

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: 020080/S005**

**Trade Name: Imitrex**

**Generic Name: Sumatriptan succinate**

**Sponsor: Glaxo-Wellcome**

**Approval Date: December 23, 1996**

NDA 20-080/S-005

Glaxo Wellcome Inc.  
Attention: Mr. James E. Murray  
Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709

DEC 23 1996

Dear Mr. Murray:

Please refer to your March 9, 1993 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imitrex (sumatriptan succinate) Injection. Reference is also made to the Approvable letter for this supplement dated June 3, 1996, and to your response dated July 29, 1996. Finally, please also refer to the Approval letter for the supplemental application for cluster headache (S-004) dated May 22, 1996.

The supplemental application provides for the Imitrex STATdose System, a new alternative subcutaneous delivery system, and for the revised patient labeling regarding its use.

We have completed the review of this supplemental application including the submitted draft labeling 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 draft labeling in the submission dated July 29, 1996 with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

We note, however, that modifications were made to the **PRECAUTIONS, ADVERSE REACTIONS, AND INFORMATION FOR THE CONSUMER** sections of the package insert, as well as to the *Information for the Consumer* leaflet for Imitrex that were not discussed in the Approvable letter dated June 3, 1996. Please note that we have not changed the current labeling in the **PRECAUTIONS** section, subheading **Nursing Mothers**, because information was not supplied to completely characterize the time course of drug excretion into breast milk.

The **Labeling Revisions** are as follows:

1. In the **PRECAUTION** section:

**Change:** Information for Patients: See **PATIENT INFORMATION** at the end of this labeling for the text of the separate leaflet provided for patients.

**To:** Information for Patients: With the autoinjector, the needle penetrates approximately 1/4 of an inch (5 to 6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle. See **PATIENT INFORMATION** at the end of this labeling for the text of the separate leaflet provided for patients.

2. In the **ADVERSE REACTIONS** section under **Postmarketing Experience**:

**Change:** Rarely, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) has been reported following subcutaneous administration of sumatriptan. Pain, redness, stinging, contusion, and subcutaneous bleeding at the injection site have been reported.

**To:** Following subcutaneous administration of sumatriptan, pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding and on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) have been reported.

3. In the **DOSAGE AND ADMINISTRATION** section:

Please add the following to the end of the 2nd paragraph:

With this device, the needle penetrates approximately 1/4 inch (5 to 6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

4. In the **How Supplied** section:

Please add the terminal "0" to the NDC number for the Imitrex STATdose System, i.e., should be NDA 0173-0479-00.

5. In the **Information for the Consumer** section of the Professional Labeling, and in the *Information for the Consumer* leaflet, under **4. How to Use IMITREX Injection**, 1st and 2nd paragraphs:

**Change:** Before using the autoinjector, see the enclosed instruction pamphlet on loading your autoinjector and discarding the empty syringes.

For adults, the usual dose is a single injection given just below the skin, in an area that has an adequate fatty tissue layer.

**To:** Before using the autoinjector, check with your doctor on acceptable injection sites and see the enclosed instruction pamphlet on loading your autoinjector and discarding the empty syringes.

For adults, the usual dose is a single injection given just below the skin.

These revisions are terms of the supplemental NDA approval.

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 supplemental application NDA 20-080/S-005. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, further revision of that labeling may be required.

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

**ADMINISTRATIVE ISSUES:**

We note during an administrative review of our files, the following supplements were pending. We note that your supplemental application submitted March 9, 1993 supersedes these applications which is approved as of the date of this letter. Therefore, we will not review these supplement applications but they will be retained in our files.

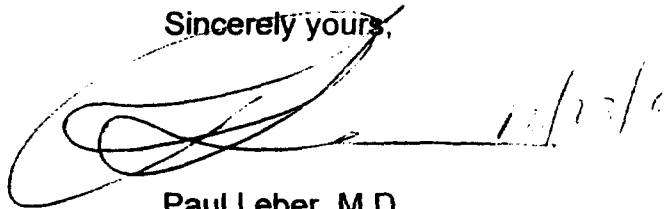
Date Submitted	NDA 20-008 SLR	DESCRIPTION
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Date Submitted	NDA 20-008 SLR	DESCRIPTION
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Should you have any additional questions concerning your application, please contact:  
Ms. Lana Chen, Project Manager at (301) 594-2777.

