filing.

I hope this explanation clarifies the Center perspective on this issue. Please feel free to let me, Dr. Wilkin, or Dr. Bilstad know if you have any further questions on this matter.

Yours sincerely,

Murray M. Lumpkin

Murray M. Lumpkin, M.D.
Deputy Center Director for Review Management
Center for Drug Evaluation and Research
Food and Drug Administration

cc: JWoodcock
JAxelrad
JBilstad
JWilkin
RCook

RECORD OF A TELEPHONE CONVERSATION

DATE: November 9, 1994

TO: Dr. Khandwala, Ph.D.
Executive Vice President
Chemex Pharmaceuticals, Inc.
(201) 944-1449

FROM: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Refuse to File

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

The project manager called Dr. Khandwala in order to return his earlier call. He acknowledged that Chemex had received a response from Dr. Lumpkin regarding the letter they had sent by telefacsimile to Dr. Woodcock's office regarding this division's Refuse to File of NDA 20-511. In the letter, Dr. Lumpkin explained the CDER policy on the readiness of facilities for inspection relative to the submission of an NDA.

He then had three further questions:

1. What is the difference in review time for a drug of priority therapeutic benefit vs. one of standard benefit. He was told the first is less than 12 months, the second is 12.

2. He asked whether the priority status of amlexanox can be changed from priority to standard so that it can be resubmitted December 1, 1994. He was told that the project manager would inquire.

3. He asked whether amlexanox will still have priority status if it is resubmitted April 1, 1995. Again, the project manager told him she would inquire.

The conversation ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas

HFD-540/CHEM SUPV/DeCamp
HFD-520/MICRO/Utrup
HFD-520/MICRO SUPV/Sheldon
HFD-540/PHARM/Mainigi
HFD-540/PHARM SUPV/Alam
HFD-713/BIOSTAT/Turney
HFD-713/BIOSTAT SUPV/Harkins
HFD-426/BIOPHARM/Ette
HFD-426/BIOPHARM SUPV/Pelsor
HFD-540/MO/Toombs
HFD-540/MO SUPV/Chambers
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes

sent 12/2/94
jh 11/10/94

RECORD OF A TELEPHONE CONVERSATION

DATE: November 10, 1994

TO: Dr. Khandwala, Ph.D.
Executive Vice President
Chemex Pharmaceuticals, Inc.
(201) 944-1449

FROM: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Resubmitting an NDA after a Refuse to File

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

The project manager reconfirmed with Dr. Khandwala that Chemex had received a response letter from Dr. Lumpkin regarding the Refuse to File of NDA 20-511. Dr. Khandwala was then informed that if he had any outstanding concerns on the Refuse to File issue, they should be officially submitted in writing to NDA 20-511.

He was then provided with the answers to his previous questions.

1. Can the status of amlexanox be changed from priority to standard so that it may be resubmitted December 1, 1994? He was told no, it can not at this point in time.

2. Will amlexanox retain priority status if it is resubmitted April 1, 1995? The therapeutic benefit status will be evaluated at the time of submission. Whether it is of a priority or a standard benefit will depend on the characteristics of amlexanox as compared to the characteristics of any other products that are marketed during the interim.

Dr. Khandwala then asked whether the application will require another 60 day review period for fileability, since it has already had that during this submission. He was informed by Rosemary Cook that is the standard procedure.

He then inquired as to whether the application may be submitted February 1, 1995, because the inspection sites would then be ready by the time of filing. Ms. Cook directed him to reread the Refuse to File letter and the letter form Dr. Lumpkin, both of which clearly state the Center's policy on this matter.

Dr. Khandwala then stated that perhaps Chemex will submit some concerns in writing to the NDA.

The conversation ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-540/CHEM SUPV/DeCamp
HFD-520/MICRO/Utrup
HFD-520/MICRO SUPV/Sheldon
HFD-540/PHARM/Mainigi
HFD-540/PHARM SUPV/Alam
HFD-713/BIOSTAT/Turney
HFD-713/BIOSTAT SUPV/Harkins
HFD-426/BIOPHARM/Ette
HFD-426/BIOPHARM SUPV/Pelsor
HFD-540/MO/Toombs
HFD-540/MO SUPV/Chambers
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes

memo in 54
11/10/94

FDA Corres.

RECORD OF A TELEPHONE CONVERSATION

DATE: November 22, 1994

TO: Martha Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.
(201) 944-1449

FROM: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: To answer questions in the applicant's November 10, 1994 letter and November 22, 1994 fax

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

First Dr. Charney and the project manager addressed the questions listed in the applicant's fax of November 22, 1994.

1. Dr. Charney was given Tom Hassall's name and telephone number and was told to call him regarding the refund of the user fee.

2. Dr. Charney was informed that this NDA will retain number 20-511 when it is resubmitted.

3. She was informed that FDA retains the NDA rather than return it to the applicant. Thus, only new information needs to be submitted.

Next the project manager and Dr. Charney addressed the issues in Chemex's letter dated November 10, 1994.

1. This issue required reviewing the 10 deficiencies listed in the Refuse to File letter dated November 3, 1994.

    a. Chemex will provide a statement declaring that their studies were conducted according to the IRB/Declaration of Helsinki. Because some studies were conducted in Japan, Dr. Charney stated that this was an issue that Chemex would like to address in a meeting with FDA.

b. Chemex will provide a statement addressing the Fraud Policy.

c. Dr. Charney clarified that amlexanox oral paste, 5% is not marketed outside of the U.S., although other dosage forms of amlexanox are marketed in Japan. She will include a statement to that effect upon resubmission. She also stated that translated package inserts from the products marketed in Japan were included in the NDA.

d. Chemex will include a statement that the integrated summary of safety includes all safety data of which the company is aware, both domestic and foreign, and a cut-off date for the summary.

e. Dr. Charney remarked that the statement that the text, tables, and data in the CANDA and archival hardcopy NDA are identical may have been submitted with the diskettes. However, Chemex will resubmit this statement, especially if new diskettes are required.

f. Dr. Charney had thought that the methods validation package was submitted with samples. She will speak to the reviewing chemist on this.

g. The statistician at Chemex will analyze the demographic, baseline disease, and efficacy tables by center. Chemex may submit a sample table first.

h. The project manager asked Dr. Charney to provide justification as to why Chemex felt it unnecessary to repeat toxicology studies using the to-be-marketed formulation. Dr. Charney responded that this was an issue that Chemex would like to address in a meeting with FDA.

i. Chemex will convert the proposed labeling sections relative to pharmacology from mg/kg to mg/m^2.

j. Chemex will submit a statement that the pharmacology/toxicology studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns.

2. Dr. Charney was informed that the CMC section, if submitted early, should be complete.

3. Dr. Charney was informed she should consult with Tom Hassall regarding a reduced user fee.

The project manager informed Dr. Charney that no meeting between this division and Chemex had yet been scheduled. Dr. Charney stated that she would discuss the above issues with Dr. Khandwala and they will decide whether to request a meeting. She will send a letter on this in the coming week.

The conversation ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-540/CHEM SUPV/DeCamp
HFD-520/MICRO/Utrup
HFD-520/MICRO SUPV/Sheldon
HFD-540/PHARM/Mainigi
HFD-540/PHARM SUPV/Alam
HFD-713/BIOSTAT/Turney
HFD-713/BIOSTAT SUPV/Harkins
HFD-426/BIOPHARM/Ette
HFD-426/BIOPHARM SUPV/Pelsor
HFD-540/MO/Toombs
HFD-540/MO SUPV/Chambers
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes

Dwhe 11-30-94
12/1/94

NDA 20-511

Chemex Pharmaceuticals, Inc.
Attention: Martha Charney
One Executive Drive
Fort Lee, NJ 07024

APR 24 [illegible]

Dear Dr. Charney:

We have received your new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Amlexanox oral paste, 5%

Therapeutic Classification: Priority

Date of resubmitted Application: April 17, 1995

Date of Receipt: April 19, 1995

Our Reference Number: 20-511

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 18, 1995, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Joanne Holmes, M.B.A.
Project Manager
Telephone: (301) 594-3939

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-511
HFD-540/Div. Files
HFD-80
HFD-540/CSO/J.Holmes 4/21/95

drafted: jh/April 21, 1995/NDA 20-511
Final:

ACKNOWLEDGEMENT (AC)

cc:
HFD-540/~~Rappaport~~ Chem/Pappas
HFD-540/mo/Toombs
HFD-540/PH/Mainigi
HFD-426/Bioph/EHe
HFD-713/Stat/Turney
HFD-520/~~Sheldo~~ Micro/Sheldon

RECORD OF A TELEPHONE CONVERSATION

DATE: June 7, 1995

TO: Dr. Martha Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.
(201) 944-1449

FROM: Ms. Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Fileability of the NDA and request for information

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

Ms. Holmes informed Dr. Charney that the NDA is fileable. She also requested further clarification of the term "dab," which is the suggested dose on the proposed label. Specifically, the pharmacologist wanted to know what a dab corresponds to in relation to the doses used in the preclinical studies. Dr. Charney was asked to provide information on the weight or volume of the amount of paste needed to cover a typical lesion, or the largest dab to be used per person.

She responded that in one of the appendices to the clinical section, there are data showing the weights of the tubes of product both before and after the patient applied the drug, with the average amounts of drug applied. This was obtained in order to provide an idea of the upper limit of general usage of the product. However, she will speak with the clinical staff in order to correlate the maximum dosage a person would apply to the animal data. She will also verify the location of the data on the tube weights and inform Ms. Holmes next week of that information.

The conversation ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-540/CHEM SUPV/DeCamp
HFD-160/MICRO/Hussong
HFD-540/PHARM/Wedig

HFD-713/BIOSTAT/Turney
HFD-426/BIOPHARM/Ette

HFD-540/MO/Huene
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes 6/7/95

RECORD OF A TELEPHONE CONVERSATION

DATE: June 13, 1995

TO: Martha Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.
(201) 944-1449

FROM: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Request for information for the Environmental Assessment

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

Ms. Holmes informed Dr. Charney that a letter from the Japanese government must be obtained. This letter must state that the Japanese manufacturing facility is in compliance with that country's environmental laws. It must also specify the name of the drug being manufactured, amlexanox. If the letter is not in English, a certified translation must also be submitted.

The conversation ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-160/MICRO /Hussong
HFD-540/PHARM/Wedig
HFD-713/BIOSTAT/Turney
HFD-426/BIOPHARM/Ette
HFD-540/MO/Huene
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes 6/15/95

RECORD OF A TELEPHONE CONVERSATION

DATE: July 14, 1995

TO: Martha Charney, Ph.D.
Vice President, Regulatory Affairs
Chemex Pharmaceuticals, Inc.
(201) 944-1449
(201)-944-9474 fax

FROM: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Questions from the Reviewing Medical Officer

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Chemex Pharmaceuticals, Inc.

Ms. Holmes informed Dr. Charney that some questions from the Reviewing Medical Officer would be sent to her via telefacsimile.

These questions are attached.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-160/MICRO /Hussong
HFD-540/PHARM/Wedig
HFD-713/BIOSTAT/Turney
HFD-426/BIOPHARM/Ette
HFD-540/MO/Huene
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes JH 8/2/95

Dr. Charney -

I have the following questions concerning your study # 107, which also apply to study 106. The questions on tabulations of ulcer healing also apply to those on resolution of pain.