Sincerely yours,



Paul Leber, M.D.  
Director  
Division of Neuropharmacological Drug  
Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Registered Mail

JUN 3 1996

NDA 20-080/S-005

Glaxo Wellcome  
Attention: James E. Murray  
Regulatory Affairs  
Five Moore Drive  
Research Triangle Park, North Carolina 27709

Dear Mr. Murray:

Please refer to your March 9, 1993 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imitrex® (sumatriptan succinate) Injection.

The supplemental application provides for the Imitrex STATdose System, a new alternative subcutaneous injection delivery system.

We have completed the review of this supplemental application and it is approvable. Before this supplement may be approved, however, you must address the following concerns.

- 1) The draft labelling you have submitted with this supplement is inadequate, because it does not include a description of this product. While we realize that you have not yet made several marketing decisions regarding the introduction of this new injector system (e.g., whether or not it will be co-marketed with the existing approved autoinjector), we cannot approve an application without associated relevant labelling; the currently proposed labelling is, in this context, not adequate. Please submit draft labelling that includes a description of the STATdose autoinjector system in the How Supplied section added to the most recently approved Imitrex Injection labelling.
- 2) As discussed in a telephone conversation between you and Don Grilley and Russell Katz of this Division on May 6, 1996, you must submit

a revised Patient Instruction Sheet that includes replacement of pictures of the previously approved autoinjector with appropriate pictures of the STATdose System.

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.

If you have any questions regarding this matter, please contact Mr. Grilley, Regulatory Management Officer at 301-594-2777.

Sincerely yours,

Handwritten signature of Paul Leber, dated 6/3/96.

Paul Leber, M.D.  
Director  
Division of Neuropharmacological  
Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research



## **MEMORANDUM**

**DATE:** May 30, 1996

**FROM:** Deputy Director  
Division of Neuropharmacological Drug Products/HFD-120

**TO:** File, NDA 20-080/S-005

**SUBJECT:** Supervisory Review of Supplement for a New Imitrex Autoinjector

Glaxo, Inc. submitted Supplement 005 to NDA 20-080 for a new Imitrex Autoinjector and associated drug cartridges (so-called STATDose autoinjector) on March 9, 1993. Currently, Imitrex is available in vials and pre-filled syringes, the latter to be inserted into an autoinjector. This current supplement proposes a new autoinjector and drug filled cartridges. In short, cartridges for this new system are purchased in a 2 cartridge case. The new autoinjector screws directly onto a cartridge while it is still in the case, and once the cartridge is loaded into the autoinjector by this maneuver, the autoinjector is ready to be used. The autoinjector will not inject, however, until a button is pushed and the end through which the drug is to be delivered is in contact with the skin and depressed against it. This device is approved in Denmark, Israel, and South Africa, and has been marketed in these 3 countries since early 1992.

In support of this new drug delivery system, the sponsor has submitted the results of 3 controlled trials, designated S2B-210, S2B-211, and S2B-S75, the first 2 of identical design. These 2 were single dose, randomized, double-blind, parallel group studies in which patients treated a single migraine headache with sumatriptan 6 mg or placebo given subcutaneously via the new autoinjector. A total of 158 (80 and 78 respectively) patients were enrolled in both studies. The last study was essentially the same as the previous 2, save for an unbalanced randomization (60 and 26 patients received sumatriptan and placebo, respectively), and outcome assessment at 1 hour instead of at 2 hours in the first 2 studies. These studies have been reviewed by Dr. Collins of this Division and Dr. Hoberman of the Division of Biometrics. All three

studies demonstrate highly significant results in favor of sumatriptan. In particular, the response rates in these studies were essentially the same as the response rates in the original NDA (in fact, the response rates are somewhat greater in these new studies, both for drug and placebo).

As Dr. Collins describes, 119 patients received a total of 139 injections (20 patients received 2 injections). The adverse event profile mirrors that known to be associated with subcutaneous injection of 6 mg of sumatriptan. There were several patient reports of difficulty using the device and device malfunction, a number of which appeared to be due to inadequate understanding about how the device is to be used.

The application also includes a copy of an instructional sheet to be given to patients which describes, both in narrative as well as pictures, how the device is to be loaded and used. The narrative is clear. In general, the pictures are also clear; however, the pictures demonstrating the application of the device to the skin are pictures of the **old, already marketed autoinjector**. This is clearly an error, as discussed with Jim Murray of the firm in a telephone conversation on May 6, 1996. A revised sheet will be sent to us in the near future.