1. In the tables on time to first occurrence of ulcer healing and to complete pain relief, do the p values provided represent those for the median time to heal or for the cumulative percent healed?

2. In the group of evaluable patients - that is, with the exclusion of the protocol violators and the patients that were discontinued prematurely - it appears that there should be 194 patients in the Amlexanox group and 190 patients in the vehicle group. Table 9.2 correlates with this, listing 194 Amlexanox patients and 191 vehicle patients. The other tables, however list other denominators. For example, Table 11a2. has 197 Amlexanox patients and 194 vehicle patients at day 7. Table 12.2 has the number of patients at risk as 198 in the Amlexanox group and 195 in the vehicle group.

3. In the table on ulcer healing - time to first occurrence (table 12.2), why do the numbers differ from those in the table on percent healed on each day (Table 11a2.)? For example on day 7 under table 11a2. the % healed is 68.5% in the Amlexanox group and 53.6% in the vehicle group, while in table 12.2 the % healed at day 7 is 69.1% in the Amlexanox group and 54.1% in the vehicle group.

4. What is the difference between what is designated as the percent of patients with healed ulcers and the cumulative percent of patients with healed ulcers - these are reported as two separate efficacy parameters. Also, why is the cumulative percent healed reported as an estimated percent rather than an actual percent?

Phyllis A. Hauck

RECORD OF A TELEPHONE CONVERSATION

DATE: October 18, 1995

TO: Atul Khandwala, Ph.D., Vice President, Rx Pharmaceutical Products, Research and Development
Richard Bourne
Block Drug Company, Inc.
(201) 434-3000, ext 1422

FROM: Jonathan Wilkin, MD, Division Director
Joanne Holmes, Project Manager
Rosemary Cook, Supervisory Project Manager
Division of Topical Drug Products
(301) 594-4877

SUBJECT: Discussion of the October 12, 1995, letter regarding review of the NDA

NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Block Drug Company

Reference wa made to an October 12, 1995 letter from Dr. Khandwala of Block Drug Company to Dr. Wilkin, regarding the status of the review of NDA 20-511. Dr. Wilkin pointed to a discrepancy in the letter regarding the date the NDA was initially received by the Agency and the date the NDA was first eligible for filing. Dr. Wilkin clarified that the cover letter of the submission was dated September 6, 1994, with the Agency's receipt date of September 7, 1995. He explained that the the filing date for an NDA is 60 days after the Agency's receipt date.

Dr. Wilkin went on to say that not only were the facilities not ready for inspection at that time of submission, but that with a 4 month deadline for standard applications, this NDA would not have met that date whether it was classified as either a P or an S.

Dr. Khandwala stated that if Chemex had accepted a standard review, and the application were submitted in December, 1994, the facilities would have been ready.

Dr. Wilkin responded that there is no precedent for industry to use their own interests to change a classification from a priority to a standard, nor is it not the Agency's policy to allow applicants to change the classification. Dr. Khandwala accepted this explanation.

Dr. Wilkin then referred to point number 5 in the letter, stating that he was unclear as to Dr. [illegible] Dr. Khandwala that nothing punitive was intended.

Furthermore, Dr. Khandwala had already pursued the issue with a higher office level.

Furthermore, Dr. Khandwala had already pursued the issue with a higher office level.

Dr. Khandwala accepted this. He stated that he merely wrote this up from Dr. Charney's notes. It was agreed that the record would reflect merely that the letter was received by Chemex.

Dr. Wilkin then confimred that Dr. Khandwala was inquiring as to when the NDA will leave the Division and go on to the Office level, where the action will receive final signature. He further stated that at no time would he be speaking on behalf of the Office. He informed Dr. Khandwala that the team members reviewing this application would be meeting later in the week. At that time, the Division would have a clearer picture regarding its completion.

Mr. Bourne asked if Block could be informed as to when the application leaves the Division. Dr. Wilkin responded they could.

Dr. Khandwala stated that in the appendix to the October 12, letter, and as he felt he was led to believe by Dr. Lumpkin, it was the intention of the Division to complete the application in 6 months. He asked if he could call Dr. Lumpkin to discuss when the Office would complete the application.

Dr. Wilkin stated that he did not recommend this. While it is CDER and Division policy to strive to complete a priority application in 6 months, it is not part of PDUFA at this time. He assured Dr. Khandwala that this application has been moved ahead of standard applications.

Dr. Khandwala stated that the Regulatory Due Date is at 180 days, and therefore he has been pressured by his higher management to contact the Agency's higher management.

Dr. Wilkin repeated that it was not his recommendation that Block contact Dr. Lumpkin.

Dr. Khandwala stated that they felt that Dr. Lumpkin gave them the impression that the review of the application would be completed in 6 months. Mr. Bourne went on to say that Chemex and Block have tailored everything to a 6 month review period, and now feel that this Division has changed this based on the current workload.

Dr. Wilkin asked Dr. Khandwala to clarify as to whether he heard a promise by Dr. Lumpkin that the Division would complete the review in 6 months, as opposed to his saying that the Division intends to complete it in 6 months.

Dr. Khandwala said that there was no promise given.

Dr. Wilkin stated that the Division has indicated to Dr. Bilstad, the former Office Director, and Dr. Weintraub, the current Office Director, there is every intention of completing this application as soon as possible. A better estimate of when it will leave the Division will be available later in the week.

Dr. Khandwala stated that it would be helpful to him to know what disciplines remain outstanding.

Dr. Wilkin responded that this might be so, but only for reviews that have undergone supervisory review. He reiterated that any times we may be able to provide are merely projections, not promises. He offered Dr. Khandwala weekly or biweekly updates, and assured him that for the reviewers, NDA 20-511 is a priority.

Dr. Khandwala then referred to an earlier discussion between himself and Ms. Holmes, regarding a request to meet with the Reviewing and Supervisory Chemists to discuss the tube labeling. He was encouraged by Ms. Holmes to wait for the completion of the application. He asked Dr. Wilkin if they could receive an approval on the tube label at this time.

Dr. Wilkin responded that such a meeting would be difficult to schedule between now and the end of the year. He questioned Dr. Khandwala as to whether he would want to know more about the application before investing heavily in any one part. There are still parts of this application outstanding, including the clinical review.

Dr. Khandwala understood that it is Block's risk to print the tube. His management will be so advised.

Mr. Bourne expressed concern that once an approvable letter is received, there is further discussion on the labeling of the package insert before the application is finally approved. He asked if they may bypass the approvable stage and go on to an approval.

Dr. Wilkin informed him that there are often issues at the approvable stage that require changes to the application. If the application arrives as that stage, the Division and Block can work on the labeling. He emphasized, though, that problems in labeling come in many shapes and sizes. It is the policy of the Division to inform the applicant of the problem, and to expect a submission in return.

The conversation ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-160/MICRO /Hussong
HFD-540/PHARM/Wedig
HFD-713/BIOSTAT/Turney
HFD-426/BIOPHARM/Ette
HFD-540/MO/Huene
HFD-540/DEP DIR/Katz
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes

RECORD OF A TELEPHONE CONVERSATION

DATE: October 20, 1995

TO: Dr. Khandwala, Ph.D.
Vice President, Rx Pharmaceutical Products, Research and Development
Block Drug Company, Inc.
(201) 434-3000, ext 1422

FROM: Joanne Holmes, Project Manager
Rosemary Cook, Supervisory Project Manager
Division of Topical Drug Products
(301) 594-4877

SUBJECT: Status of the NDA review

NDA NUMBER: NDA 20-511

DRUG: Amlexanox oral paste, 5%

SPONSOR: Block Drug Company

Ms. Holmes informed Dr. Khandwala that the end of December, 1995 is the projected date for completion of the amlexanox review by the Division. She emphasized that this date is a projection, not a promise.

Dr. Khandwala asked which reviews are complete, to which Ms. Holmes responded that chemistry, microbiology, and pharmacology are finished. Clinical, biopharmacology, and statistical reviews remain ongoing.

Dr. Khandwala stated that he would convey this to his management.

Ms. Cook assured Dr. Khandwala that this review is progressing at a faster rate than other applications in this division which have been given a standard therapeutic classification. She assured him that it is the Division's intention to supply him with a realistic date.

Dr. Khandwala then confirmed the above comments, and asked again for confirmation that Ms. Holmes and Ms. Cook could not project when the Office might complete the review of the application. This confirmation was supplied.

This conversation ended amicably.

Shortly after the above conversation, Dr. Khandwala called Ms. Holmes and Ms. Cook again to request whether there were any review issues to convey at this time.

Ms. Holmes responded that a completed review is merely one step of the process. The next

step is to craft a comment list for the action letter/sponsor. At this time, the comment list has not been finalized among all of the members of the corporate structure who need to concur. The Division prefers to work on the wording of such a comment list in order to minimize misunderstanding and therefore to provide a product of maximum utility to the sponsor. While the comments do originate from within a particular review, they undergo editorial review to facilitate communication.

Dr. Khandwala asked if there were any questions that would require them to provide further information. Ms. Holmes repeated the above remarks. Ms. Cook added that with some reviews still ongoing, it is too early to say. She also reiterated Ms. Holmes' remarks.

Dr. Khandwala stated that, in the past, reviewers have asked for information as issues have arisen. Ms. Cook agreed to convey this to Dr. Wilkin.

Dr. Khandwala asked if there were only comments, rather than requests for information, at this time.

Ms. Holmes replied that applications are reviewed by an interdependent review team. It would be premature at this time to deliver comments or requests for information until the impact of the outstanding reviews can be determined and the conclusions of all of the reviews may be provided to the entire review team in a complete context.

This conversation also ended amicably.

cc:
Orig NDA 20-511
HFD-540
HFD-540/CHEM/Pappas
HFD-160/MICRO /Hussong
HFD-540/PHARM/Wedig
HFD-713/BIOSTAT/Turney
HFD-426/BIOPHARM/Ette
HFD-540/MO/Huene
HFD-540/DEP DIR/Katz
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Biometrics
HFD-713, Room 18B-45
5600 Fisher's Lane
Rockville, Maryland 20857
Telephone: (301) 443-4594
FAX: (301) 443-9279

DATE: October 3, 1994

FROM: Elizabeth A. Turney, M.S., Mathematical Statistician

TO: Michael Miller, Ph.D., Consulting Statistician
Oxford Research International Corporation
1425 Broad Street
Clifton, NJ 07013-4221

SUBJECT: Comments regarding the test set of SAS files submitted for NDA 20-511, amlexanox oral paste, 5%

Dear Dr. Miller,

I received your test set of SAS files for studies 107 and 108 on September 27, 1994. I was successful in converting the SAS transport file EF107108.TSD to SAS datasets ULCPN107.SD2 and ULCPN108.SD2, and I am able to read these datasets on my computer system. I can also read the PROC CONTENTS list file (EXP.LST) and the SAS program files (SRV107.SAS, SRV108.SAS, SRVSTRAT.SAS, FRQ107.SAS and FRQ108.SAS).

The basic format and content of the files is generally acceptable. However, several clarifications and/or additional items are needed. My comments are as follows:

1. Since the default length for SAS variable labels is 40 characters, all labels in the SAS datasets which were longer than 40 characters were truncated. A more detailed description of each SAS variable in needed. The description should include an explicit definition of the variable, the definition of each code used, whether the variable came directly from the case report form or was derived from other variables in the data set, and if derived, the method of derivation. In most cases, this information cannot be readily conveyed via SAS labels. I prefer a code book which contains this information.

2. In the description of the SAS data sets, include a statement which describes the layout of the data (i.e. one record per patient, one record per patient visit, etc.).

3. The variable RACE has the code "C=" for all patients. The meaning of this code is not clear.

4. For each study, the variables STUDY and PATNO should be combined to form a patient identifier which is unique across studies.

5. In the SAS program files, if the code is not self explanatory, annotations describing the function of each block of code should be included throughout the program. This is especially necessary in programs using the SAS macro language.

If you need additional information or clarification regarding my comments, please do not hesitate to call.

Sincerely,

Elizabeth A. Turney

Elizabeth A. Turney

cc:
Orig. NDA 20-511
HFD-540/Holmes
HFD-713/Harkins
HFD-713/Turney
Martha R. Charney Ph.D., Chemex Pharmaceuticals. Inc.

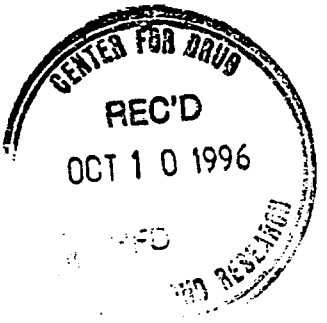
Co. Corres.

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NEW CORRESPONDENCE



October 8, 1996

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room, N-115
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Correspondence to NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5% Revisions to the Environmental Assessment

Dear Dr. Wilkin:

Pursuant to my conversation with Dr. Vincent on September 19, 1996, I have enclosed revised pages for the Amlexanox Environmental Assessment which was originally submitted in Section 4 of Volume 8.1 (NDA No. 20-511) on August 2, 1996. Please replace the pages in the original document with the attached replacement pages.

The second page of the Environmental Assessment has been revised to name Block Drug Company, Inc. as the applicant. In addition, the amlexanox drug substance (AA-673) MSDS was originally marked as confidential. It has been revised to reflect that this document is not confidential; therefore, it may be included in the non-confidential appendices of the Environmental Assessment for the Aphthasol (amlexanox oral paste), oral paste, 5% NDA (20-511).

If you have any questions, please call me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.

Submitted in Duplicate
Desk Copies: Dr. Roy Blay, Dr. Phillip Vincent

REVIEWS COMPLETED

DSC ACTION:

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

August 2, 1996

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Center for Drug Evaluation and Research
Document Control Room, N-115
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%
Volume 8.1 - Amendment to Approvable Letter of April 16, 1996

Dear Dr. Wilkin:

Attached please find a one-volume amendment (2 copies) to NDA 20-511 which is in response to FDA's letter dated April 16, 1996.

Included herein is the package insert which was prepared as a result of the discussion and agreements reached during our meeting of July 8, 1996. After it is finalized, we will prepare and submit two copies of the introductory promotional material and package insert to the Division of Drug Marketing, Advertising and Communications and one copy of the introductory promotional material to the Division of Dermatologic and Dental Drug Products.

If you have any questions, please call me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.

Submitted in Duplicate
Acknowledgment Copy
cc: Dr. Roy Blay (desk copy)

Cover letter - dated

C. Provide details of any significant changes or findings, if any.

There are no significant changes or findings since the NDA submission.

D. Summarize worldwide experience on the safety of this drug.

A worldwide safety report for Amlexanox (AA-673) is provided in Section 3 of this submission. This report consists of three parts:

1. **"Periodic Report for Adverse Event in Japan from January 1, 1995 to June 30, 1995. AA-673" This report is dated July 11, 1995 and includes all adverse events obtained initially during the first half of 1995.**

2. **"Periodic Report for Adverse Event in Japan from July 1, 1995 to December 31, 1995. AA-673" This report is dated Janurary 17, 1996 and includes all adverse events obtained initially during the last half of 1995.**

3. **"Periodic Report for Adverse Event in Japan. AA-673" It is dated January 18, 1996. This report contains follow-up information obtained (during the period of July 1, 1995 to December 31, 1995) from previous adverse events.**

4. **"Periodic Report for Adverse Event in Japan from January 1, 1996 to June 30, 1996. AA-673" This report is dated July 15, 1996 and includes all adverse events obtained initially during the first half of 1996.**

E. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

There were no patient deaths during any of the clinical studies conducted under IND The case report forms for the premature discontinuations were submitted in the NDA (Volumes 1.57, 1.58 and 1.59).

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led up to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including but not limited to: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels.

There were no ongoing trials at the time of the NDA submission, therefore, there is no new safety information with respect to amlexanox oral paste, 5%. A worldwide safety report for Amlexanox (AA-673), which covers uses of the drug including those involving indications not being sought in NDA 20-511 and other dosage forms, is provided in Section 3 of this submission.

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
HFD-540
Document Control Room 12B-30
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20582

September 21, 1995

Re: **NDA 20-511 APHTHASOL (AMLEXANOX ORAL PASTE, 5%)**
SAFETY UPDATE

Dear Dr. Wilkin:

As a follow up to my conversation this morning with Ms. Joanne Holmes, CSO for the above NDA, this is to inform you that Chemex Pharmaceuticals, Inc. have not conducted any additional animal or clinical studies with 5%amlexanox oral paste, since the submission of the original NDA on September 4, 1994. Therefore we have no additional safety data to submit to the NDA.

Sincerely,

Atul Khandwala, Ph.D.
Consultant

Desk Copies (3)

Chemex Pharmaceuticals, Inc.

Phone: (201)944-1449
Fax: (201)944-9474

To: Ms. J. Holmes

June 14, 1995

From: Dr. M. Charney

Fax is 5 pages

Subject: **NDA 20-511; Amlexanox Oral Paste, 5%**

We have discussed the question raised by Dr. Wedig regarding the size of ulcer which would be covered by the "dab" of paste referred to in the Package Insert. Enclosed is a discussion prepared by Dr. Van Inwegen.

It was concluded that a small dab was approximately 60 mg of paste. This amount would cover ulcers up to 1.0 cm in diameter. To aid the patient and to make the recommended dose more specific, the proposed Package Insert has been revised to describe the dab more accurately. The sections which were revised are enclosed.

If there are no further comments from Dr. Wedig on this issue, the revised Package Insert will be submitted as official correspondence to the NDA.

Location within NDA for data on usage in clinical studies:

Study	102	Vol. 1.40, p 42
Study	106	Vol. 1.38, p 87
Study	107	Vol. 4.6, p 125
Study	108	Vol. 4.11, p 102

Martha R Charney

MD/ P. Heune – call RE.

ISSUE RAISED BY TOXICOLOGIST: *The labeling for the product indicates that the patient should apply a "dab" of paste directly to the aphthous ulcer and the toxicologist wanted to know the maximum amount this would be for a single ulcer and what size ulcer this would cover. This information was needed to correlate the toxicology data to the clinical use.*

RESPONSE: *Different approaches for determining patient usage provide a reasonable estimate of 60 mg as the upper limit of anticipated use for each application to ulcers and visual examination indicates that this amount is more than sufficient to cover a vast majority of minor aphthous ulcers. Package labeling can be better worded to help define this amount as a line of paste approximately 5 mm or 1/4 inch long.*

SUMMARY

Aphthasol™ (Amlexanox oral paste, 5%) is a viscous, non-aqueous paste that is squeezed from the tube onto the finger and then directly applied to the aphthous ulcer. The physical consistency of this thick paste and its method of application make it extremely difficult to obtain accurate determinations of patient usage. However, reasonable estimates of the anticipated upper limit of usage was obtained with the following different approaches in order to correlate the amount of 5% Amlexanox paste used by patients with the toxicology studies:

- net weights of tubes used by patients in clinical studies;
- weights of estimated amounts of 5% Amlexanox paste that were considered sufficient to cover ulcers.

Both of these methods of estimating the amounts of paste used by patients has some limitations in the accuracy of determining the actual amounts used by patients. Although both approaches provide estimated amounts that are overestimates of actual usage, both estimates are relatively consistent and provide a reasonable anticipated upper limit on the amount of actual patient usage. This estimated amount of approximately 60 mg of paste per application was the figure used in the NDA for calculations of margins of safety.

REVISION OF PACKAGE INSERT

In regards to the information provided in the package insert, a better description than a "dab" as the amount of paste to be used can be provided. Based on the aperture of the tubes, dispensing a line of paste approximately 1 cm roughly corresponds to 100 mg of paste. Thus, defining a dab as approximately 5 mm or approximately 1/4 inch would give patients a good estimate of recommended dosage for dispensing about 60 mg of paste which is sufficient to cover ulcers of up to 1 cm in diameter. This proposed change in the package insert is attached.

RESULTS OF ESTIMATING PATIENT USAGE OF 5% AMLEXANOX PASTE

A. Oral Paste Usage in Clinical Studies

METHOD: In each of the Phase 2-3 clinical studies, tubes of medication were weighed prior to shipment to study centers and again at the end of the study upon return to Chemex

Pharmaceuticals. The weight difference was used to estimate the average amount of test material used by each patient. Table 1 summarizes the estimated amount of study material removed from the tubes by each patient in the efficacy studies.

PROBLEM: Due to the consistency of the paste, a fair amount of material that is removed from the tubes is not placed into the mouth or applied to the ulcer since a significant amount stays on the fingers particularly after it becomes wet from saliva; the material which stays on the fingers is most likely physically removed and not put in the mouth. Thus, *the amount of paste usage estimated from the difference in tube weights before and after study is at best a rough estimate of the upper limit for the amount of paste actually used by patients; i.e. it probably overestimates systemic exposure.* Although the amount of material left on the fingers can not be accurately determined, gross visual observation estimates of remaining material varied from 20% to 50% of the total material applied to the fingers.

RESULTS: The data in Table 1 show that patients removed an average of 32.5 to 96.3 mg of 5% Amlexanox paste for each application during the course of these studies. Thus, the amount of amlexanox ranged from 1.6 to 4.8 mg per application. If all of the paste were actually ingested by the patient, then assuming average body weight of 60 kilograms, the mean body burden of amlexanox/kg/day was calculated to be about 0.2 mg/kg/day.

TABLE 1: ORAL PASTE USAGE IN PHASE II/III SAFETY AND EFFICACY STUDIES

	Values Based on Net Tube Weights				
Study Number	102	106	107	108	111
Mean Total Grams of Paste per Patient	1.05	1.72	0.97	0.98	3.64
Mean Number of Applications per Patient	14.3	20.6	15.9	16.4	112
Mean Mg Paste per Application	74.3	96.3	59.9	60.5	32.5
Mean Mg Amlexanox per Application	3.7	4.8	3.0	3.0	1.6
Mean Mg Amlexanox per Patient per Day	14.8	16.7	12.3	12.2	6.5
Weighted Mean Mg Amlexanox per Patient per Day	12.4 mg/day 0.21 mg/kg/day (60 kg person) 6.7 mg/m^2/day (1.88 m^2 person)				

B. Estimated from Weights of Materials Removed From Tubes

METHOD: Paste considered to be sufficient to cover aphthous ulcers was removed from tubes by 4 different Chemex employees that were involved in the clinical studies. These amounts were weighed and potential coverage of lesions estimated from the "dabs" of material.

PROBLEM: Same as associated with measurements of tube weights; i.e. the amount removed overestimates the amount put into the mouth.