## **CONCLUSIONS**

The sponsor has presented evidence from controlled trials demonstrating that sumatriptan is effective when delivered via the new STATDose autoinjector. Although the experience with this autoinjector is relatively limited, and, therefore, the rate of possible malfunction that can be excluded is perhaps not as great as we would like, its performance in the controlled trials and apparently successful marketing for 4 years in many countries support its reliability. Further, the sponsor has performed quality testing on several hundred units which examined the amount of volume delivered (see Volume 2 of the supplement, page 27). These data support the conclusion that the product performs reliably. A telephone conversation with Dr. Brenda Bolden of the General Hospital Devices Branch of CDRH also confirms that the amount of clinical data on the product's performance is considerably greater than that ordinarily available for similar products.

(Incidentally, a memo from the Chief of the General Hospital Devices Branch, Pilot Division, of CDRH concludes that, since the STATDose autoinjector is not a stand alone device and cannot be used independently from the drug, the application is rightly reviewed in CDER.)

In addition, the sponsor has committed to resubmitting a corrected patient instructional sheet.

There is one additional outstanding concern. Because the sponsor is apparently not going to market this product immediately after it is approved, they have submitted labelling that does not include a description of it in the How Supplied section. That is, the submitted draft labelling makes no mention of this product at all. I believe that the application can only be approved with adequate labelling, and the approval of the application with labelling that makes no mention of the subject of the approval appears to be a non sequitor, and cannot be done. For this reason, the sponsor should submit labelling that includes a description of the product in the How Supplied section.

## **RECOMMENDATION**

The sponsor should be sent the attached Approvable letter.



Russell Katz, M.D.

Cc:  
NDA 20-080/S-005  
HFD-120  
HFD-120/Katz/Leber/Grilley/Blum  
HFD-713/Hoberman

Memorandum of Consultation

Date: February 13, 1995

Between: David Collins, M.D., HFD-120 153

and: David Hoberman, Ph.D., HFD-713

Subject: Imitrex self-injection supplement (NDA 20-080/SCP-005)

Studies S2B-210 and S2B-211 both clearly demonstrate the efficacy of self-injected sumatriptan. With 40 patients per group in each study, the sumatriptan group showed highly statistically significant differences compared to placebo with respect to primary efficacy outcomes (headache severity as measured by pain scores) and secondary outcomes (clinical disability, associated symptoms, time to meaningful relief, and time to rescue medication). Neither study, however, demonstrated a benefit for significant worsening of headache within 24 hours.

There were no unresolved statistical issues.



David Hoberman, Ph.D.

cc:  
Orig. NDA 20-080/SCP-005  
HFD-120  
HFD-120/Dr. Leber  
HFD-120/Dr. Collins  
HFD-120/Dr. Katz  
HFD-120/Mr. Grilley  
HFD-344/Dr. Lisook  
HFD-713/Dr. Nevius  
HFD-713/Dr. Hoberman  
HFD-713/Dr. Dubey [File DRU 1.3.2]  
chron

# Glaxo

Glaxo Inc.

# ORIGINAL

# NDA SUPPLEMENT

March 9, 1993

Paul Leber, M.D.  
Division of Neuropharmacological Drug Products  
Food and Drug Administration  
Office of Drug Evaluation I  
HFD-120, Room 10B-30  
ATTN: DOCUMENT CONTROL ROOM  
Center for Drug Evaluation and Research  
5600 Fisher Lane  
Rockville, Maryland 20857

NDA NO. 20080 REF. NO. SCP-000  
NDA SUPPL FOR Package

RE: NDA 20-080  
Imitrex™ (sumatriptan succinate) Injection  
sNDA for Imitrex™ STATdose System



Dear Dr. Leber:

This supplemental application for NDA 20-080, Imitrex® (sumatriptan succinate) Injection, provides for the Imitrex™ STATdose System, a new alternative subcutaneous injection delivery system for Imitrex Injection which is also referred to within as the Glaxo Autoinjector.

NDA 20-080 was approved by the Agency on December 28, 1992 for the subcutaneous administration of sumatriptan succinate for the acute treatment of migraine (with or without aura). The currently approved delivery systems in the NDA include a 6mg single-dose vial, and a 6mg unit-of-use syringe which can be used independently or with the Imitrex SELFdose Unit (autoinjector).

This supplement provides for a new alternative self-injection presentation. The Imitrex™ STATdose System with modified (short barrelled) syringe required for its use, are described herein. The syringe for the new autoinjector is similar to that previously approved under NDA 20-080 for use with the Imitrex™ SELFdose System, with the exception that the syringe flange shape has been modified, the barrel length shortened, and the nonproduct contact plunger rod mechanism removed. The plunger rod has been incorporated into the design of the Imitrex™ STATdose System and as a result, the modified syringe can be used only in the Imitrex™ STATdose System. The solution contact materials are unchanged.