RESULTS: The mean weighed amounts of a dab of paste removed form the tubes was determined to be 57 $\pm$ 12 mg of paste (range = 35 to 70 mg). The area of these dabs were approximately 5 mm in diameter with a height of about 5 mm. When smeared on a piece of paper, this amount of paste easily covers an area of about 1 x 0.75 cm which is larger than most all minor aphthous ulcers. Thus, the removal of this amount is more than sufficient to cover most all aphthous ulcers.

As another method to estimate weights of a dab, 15 different measurements of a 10 cm line of paste were made and it was determined that each 1 cm of paste corresponds to 97 $\pm$ 5 mg of paste. On this basis approximately 5 mm of paste removed from the tubes corresponds to about 50 mg of paste and 1/4 inch of paste corresponds to about 60 mg of paste. Thus, the instructions to patients for use can be modified to indicate the application of this amount of material which is more than sufficient to cover the ulcers.

Revision of Package Insert for Aphthasol®

Below are revisions to two sections of the package insert. These revisions were made to more accurately define a "dab" to the patient. The new wording is in bold italics, and the original wording is in parentheses.

Information for Patients:

1. The paste should be applied as soon as possible after noticing the symptoms of an aphthous ulcer and continue to be used four times a day, preferably following oral hygiene after breakfast, lunch, dinner and at bedtime.

2. ***Squeeze a dab of paste approximately 1/4 inch (0.5 cm) onto a finger tip. With gentle pressure, dab the paste onto the ulcer in the mouth. Repeat, if there is more than one aphthous ulcer.***

   (Original: Apply enough of the oral paste with a finger tip to cover the lesion. Dab on, do not rub in.)

3. Wash hands immediately after applying amlexanox oral paste, 5%, directly to ulcers with finger tips.

4. In case of contact with eye, promptly wash eye with water.

5. Use of the medication should be continued until the ulcer heals. If significant healing or pain reduction has not occurred in 10 days, consult your dentist or physician.

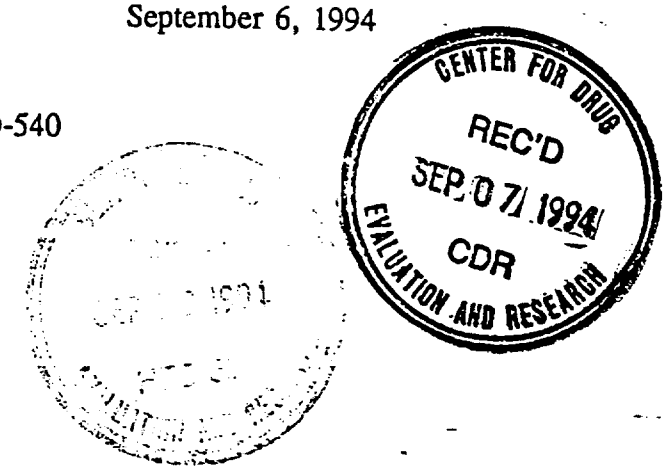
Dosage and Administration: The paste should be applied as soon as possible after noticing the symptoms of an aphthous ulcer and should to be used four times a day, preferably following oral hygiene after breakfast, lunch, dinner and at bedtime. ***Squeeze a dab of paste approximately 1/4 inch (0.5 cm) onto a finger tip. With gentle pressure, dab the paste onto the ulcer in the mouth. Repeat, if there is more than one aphthous ulcer.*** (Original: Apply just enough of the oral paste with a finger tip to cover the lesion. Dab on, do not rub in.) Use of the medication should be continued until the ulcer heals. If significant healing or pain reduction has not occurred in 10 days, consult your dentist or physician.

trip N

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

September 6, 1994



Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-511**
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

Enclosed is an original New Drug Application for Amlexanox Oral Paste, 5%. The required user fee payment was submitted August 17, 1994. A copy of the Chemistry, Manufacturing and Controls Section (Volumes 1.1 to 1.5) is being sent concurrently to the FDA District Office in West Orange, New Jersey. The Methods Validation Package and samples will be ready for shipment to the FDA when requested.

The facilities for the production of the drug product, Reedco (Division of Block Drug Co.), Humacao, Puerto Rico, will be available for inspection on October 31, 1994 or any later date. Due to a scheduled renovation, the facilities for the production of the bulk drug substance, will not be available for inspection until April 1, 1995. However, on April 1, 1995, the plant will be ready for inspection and for the synthetic production of amlexanox.

Please note that amlexanox oral paste, 5%, is the generic name for the product. A trade name has not been selected yet.

We appreciate the reviews and discussions by your staff during the IND stage of the development of this product. If you have any questions, please contact the undersigned.

Sincerely yours,

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Desk Copies: 5 copies of Vol. 1.1 for Ms. S. Childs

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

September 15, 1994

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

At the request of the FDA reviewers at the Pre-NDA Meeting on July 20, 1994, electronic copies of selected summaries, reports and data sets have been sent to Ms. S. Childs for distribution to the reviewers. To the best of our ability, the electronic files are identical to the documents included in the NDA. All disks have been scanned by Norton Antivirus, 3.0.

In a phone conversation between our consulting statistician, Dr. M. Miller, and the reviewing statistician, Ms. E. Turney, it was agreed that initially a test set of statistical files would be provided, and if Ms. Turney verified that the files could be read on her system, then the complete data sets and auxiliary information needed for SAS processing would be sent.

Attached are lists of the files included on the disks.

Sincerely yours,

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Desk Copy with 9 diskettes: Ms. S. Childs

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

September 29, 1994

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

Enclosed are five floppy disks with the complete SAS data sets, the related SAS programs, and the statistical reports for the pivotal clinical studies included in the NDA. Also enclosed is auxiliary printed information to help in the use of the disks. The information in this package was requested by Ms. E. Turney, Reviewing Mathematical Statistician, at the Pre-NDA meeting.

Sincerely yours,

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Archival Copy (sent to 12420 Parklawn Dr.):
Original of cover letter
Vol. 2.1 containing printed material related to electronic files on disks

Review Copy for Ms. E. Turney (c/o Ms. J. Holmes):
Cover letter
Vol. 2.1 containing printed matter related to electronic files on disks
Five floppy disks

Desk Copy for Ms. J. Holmes:
Cover letter

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

Atul Khandwala, Ph.D.
Executive Vice President

Janet Woodcock, M.D.
Director, Center for Drug Evaluation & Research
HFD-1, 5600 Fisher Avenue
Rockville, MD 20857

November 4, 1994

VIA FACSIMILE

Re: Request for Immediate Delay in Sending "Refusal to File" Letter for NDA 20-511
(5% Amlexanox for Treatment of Aphthous Ulcer)

Dear Dr. Woodcock:

Due to the urgency of the matter and the inability to contact Dr. J. Wilkin (Director, Dermatology Division), we are sending you this facsimile.

We were informed today by Ms. Joanne Holmes (CSO, Dermatology Division) that we will receive a facsimile on Monday, November 6, 1994, indicating that the above referenced NDA would not be accepted for review. She told us that **the only reason** for the "Refuse to File" letter was the unavailability of Bulk Drug Substance Manufacturing Facility for immediate inspection. She told us that this NDA was on a priority review list since no other drug is available for this indication. When we told Ms. Holmes that we were unaware of any FDA issued policy covering this issue, she informed us that this was the Dermatology Division policy. According to this policy, an NDA classified for priority review requires that manufacturing facilities be ready for immediate inspection and for an NDA classified for standard review, manufacturing facilities must be ready for inspection within 4 months.

We request that the agency delay sending the refuse to file letter until we have had an opportunity to discuss this issue with you and other agency personnel. We are a small company which would be substantially harmed by receipt of a "Refuse to File" letter, particularly for a reason that we believe is not justified based on all of our previous discussions with the agency. We are not asking for any special treatment, but would like to have the opportunity to confirm that this reason for "Refuse to File" letter is now an accepted FDA policy.

Our Bulk Drug Substance Plant will be available for inspection by April 1, 1995, which should not hinder the review of this NDA.

Sincerely,

Khandwal

cc: Dr. J. Wilkin (Facsimile)
Dr. J. Bilstad
Ms. J. Holmes

Chemex Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

Atul Khandwala, Ph.D.
Executive Vice President

Janet Woodcock, M.D.
Director, Center for Drug Evaluation & Research
HFD-1, 5600 Fisher Avenue

Rockville, MD 20857

November 7, 1994

VIA FEDERAL EXPRESS

Re: Request for Immediate Delay in Sending "Refusal to File" Letter for NDA 20-511
(5% Amlexanox for Treatment of Aphthous Ulcer)

Dear Dr. Woodcock:

The attached letter was meant to be sent by facsimile to you on Friday, November 4th. Through an electronic mixup you did not receive the letter in time to achieve the objective of the letter which was to delay the agency from sending us an "Refusal to File" letter for above mentioned NDA. We have today received the "Refuse to File" letter by Facsimile and we will be requesting a meeting with the Division of Topical Drug Products as soon as possible to resolve this issue.

We apologize for any inconvenience this might have caused you.

Sincerely,

cc: Dr. J. Wilkin
Dr. J. Bilstad
Ms. J. Holmes

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

November 7, 1994

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

We would like to request a conference at the FDA to discuss your letter of November 3, 1994. Below is the tentative agenda, attendees for Chemex and availability of dates.

Tentative agenda:

The primary objective of the meeting would be to discuss the interpretation of Section 505(b)(1)(d) of the Act and the FDA policies that led to the Division's decision to refuse to file the NDA.

A secondary objective would be to discuss the conditions and implications of a designation as a "priority therapeutic benefit".

Probable Attendees for Chemex:

Dr. A. Khandwala, Executive Vice President
Dr. M. Charney, Vice President, Regulatory Affairs

Available dates for meeting:

With the exception of November 24 and 25, 1994, any business day in November would be acceptable.

Sincerely yours,

Martha R. Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Copy: Ms. J. Holmes

Chemex
Pharmaceuticals, Inc.

DUPLICATE

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

November 10, 1994

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

We have received your letter of November 3, 1994 and also a response from Dr. Woodcock's office. On November 7, Dr, Lumpkin provided a an explanation of the policy of the Center for Drugs with respect to availability of manufacturing facilities for inspection. We would still like to request a conference at the FDA to discuss the following items:

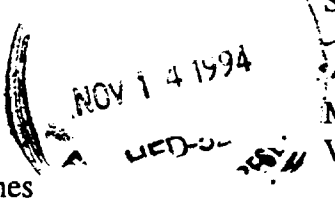
1. Items 1 through 10 in your letter of November 3, 1994. We intend to include these items when we make a resubmission, and would like to ensure that we have understood and interpreted these correctly.

2. Does the agency still have the policy that the CMC section may be submitted prior to the official NDA submission? If so, would early December be an appropriate time for such a submission? If the CMC section is submitted early, are copies submitted to the archive, the reviewers (chemistry and microbiology), and the Field Office, or only to the reviewers?

3. We would like to discuss the possibility of a reduced fee when the NDA is resubmitted. One basis for this reduction would be the limited resources of Chemex and the impact this would have on innovation.

Dr. Khandwala and I would be available for a meeting any day in November except Thanksgiving or the day after Thanksgiving. Please call either myself or Dr. Khandwala regarding the arrangements for the meeting.

Sincerely yours,



Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Copy: Ms. J. Holmes

Chemex
Pharmaceuticals, Inc. ORIGINAL

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

December 1, 1994

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

In a letter on November 10, 1994, we had requested a meeting with the agency. On November 23, Ms. J. Holmes called and provided information on most of the items that were to be the subject of the requested meeting. We have considered the information that she provided, and have decided that a meeting may not be needed if we can receive some additional responses from the agency on several of the items listed in the November 3, 1994 letter from the agency to Chemex.

Based on the information provided by Ms. Holmes, many of the items listed in the November 3 letter appear to be straight forward and will be addressed in the resubmission. However, we would like further information from the agency regarding the toxicology-related Items 8 - 10. Below are draft responses to these items. If the reviewer(s) think that the responses are acceptable, then we would not need to discuss them further. However, if the responses are not considered acceptable, we would like to schedule a meeting.

Item 8 of letter of Nov. 3: "Since the formulation to be marketed differs from the formulation used in the toxicology studies, the applicant should reconsider repeating the studies using the to-be-marketed product. If the studies will not be repeated, it is necessary to provide justification as to why such repetition should not be required."

Proposed Response: The toxicology studies were reviewed at the End-of-Phase-2 meeting, and there were no suggestions that any of the existing studies be redone. Thus, the only study that appears to be the subject of Item 8 is the seven-day hamster cheek pouch test. The following would be added to the summary of toxicology studies. It would be inserted on page 75, Volume 1.1, just before the heading "A. Acute Toxicity Studies."

The final clinical formulation for the oral paste differs slightly from the formulation used in the seven-day hamster cheek pouch test, as shown below:

Ingredient	Hamster study: CHX 3673-5N3	Clinical studies: CHX 3673-5N4 or B0960
Amlexanox	5.0%	5.0%
Mineral oil	%	%
Gelatin	%	%
Pectin	%	%
Microcrystalline wax	%	
CMC	%	%
CMC	%	%
Glyceryl monostearate		%
White petrolatum		%
Benzyl alcohol	%	%

In the final clinical formulation, the microcrystalline wax has been replaced by white petrolatum and glyceryl monostearate. The concentration of benzyl alcohol was increased to provide greater preservation. The two materials used to replace the wax are commonly used cosmetic and pharmaceutical excipients and have a long history of human use without adverse effects. Furthermore, the use of these two materials to replace the microcrystalline wax would not be expected to alter the results and/or conclusions of the already conducted study, and repetition of the study is not warranted. Furthermore, in recognition of the requirement of Animal Care and Use Committees, repeating this study may represent an unwarranted use of laboratory animals, particularly since a 28-day human study of the final formulation has been completed.

Item 10 of Nov. 3 letter: "A statement that the pharmacology/toxicology studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns."

Proposed Response: The following statement would be added to the summary of the toxicology studies, probably just after the proposed addition for Item 8.

The nonclinical studies contained in this application were carried out using acceptable, state-of-the-art protocols for the time period in which they were conducted, and were conducted under procedures that reflect appropriate care and use of laboratory animals.

Item 9 of Nov. 3 letter: "The proposed labeling sections relative to pharmacology must be appropriate (including human dose multiples expressed in either mg/m^2 or

comparative serum/plasma levels) and in accordance with 21 CFR 201.57."

Proposed Response: The statements in the proposed package insert which refer to the ratios of doses for animal to those for human in mg/kg will be recalculated to a mg/m^2 basis. For the conversion of kg to m^2 for humans, we assumed an average person of 70 kg and 180 cm and used the nomogram in the Geigy Scientific Tables (Volume 1, page 227, Eighth edition, 1981) to obtain a body surface area of 1.88 m^2. The nomogram is based on the formula of Du Bois and Du Bois, *Arch Intern Med* 17:863 (1916).

For the conversions of kg to m^2 for animals, we have preliminarily used the charts in "Handbook of Biological Data" edited by W. S. Spector, W.B. Saunders Co., publisher, 1956. For both rats and rabbits, several constants were listed; we used the largest constant, which will provide the most conservative estimate.

If these responses are not satisfactory, we would like to request a meeting to discuss these items. Any questions that we may have about the other items in the letter of November 3 can probably be handled by phone or fax. We appreciate your help with this.

Sincerely yours,

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Copies: Ms. J. Holmes plus six desk copies for reviewers

Chemex
Pharmaceuticals, Inc.

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Atul Khandwala, Ph.D.
Executive Vice President

December 5, 1994

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Enclosed is a letter of correspondence sent to the agency on December 1, 1994. On December 5, Ms. J. Holmes called and requested that seven copies be submitted to the NDA. This submission is in response to her request.

Sincerely yours,

Atul Khandwala, Ph.D.
Executive V.P., Research & Devel.

Chemex
Pharmaceuticals, Inc.

DUPLICATE

[redacted]
RS

Fort Lee Executive Park 1 • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

April 17, 1995

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

Enclosed is a resubmission of the NDA for Amlexanox Oral Paste, 5%. The items in the "Refuse to File" letter of November 3, 1994 have been addressed as follows:

Reason for refuse to file: The facility for production of the drug substance is not ready for inspection by FDA investigators.

facility at is now ready for inspection. This facility produces the bulk drug substance.

In addition, the Block Drug Co. facility at Reedco in Humacao, Puerto Rico is also ready for inspection. This facility produces the drug product.

Other items noted in Nov. 3, 1994 letter:

1. A statement regarding IRB/Declaration of Helsinki provisions of the CFR is in Section 14.

2. The Fraud Policy statement is in Section 14.

3. Copies of the current package inserts in Japanese have been obtained and are included with the English translations in Section 8.F.4.d.

4. A statement on the inclusion of safety data and the cut-off date is included in Section 14.

5. A statement on the equivalence of the electronic files with the archival NDA is in Section 14.

6. A separate methods validation package has been prepared as Section 4.

7. A center-by-center presentation of the controlled clinical studies has been prepared and is in Section 8.D.3.

8. A discussion of the formulations used in the toxicology studies has been included in the summary of toxicology information. Sections 2.E.2 and 5.B.1.

9. The annotated package insert has been revised to express the human dose multiples in mg/m^2.

10. A statement regarding the protocols for animals studies and animal welfare is in Section 14.

Other changes in NDA:

Index:

The current index is in Volume 4.1. This index indicates the location of the documents that comprise the current NDA. Of the original September, 1994 submission, some volumes are still valid in their entirety, some have been replaced entirely, and some contain valid documents even though other documents in the volume have been revised. For example, the curricula vitae for the investigators in Studies 107 and 108 have not changed, even though the other documents for the studies have been replaced.

Volume 4.1, which contains the current index, replaces entirely Volume 1.1 and delineates the location of all information for the current NDA.

CMC Section:

Two volumes of the CMC section have been replaced due to revisions of some of the documents within those volumes. Currently, Section 3 consists of Volumes 1.2, 4.2, 4.3 and 1.5. The current documents reflect more completely and accurately the synthetic manufacturing process after the renovation of the plant. The current documents also include the latest specifications and methods which were revised by Block Drug Co. to improve the clarity and to contain references to the latest USP. Also included (Sect. 3.B.8.c) are documents describing the packaging of one of the stability lots which was packaged after the September, 1994 submission. A Methods Validation package (Volume 4.4) has been added.

Microbiology Section:

This section is a copy of the CMC section and currently consists of Volumes 1.2, 4.2, 4.3, 1.5 and 4.4.

Nonclinical Section:

The summary of the toxicology information (Sect. 5.B.1) has been revised to include additional information received from and to respond to the Nov. 3, 1994 letter from the agency. The additional toxicology reports have been added. The pharmacology and ADME information has not changed. This section consists of Volumes 1.6 through 1.21 and Volume 4.5.

Pharmacokinetic Section:

This section has not changed since the September, 1994 submission. This section consists of Volumes 1.22 through 1.25.

Clinical Section:

Study 107: An audit of the clinical sites uncovered an error in the drug assignment in the data base for eight patients. The assignments were corrected, the database reanalyzed and the reports rewritten. An assessment of the impact of these changes is in Section 8.D.3.a. The new reports and data listings are included in this submission. The current information for Study 107 is in Volumes 4.6 through 4.10 and Volume 1.33.

Study 108: An audit of the database uncovered a potential inconsistency in the way data for pain measurements were handled for one patient in comparison to similar situations with other patients. The data analyses were regenerated with a correction of this potential inconsistency using a more conservative handling of the data. The reports were revised. An assessment of the impact of this change is in Section 8.D.3.b. The new reports and data listings are included in this submission. The current information for Study 108 is in Volumes 4.11 through 4.15 and Volume 1.37.

Additional information: The current Japanese package inserts were added with the English translations (Volume 4.17). Several publications related to Elics® ophthalmic solution were obtained and translated into English (Volume 4.17). Since the journals were obscure, they were not found previously using a Medline search. Site-by-site analyses have been added for the controlled studies (Volumes 4.10, 4.15, and 4.16).

Summaries: The integrated summary of effectiveness, the integrated summary

of safety and the risk-to-benefit analysis were revised to reflect the above changes and additions. These revised summaries are in Volumes 4.1 and 4.17.

Current Section Volumes: Volumes 1.27 through 1.30, 4.6 through 4.10, 1.33, 4.11 through 4.15, 1.37 through 1.41, 4.16, 1.42 through 1.46 and 4.17.

Statistical Section:

The Statistical Section has been changed to reflect the changes in the Clinical Section. The current Statistical Section consists of Volumes 1.47, 1.54 through 1.56, 4.6 through 4.16, 4.18, and 2.1.

Case Report Forms:

These have not changed since the September, 1994 submission. They are found in Volumes 1.57 through 1.59.

Diskettes:

Copies of the WordPerfect files for the summaries have been provided to each of the reviewers. Copies of the WordPerfect files for the medical reports for the clinical studies have been provided to the medical and statistical reviewers. Copies of the SAS data sets have been provided to the statistical reviewer.

If you have any questions, please contact the undersigned.

Sincerely yours,

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Desk Copies: 8 copies of Volume 4.1, Ms. J. Holmes

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

May 25, 1995

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

Enclosed is a replacement copy of the floppy disk for the Biopharmaceutics reviewer. This replacement was requested by Ms. S. Childs.

Sincerely yours,

Martha R. Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Copy: Ms. J. Holmes

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

May 31, 1995

Mr. Ernest Pappas
Room 17B-45
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Mr. Pappas:

At the request of Ms. Holmes, enclosed are two additional copies of Volume 4.4 of the NDA.

Sincerely yours,

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Copy: Ms. J. Holmes

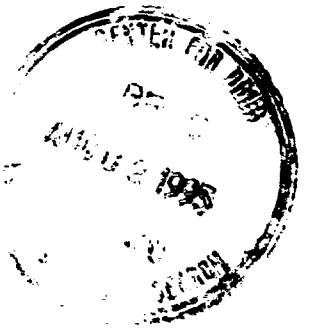
Chemex
Pharmaceuticals, Inc.

Fifth

A2

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

July 31, 1995



Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

Enclosed is a one-volume (Vol. 5.1) amendment to NDA 20-511. Contained in this volume is information to answer questions raised by various reviewers and by the investigator who inspected the Reedco facility in Puerto Rico.

Since some of the information is of general interest (e.g. the revised package insert), we are enclosing an archival copy, a copy for each of the reviewers, and three desk copies.

Dr. Wedig raised a question about the size of a "dab" at the 45-day meeting. The response to his question is in Sections 2.A and 2.E.2.

Dr. Huene sent some questions by fax on July 17, 1995. The responses are in Section 8.D.

Ms. DeWoskin issued a Form 483 to Dr. Augustine of Chemex on June 22, 1995. A formal response was sent to the FDA District Office in San Juan, Puerto Rico on June 26, 1995. As part of the response, we committed to including additional data and explanations in a revised stability report. This revised stability report is in Section 3.B.7.

Dr. DeCamp and Mr. Pappas, in a telephone conversation on June 8, 1995, had the following questions and comments:

1. For the Environmental Assessment, a letter from the Japanese government stating that the plant of (site of manufacture of amlexanox bulk drug substance) is in compliance with environmental regulations. In a subsequent phone call, Ms. Good also requested a Statement of Compliance from the corporate person responsible for the Reedco facility of Block Drug Company (site

of manufacture of the finished product). Both these statements of compliance are in Section 3.C.

2. References to Drug Master Files were requested for the Glaminate® tubes and their components. has provided a letter of reference to DMF which contains the necessary information for the Glaminate® tubes and the components of the tubes.

3. There were inadvertent references in the NDA to possible use of 5 and 10-gram tubes for the product. At present, only 5-gram tubes will be used. An explanation of this is in Section 3.B.5.c.

4. Some of the methods employed by Block Drug to test the Glaminate® tubes were titles as applying to aluminum tubes only. These methods have been re-titled to include laminate tubes and are in Section 3.B.5.c.

5. For the specifications for the product, it was requested that appearance be evaluated both with the unaided eye and microscopically. Based on the non-aqueous formulation which contains % mineral oil, any separation occurring microscopically would also be visible to the unaided eye. The microscopic separation would be more important with an emulsion type of formulation, but 5% amlexanox oral paste is a paste, not an emulsion. Thus, a visual evaluation of the appearance would provide sufficient information. A discussion of the appearance of the product is in the stability report in Section 3.B.7.

6. A table listing the amounts of ingredients used for each batch in addition to the percentaged was requested. This table is provided in Section 3.B.2.

7. For release and stability testing, it was requested that samples be taken from the top, middle and bottom of the tubes for determination of amlexanox and benzyl alcohol. This will be done for the three validation batches that will be made at Reedco. The revised stability protocol is in Section 3.B.7.

8. An update on the stability data was requested. The revised stability report, which includes data received this month, is in Section 3.B.7.

We are also including information on because we would like to use them as an alternate site for the sieving of the gelatin which is a preparatory step in the manufacture of the 5% amlexanox oral paste. This information is in Sections 3.B.4 and 3.B.5.a.

Sincerely yours,

Martha R Charney

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

Desk Copies: 3 for Ms. J. Holmes

Chemex
Pharmaceuticals, Inc.

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Atul Khandwala, Ph.D.
Executive Vice President

[redacted]
BC

ORIGINAL

August 15, 1995

Dr. Jonathan Wilkin, Director
Division of Topical Drug Products, HFD-540
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

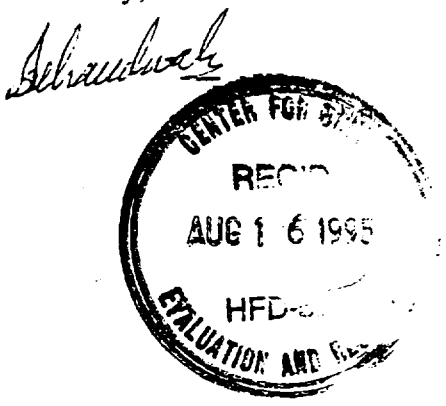
Re: NDA 20-511
Amlexanox Oral Paste, 5%

Dear Dr. Wilkin:

Enclosed are three (3) archival copies of a one-volume (Vol. 6.1) amendment to NDA 20-511. Contained in this volume is: (a) Addendum to Stability Report Submitted in Vol. 5.1, which was sent by facsimile on 8/8/95; and (b) Minutes of a meeting held on August 10, 1995 between Chemex Pharmaceuticals and the FDA San Juan District office.

If you have any questions or need additional information, please contact me.

Sincerely,



Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
HFD-540
Document Control Room 12B-30
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20582

September 21, 1995

Re: **NDA 20-511 APHTHASOL (AMLEXANOX ORAL PASTE, 5%)**
TRANSFER OF OWNERSHIP

Dear Dr. Wilkin:

Pursuant to 21 C.F.R. 214.72(a)(1), this letter serves to inform you that, effective the date of this letter all rights to NDA 20-511 (including all rights to any amendments thereto and any supplemental NDAs pending with the Food and Drug Administration which were submitted thereunder), have been transferred to:

Block Drug Company, Inc.
257 Cornelison Avenue
Jersey City, New Jersey 07302-9988

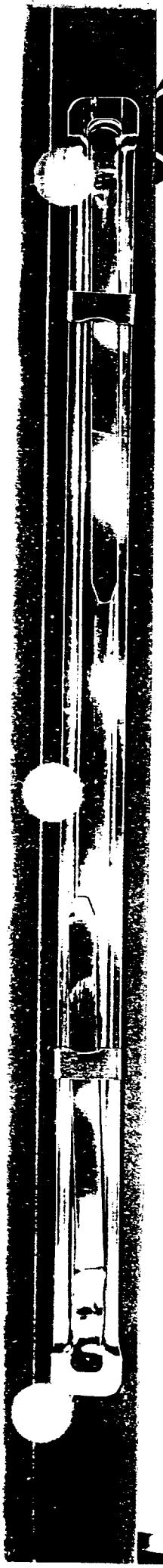
Chemex Pharmaceuticals, Inc. have agreed to supply Block with a complete copy of the NDA application including all supplements and records required to be kept under 21 C.F.R. 314.81.

Henceforth all correspondence should be directed to Dr. Atul Khandwala during the review of the NDA and to Dr. Richard Bourne, thereafter, both of whom are employees of Block Drug at 257 Cornelison Avenue, Jersey City, New Jersey 07302-9988. The telephone number for Dr. Khandwala is (201) 434-3000 x 1422 and for Dr. Bourne is (201) 434-3000 x 1995.

Included in this submission is a completed and signed Form 356h.

Sincerely,

Herbert H. McDade, Jr.
President
Chemex Pharmaceuticals, Inc.



Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park I • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
HFD-540
Document Control Room 12B-30
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20582

September 21, 1995

ORIGINAL

RECD
SEP 27 1995

Re: **IND . APHTHASOL (AMLEXANOX ORAL PASTE, 5%)**
TRANSFER OF OWNERSHIP

Dear Dr. Wilkin:

This letter serves as notification that effective on the data of this letter, all rights and responsibilities for this application are being transferred from Chemex Pharmaceuticals, Inc. to :

Block Drug Company, Inc.
257 Cornelison Avenue
Jersey City, New Jersey 07302-9988

Under separate cover, transfer of NDA 20-511 to the same firm has been made to the Agency.

Chemex has agreed to supply Block with a complete copy of the IND application including all supplements and records required to be kept under the applicable regulations.

Henceforth all correspondence should be directed to Dr. Atul Khandwala during the review of the NDA and to Dr. Richard Bourne, thereafter, both of whom are employees of Block Drug at 257 Cornelison Avenue, Jersey City, New Jersey 07302-9988. The telephone number for Dr. Khandwala is (201) 434-3000 x 1422 and for Dr. Bourne is (201) 434-3000 x 1995.

Sincerely,

Herbert H. McDade, Jr.
President
Chemex Pharmaceuticals, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001. Expiration Date: April 30, 1996. See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS. —

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Chemex Pharmaceuticals, Inc.	September 21, 1995
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
One Executive Drive Fort Lee, NJ 07024	201-944-1449
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) 20-511

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Amlexanox Oral Paste, 5%	Apthasol™

CODE NAME *(If any)*	CHEMICAL NAME
AA-673	2-Amino-7-isopropyl-5-oxo-[1]benzpyrano-[2,3-b] pyridine-3-carboxylic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Oral Paste	Topical	5%

PROPOSED INDICATIONS FOR USE

Aphthous Ulcers

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

DMF
IND
IND

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314 70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
▨	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)* Change of ownership of NDA 20-511 from Chemex Pharmaceuticals, Inc. to Block Drug Company

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Herbert McDade, Jr. President	Herbert McDade Jr	09/21/1995

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
One Executive Drive Fort Lee, NJ 07020	201-944-1449

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

FORM FDA 356h (10/93)

Chemex
Pharmaceuticals, Inc.

Fort Lee Executive Park 1 • One Executive Drive • Fort Lee, NJ 07024 • (201) 944-1449 • Telefax (201) 944-9474 • Telex 530005

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
HFD-540
Document Control Room 12B-30
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20582

September 21, 1995

Re: **NDA 20-511 APHTHASOL (AMLEXANOX ORAL PASTE, 5%)**
TRANSFER OF OWNERSHIP

Dear Dr. Wilkin:

Pursuant to 21 C.F.R. 214.72(a)(1), this letter serves to inform you that, effective the date of this letter all rights to NDA 20-511 (including all rights to any amendments thereto and any supplemental NDAs pending with the Food and Drug Administration which were submitted thereunder), have been transferred to:

Block Drug Company, Inc.
257 Cornelison Avenue
Jersey City, New Jersey 07302-9988

Chemex Pharmaceuticals, Inc. have agreed to supply Block with a complete copy of the NDA application including all supplements and records required to be kept under 21 C.F.R. 314.81.

Henceforth all correspondence should be directed to Dr. Atul Khandwala during the review of the NDA and to Dr. Richard Bourne, thereafter, both of whom are employees of Block Drug at 257 Cornelison Avenue, Jersey City, New Jersey 07302-9988. The telephone number for Dr. Khandwala is (201) 434-3000 x 1422 and for Dr. Bourne is (201) 434-3000 x 1995.

Included in this submission is a completed and signed Form 356h.

Sincerely,

Herbert H. McDade, Jr.
President
Chemex Pharmaceuticals, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT Block Drug Company, Inc.	DATE OF SUBMISSION September 19, 1995
ADDRESS (Number, Street, City, State and Zip Code) 257 Cornelison Avenue Jersey City, NJ 07302	TELEPHONE NO. (Include Area Code) (201) 434-3000, ext. 1995
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 20-511

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
Amlexanox Oral Paste, 5%	Aphthasol

CODE NAME (If any)	CHEMICAL NAME

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Cream	Topical	5%

PROPOSED INDICATIONS FOR USE

Aphthous Ulcers

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

Transfer of Ownership
IND

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☐ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
▨	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter, and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Richard K. Bourne, Ph.D.	Richard K Bourne	September 19, 1995

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
257 Cornelison Avenue Jersey City, NJ 07302	(201) 434-3000, ext. 1995

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h (6/92)

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000
FAX (201) 434-0842

ATUL KHANDWALA, Ph.D.
Vice-President
Rx Pharmaceutical Products
Research and Development

CONFIDENTIAL

October 12, 1995

VIA FACSIMILE

Dr. Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
HFD-540
Document Control Room 12B-30
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20582

RE: NDA 20-511

Dear Dr. Wilkin:

I attempted to contact you by phone yesterday to discuss the status of the review of the NDA. There are a number of important issues that I must discuss with you directly. Rosemary Cook and Joanne Holmes informed me yesterday, for the first time, that under PDUFA, the due date for this NDA is April 19, 1996. They also indicated that it was and is the intention of the Division of Topical Drugs Evaluation to try and complete review of priority rated NDAs in 6 months. This was an astonishing piece of information since we were always lead to believe that the review time for a priority rated NDA was 6 months. Thus, an NDA (originally filed in September 1994) which was granted priority review, has now turned into a potential review time of at least 14 months and which could be as long as 20 months (if action is taken in April 1996) from the original date of filing. In addition, because of the priority classification, we received the Refuse to File Letter and lost of the original filing fee.

Based on the facts (listed in chronological order in attached Appendix I) my management believes that we have been mislead and unfairly treated concerning the review schedule of the above referenced NDA.

The Refuse to File letter sent to us in November of 1994 was the first time we were informed that the manufacturing facility must be available for inspection immediately, because this NDA was classified for priority review. In a subsequent conversation I had with Dr. Murray Lumpkin on November 10, 1994, he emphasized that only if manufacturing plants are available for immediate inspection can the agency be sure that all reviews are completed in 6 months for priority rated NDAs.

On the same day, the CSO advised us that we could not voluntarily accept a standard review which would have allowed us to file the NDA on December 1, 1994 ensuring an FDA decision on the NDA by the end of November 1995.

As you may know, both the manufacturing facilities have passed the GMP inspections and from my conversation with Ms. Holmes on October 10, 1995 there are no outstanding questions from any reviewer that we have not answered. We have been very diligent in responding to all of the queries from reviewers, and a look at the record would confirm that. It is therefore difficult for me to explain to my management what has delayed the completion of review of a priority rated NDA.

I am asking for your help to expedite the completion of review of the NDA, and to that end if we can help in anyway we are prepared to do what may be asked of us. I am willing to meet with you at your convenience or talk with you on the phone so that a situation, which my management believes to be an inappropriately long tine for the review of this priority NDA can be rectified immediately.

Thank you for your attention to important matter.

Sincerely,

Ashwani Vaid

APPENDIX I

October 12, 1995

CHRONOLOGY OF EVENTS DURING THE REVIEW OF NDA 20-511

1. **9/6/94** - Original NDA filed.

2. **11/4/94** - Phone call informing us that we were to receive a refuse to file letter because plants were not going to be ready for inspection until 4/1/95 and that the NDA was assigned priority status and plants must be ready immediately for inspection. This was the main reason for RTF letter.

3. **11/4/94** - Letter to Dr. Janet Woodcock, Director of CDER requesting immediate delay in sending RTF letter. Reason cited was that the plant availability policy of the agency was never discussed or publicized.

4. **11/7/94** - RTF letter stamped 11/3/95 was faxed to us.

5. **11/7/94** - Dr. Khandwala Called Dr. Lumpkin. CSO called to inform us that she was instructed to send RTF letter without teleconference since we had written to Dr. Woodcook.

6. **11/10/94** - Dr. Khandwala talked with Dr. Lumpkin. He emphasized need for immediate availability of the plant in order for the agency to complete all reviews within 6 months for priority NDA. Clarified that 6 month review clock for priority NDA started from the date of receipt and not the acceptance of the NDA by the agency.

   Dr. Khandwala pointed out to Dr. Lumpkin that this policy was not publicized and as a matter of fact at a User Fee meeting that I attended in Washington, it was stated that Chemistry issues should not be reasons for RTF letter. He recognized that some of the unofficial guidelines or policies of the agencies were not known to all companies.

7. **11/10/94** - Received letter from Dr. Lumpkin dated 11/7/94, indicating the agency's policy of requiring that manufacturing plants be available for immediate inspection for priority rated NDA and within 4 months for standard review.

8. **11/10/94** - Call from CSO - Iinformed us that possibility of resubmitting NDA in December and having a standard review time of 12 months was not an option. We had proposed this because if we had filed in December, with standard review, we would be in compliance with agency requirement that plant be ready in 4 months.

APPENDIX I (Continued)

9. **4/19/95** - Resubmitted NDA received by the Division of Topical Drug Products. NDA still classified for priority review.

10. **6/21/95** - CSO telephoned acceptance of the NDA.

11. **5/5/95 to 7/31/95** - Inquiries from several reviewers which were answered promptly.

12. **6/7-8/95** - plant passed GMP inspection.

13. **6/14 - 7/7/95** - Humacao Plant passed GMP inspection.

14. **9/8/95** - Call from CSO asking for a safety update - provided next day. She indicated that the NDA was being actively reviewed and that there were no unanswered questions. However, she indicated that the Division would not allow approval of tube labelling.

15. **10/10/95** - Call to CSO. For the first time she informed us that due date under PDUFA is April 19, 1996. It is the Division's intention to complete review as soon as possible.

16. **10/11/95** - Call to Dr. Wilkin was returned by CSO and supervisory CSO. Best they could do was to call us next week to inform us when the Division was likely to finish the review. No comment on how and when the office would act.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO ASS**

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Block Drug Co., Inc.	October 13, 1995
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
257 Cornelison Avenue Jersey City, NJ 07302	(201) 434-3000
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	20-511

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Amlexanox Oral Paste, 5%	Aphthasol™

CODE NAME *(If any)*	CHEMICAL NAME
AA-673 CHX 3673	2-amino-7-isopropyl-5-0x0-5H[1]benzopyrano-[2,3-b] pyridine-3-carboxylic acid

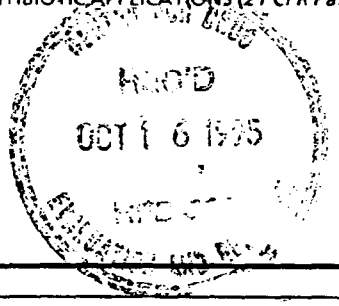
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Oral paste	Topical	5%

PROPOSED INDICATIONS FOR USE

Aphthous Ulcers

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

DMF
IND
IND



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

ORIGINAL

PeH 1/29/96

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000
FAX (201) 434-0842

ATUL KHANDWALA, Ph.D.
Vice-President
Rx Pharmaceutical Products
Research and Development

NEW CORRESPONDENCE

December 21, 1995

Ms. Joanne Holmes
Project Manager
Division of Dermatologic and Topical Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Attention Document Control Room
Rockville, MD 20857

VIA FACSIMILE

3 COPIES BY FEDERAL EXPRESS

RE: NDA 20-511

Dear Joanne:

Attached please find our draft response to Chemistry questions faxed to us on December 7th. As you will notice some of our responses are dependent on getting the information from expected in early January, 1996). We hope to submit a formal response to Chemistry questions soon after our requested meeting in the third week of January. The agenda for that meeting would be to resolve any issues that were not satisfactorily answered in our draft response.

If you have questions or need further clarification on our response, please call me. Block Drug will be closed for the holidays next week, but you can reach me at 201-224-9303 (Tel) and 201-224-9727 (Fax).

Thank you for your help and assistance.

Sincerely,

Atul Khandwala

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000
FAX (201) 434-0842

PUL KHANDWALA, Ph.D.
Vice-President
Pharmaceutical Products
Research and Development

February 7, 1996

Ms. Joanne Holmes
Project Manager
Division of Dermatologic and Topical Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-511

Dear Joanne:

Attached please find the minutes from our teleconference last Thursday, 2/1/96. These minutes contain *the original FDA questions (italicized)*, the draft responses and discussion from Block Drug and the **agreements which were reached on each point (in bold).**

We expect to submit our formal response to the Chemistry questions by the end of February. Our formal response will address all of the issues that are contained in these minutes. Three copies of these minutes will also be filed with our formal response.

We believe these minutes to be an accurate and complete record of our telephone conference.

If you have any questions or disagree with any of agreements reached during teleconference, please contact me. We would also appreciate a copy of your minutes when they are prepared.

Thank you for your help and assistance.

Sincerely,

FEB 13 1996

ORIGINAL
AMENDMENT
BC

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-9988
Telephone (201) 434-3000
FAX (201) 434-0842

search and Development Laboratories

CHARD K. BOURNE, Ph.D.
President - Corporate Regulatory Affairs

Writer's Extension 1-995/996

March 7, 1996

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, N-115
9201 Corporate Blvd.
Rockville, MD 20852

RE: NDA 20-511

Dear Dr. Wilkin:

Attached please find a one-volume amendment (3 copies) to NDA 20-511 which is in response to comments from Chemistry Reviewers dated December 7, 1995. A draft response was provided by Block Drug Company on December 21, 1995 which was the subject of a telephone conference with Dr. DeCamp, Mr. Pappas and Ms. Holmes on February 1, 1996. At this telephone conference, all issues raised by Dr. DeCamp and Mr. Pappas were satisfactorily resolved subject to final review of this submission. Minutes of the telephone conference were submitted on February 7, 1996.

Thank you for your assistance.

Sincerely,

Richard K Bourne

Richard K. Bourne

ORIGINAL

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NEW CORRESPONDENCE

April 19, 1996

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V, HFD-540
Center for Drug Evaluation and Research
Document Control Room, N115
Food and Drug Administration
5601 Fishers Lane
Rockville, MD 20857

RE: NDA 20-511

Dear Dr. Weintraub:

We acknowledge receipt of your communication dated April 16, 1996. Pursuant to 21 CFR 314.110, this letter serves to notify you of our intent to file an amendment to NDA 20-511, in which the issues itemized in your April 16, 1996 correspondence will be addressed.

If you have any questions, please contact me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

Submission in Triplicate
Acknowledgment Copy

CENTER FOR DRUG
REC'D
APR 2 5 1996
HFD-
EVALUATION

REVIEWS COMPLETED
CSO ACTION
LETTER NDA
CSO INITIALS

ORIGINAL

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

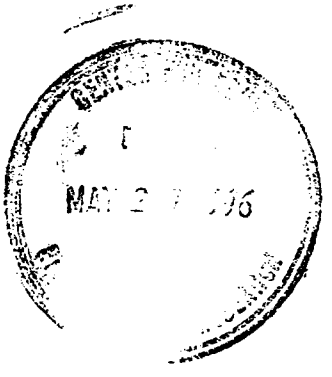
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ALSO TRANSMITTED BY FACSIMILE

6/10/96

May 23, 1996

NEW CORRESPONDENCE



Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%

Dear Dr. Wilkin:

Reference is made to the "approvable" letter dated April 16, 1996 for Aphthasol (amlexanox oral paste), oral paste, 5%. On April 19, 1996 we sent a notice of our intent to file an amendment to the subject NDA. As documented in your communication dated April 16, 1996, extensive revisions were made to the original package insert submitted in the NDA. We would like to request a meeting with the Division of Dermatologic and Dental Drug Products to discuss labeling for Aphthasol oral paste. We will be available to meet anytime during the weeks of June 24 and July 1, 1996. We will submit the completed response to the "approvable" letter as an amendment to the NDA subsequent to the meeting. This amendment will include the finalized package insert reflecting the changes agreed upon at the meeting, and the responses to the questions raised in the "approvable" letter. Below is additional information which may be helpful in scheduling this meeting.

Listing of the Specific Objectives/Outcomes Expected from the Meeting

- reach agreement on the Clinical and Indication sections of the proposed package insert

REVIEWS COMPLETED

OSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

OSO INITIALS DATE

Tentative Agenda

- discuss the Clinical and Indication sections of the proposed package insert

Attendees from Block Drug Company, Inc.

- Richard Bourne, Ph.D., Vice President Regulatory Affairs
- Richard Brown, M.D., Vice President Regulatory and Medical Affairs
- Frederick Curro, D.M.D., Ph.D., Vice President/Director Corporate Clinical and Medical Affairs
- Michael Friedman, Ph.D., Associate Director Statistics
- Sandra Wells, Ph.D., Regulatory Affairs Specialist
- Atul Khandwala, Ph.D., Consultant

Requested Participants from CDER

- Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540
- Ralph Harkins, Ph.D.. Biostatistics Supervisor, DOBIV, HFD-725
- Phyllis Huene, M.D., Medical Officer, DODDDP, HFD-540
- Roy Blay, Ph.D., Regulatory Management Officer

A briefing package which will include information pertinent to the meeting and a more specific agenda will be provided at least two weeks in advance of the scheduled meeting.

We appreciate your attention to this matter. I will be in contact with Ms. Childs by phone regarding the scheduling of this meeting.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

Submission in Triplicate
Acknowledgment Copy
Desk Copy to Ms. Sandy Childs

ORIGINAL

BLOCK DRUG COMPANY, INC.

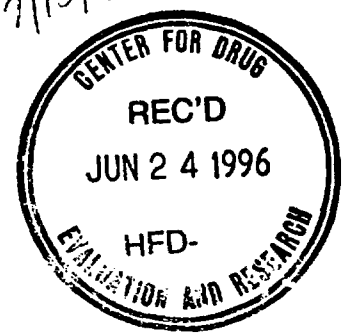
257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL RETURN RECEIPT REQUESTED

NEW CORRESPONDENCE

1a 2d
7/15/96

June 21, 1996



Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Center for Drug Evaluation and Research
Document Control Room, N-115
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%

Dear Dr. Wilkin:

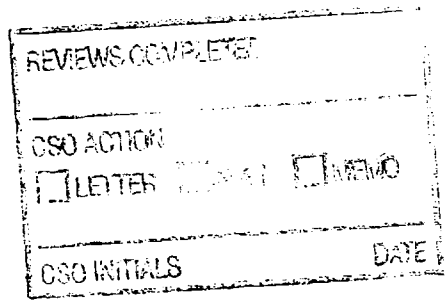
Reference is made to the enclosed "Approvable Letter" dated April 16, 1996 which included extensive revisions to the labeling for Aphthasol oral paste, 5%. We have reviewed these changes and feel that several additional revisions are necessary to make the package insert clear and informative for prescribing dentists and physicians. A meeting has been scheduled to discuss the labeling of Aphthasol Oral Paste, 5%, for July 8, 1996 at 2:00 P.M. Enclosed is the background document in preparation for this meeting. Our objective is to reach agreement on the "Clinical Studies" and "Indications and Usage" sections of the proposed package insert. We have included herein justification for each of our recommended revisions to these sections of the package insert.

Please contact me at (201) 434-3000, extension 1774 if you have any questions or require additional information before the meeting.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

Submitted in Duplicate
Acknowledgment Copy



DUPLICATE
NEW CORRESP
NO

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

July 16, 1996

CENTER FOR DRUG REC'D JUL 19 1996 HFD EVALUATION AND RESEARCH

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Center for Drug Evaluation and Research
Document Control Room, N-115
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%
Minutes from Meeting of July 8, 1996

Dear Dr. Wilkin:

We appreciate your meeting with us to discuss proposed labeling for Aphthasol oral paste, 5%. We feel it was a very productive meeting and would like to thank Dr. Blay and Ms. Childs for their efforts in coordinating this meeting.

Attached are our minutes of the meeting. If any of the attendees have any additions or corrections please let me know. Also, we are looking forward to receiving a copy of FDA's minutes so that we may make the revisions to the package insert as agreed upon at the meeting and submit an amendment addressing the issues outlined in the approvable letter as soon as possible.

Sincerely,

Sandra M. Wells, Ph.D.

Submitted in Duplicate
Acknowledgment Copy
5 Desk Copies: Dr. Roy Blay

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL - RETURN RECEIPT REQUESTED
ALSO TRANSMITTED BY FACSIMILE

September 6, 1996

Roy Blay, Ph.D.
Consumer Safety Officer
Division of Dermatologic and
Dental Drug Products, HFD-540
Document Control Room, N-115
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%
Correspondence

Dear Dr. Blay:

Pursuant to your telephone conversation with Dr. Bourne on August 30, I have enclosed a copy of the letter sent by Dr. Khandwala (dated September 21, 1995) informing the Division that NDA 20-511 was transferred from Chemex Pharmaceuticals, Inc. to Block Drug Company, Inc. Block Drug Company, Inc. divested its pharmaceutical division, Reed and Carnrick on June 30, 1995.

Also enclosed are copies of the revised carton labels reflecting changes to the "Usual Dosage" section of the carton based on the changes made to the clinical section of the package insert. The expiration date and lot number will appear on both the carton and on the crimp of the tube.

Please call me at (201) 434-3000, extension 1774 if you have any questions regarding these issues.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

Submitted in Duplicate
Desk Copies to Dr. Roy Blay and Mr. Ernie Pappas

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0316
Expiration Date: December 31, 1997
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT
Block Drug Company, Inc.

DATE OF SUBMISSION
September 9, 1996

TELEPHONE NO. *(Include Area Code)*
(201) 434-3000

FACSIMILE (FAX) Number *(Include Area Code)*
(201) 332-2362

APPLICANT ADDRESS *(Number, Street, City, State, County, and ZIP Code or Mail Code)*:
257 Cornelison Avenue
Jersey City, NJ 07302

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, State, and ZIP Code telephone & FAX number)* IF APPLICABLE

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously issued)

PRODUCT DESCRIPTION

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Amlexanox Oral Paste, 5%

PROPRIETARY NAME *(trade name)* IF ANY
Aphthasol™

CHEMICAL/BIOCHEMICAL NAME *(If any)*
2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano-[2,3-b]pyridine-3-carboxylic acid

CODE NAME *(If any)*
AA-673, CHX 3673

DOSAGE FORM:
Oral Paste

STRENGTHS:
5%

ROUTE OF ADMINISTRATION:
Topical

PROPOSED INDICATIONS FOR USE:
Treatment of Aphthous Ulcers

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGIC APPLICATION (21 CFR part 601)

IF A NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ NOTIFICATION ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

REASON FOR SUBMISSION
Correspondence to NDA 20-511

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

DMF	IND
IND	NDA 20-511

References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current lication)

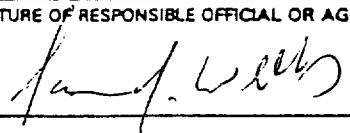
This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1))
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i))
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3))
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5))
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6))
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1))
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification
	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

TIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72 and 601.12..
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.
The data and information in this submission have been reviewed and are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Sandra M. Wells, Ph.D. Regulatory Affairs Specialist	September 9, 1996

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0316)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number

se DO NOT RETURN this form to this address.

ORIGINAL

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

September 24, 1996

BC

NDA 020-511 AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room, N-115
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG
REC'D
SEP 27 1996
HFD
EVALUATION AND RESEARCH

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%
Volume 9.1 - Methods Validation Package

Dear Dr. Wilkin:

Pursuant to Dr. Blay's fax of 7/30/96 requesting methods validation information, I have enclosed a one-volume submission (2 copies) to NDA 20-511 which contains all the current information required for methods validation. This submission incorporates information originally submitted in Volumes 4.3 and 7.1 to provide a complete, current methods validation package which supersedes Volume 4.3, the original methods validation package. A table cross-referencing each of the documents in this submission (Volume 9.1) to the location in the original submission is found on pages 20-23 of this volume.

If you have any questions, please call me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

REVIEWS COMPLETED

Submitted in Duplicate
cc: Dr. Roy Blay (desk copy)
Mr. Ernie Pappas (desk copy)

DUPLICATE

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

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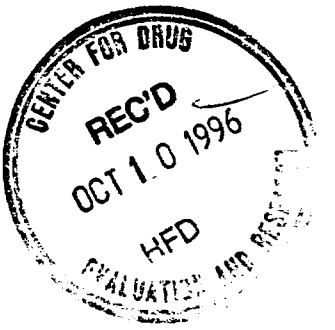


October 8, 1996

NEW CORRESPONDENCE

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room, N-115
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Correspondence to NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5% Revisions to the Environmental Assessment

Dear Dr. Wilkin:

Pursuant to my conversation with Dr. Vincent on September 19, 1996, I have enclosed revised pages for the Amlexanox Environmental Assessment which was originally submitted in Section 4 of Volume 8.1 (NDA No. 20-511) on August 2, 1996. Please replace the pages in the original document with the attached replacement pages.

The second page of the Environmental Assessment has been revised to name Block Drug Company, Inc. as the applicant. In addition, the amlexanox drug substance (AA-673) MSDS was originally marked as confidential. It has been revised to reflect that this document is not confidential; therefore, it may be included in the non-confidential appendices of the Environmental Assessment for the Aphthasol (amlexanox oral paste), oral paste, 5% NDA (20-511).

If you have any questions, please call me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.

Submitted in Duplicate
Desk Copies: Dr. Roy Blay, Dr. Phillip Vincent

ORIGINAL

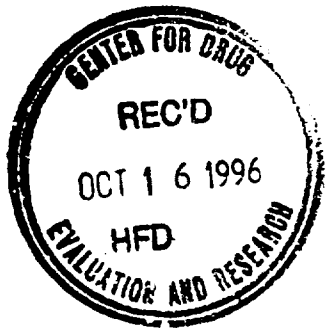
NC

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

UPS NEXT DAY

NEW CORRESPONDENCE



October 15, 1996

Roy Blay, Ph.D.
Consumer Safety Officer
Division of Dermatologic and Dental
Drug Products, HFD-540
Center for Drug Evaluation and Research
Bldg. 2, Room 219
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%
Package Insert

Dear Dr. Blay:

Pursuant to your request, enclosed is a floppy disk containing the Aphthasol oral paste, 5% package insert. The PCX file containing the graph on page 3 of the package insert is also contained on this disk.

If you have any questions, please call me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

Acknowledgment Copy

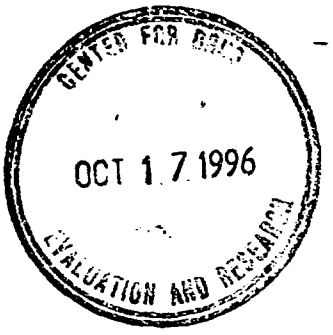
ORIGINAL

BLOCK DRUG COMPANY, INC.

257 Cornelison Avenue Jersey City, N.J. 07302-3198
Telephone (201) 434-3000

UPS NEXT DAY

NEW CORRESPONDENCE



October 16, 1996

Mr. Ernie Pappas
Chemistry Reviewer
Division of Dermatologic and
Dental Drug Products, HFD-540
CDER, FDA
Building 2, Room N-208
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-511 - Aphthasol (amlexanox oral paste), oral paste, 5%
Additional Copies of Volume 9.1 - Methods Validation Package

Dear Mr. Pappas:

As requested per your telephone call this morning, please find two additional copies of Volume 9.1 (originally submitted September 24, 1996) containing the Methods Validation Package for amlexanox oral paste, 5% (NDA 20-511).

I I can be of further assistance, please call me at (201) 434-3000, extension 1774.

Sincerely,

Sandra M. Wells, Ph.D.
Regulatory Affairs Specialist

Enclosure
Acknowledgment Copy