To support the use of the new, alternative autoinjector, the results of two clinical studies, S2B210 and S2B211, along with supportive data from a third study, S2B-S75 are submitted.

# CHEMISTS REVIEW OF SUPPLEMENT

1. ORGANIZATION: HFD-120  
2. NDA NUMBER: 20-080  
4. SUPPLEMENT NUMBERS/DATES: S-005  
LETTERDATE 09-MAR-93  
STAMPDATE 11-MAR-93  
5. AMENDMENTS/REPORTS/DATES:  
LETTERDATE 16-JUN-95 fax 20-JUN-95  
STAMPDATE 20-JUN-95  
6. REC'D BY CHM: 12-MAR-93 20-JUN-95

7. APPLICANT NAME AND ADDRESS:

GLAXO, Inc.  
Five Moore Drive  
Research Triangle Park, N.C. 27709 #N 20 1995

8. NAME OF DRUG:

IMITREX INJECTION

9. NONPROPRIETARY NAME:

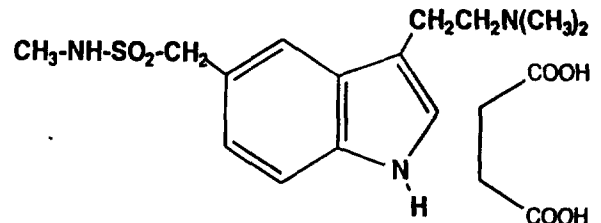
SUMATRIPTAN SUCCINATE

10. CHEMICAL NAME/STRUCTURE:

3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-  
methanesulfonamide, butane-1,4-dioate (1:1)

C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S • C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>

CAS # 103628-48-4



11. DOSAGE FORM(S):

INJECTION, 0.5 mL syringe; 0.5 mL (2 mL vial)

12. POTENCY(IES):

12 mg/mL -- DOSE is 6 mg/syringe

13. PHARM. CATEGORY:

ANTI-MIGRAINE

14. HOW DISPENSED:

XXX (Rx) \_\_\_ (OTC)

15. RECORDS AND REPORTS CURRENT:

XXX (YES) \_\_\_ (NO)

16. RELATED IND/NDA/DMF(S):

NDA 20-132 [Imitrex Tablets]

17. SUPPLEMENT PROVIDES FOR: the Imitrex STATdose System, an alternative subcutaneous injection delivery system, also referred to as the Glaxo Autoinjector

18. COMMENTS: Change is

contact with drug product are not changed.

1. Components in

19. CONCLUSIONS AND RECOMMENDATIONS:

Recommend APPROVAL of NDA 20-080/S-005. Concurrence of MDO required.

20. REVIEWER NAME

SIGNATURE

DATE COMPLETED

Stanley W. Blum, Ph.D.

20-JUN-95

Copies:

ORIG: NDA 20-080

HFD-120

HFD-120/DGrilley

HFD-120/SBlum/20-JUN-95

INIT: SWB/

filename:

N020080 S-005

**Glaxo**

ORIGINAL

NDA 20-080/S-005

June 16, 1995

Paul D. Leber, M.D., Director  
Division of Neuropharmacological Drug Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Food and Drug Administration  
HFD-120  
5600 Fishers Lane  
Rockville, MD 20857



**Re: NDA 20-080/S-005; Imitrex® (sumatriptan succinate) Injection  
Amendment to Pending Application  
Imitrex® STATdose System**

Dear Dr. Leber:

Reference is made to our supplemental application dated March 9, 1993 (S-005) which provided for the Imitrex® STATdose System, a new alternative subcutaneous injection delivery system for Imitrex Injection, also referred to in the submission as the Glaxo Autoinjector. Reference is also made to a June 6, 1995 telephone request from Dr. Stan Blum to myself for additional details on the individual components, operation and controls of the autoinjector.

In response to Dr. Blum's request, we wish to call the Agency's attention to the following portions of the March 9, 1993 supplemental application:

**Method of Operation**

Vol. 1, p.14 Instructions for Use Leaflet

Vol. 2., p.20 Section E2.2.3 Glaxo Autoinjector Operation

**Components, Composition and Controls**

Vol. 2, pp16-23

**Manufacturers**

Vol.2, p5, p16

To further detail the individual components of the autoinjector, appended is **Figure 1** which provides an engineering drawing of the components (and composition) of the autoinjector. The appended **Figure 2** provides an exploded engineering drawing which

Paul D. Leber, M.D.

June 16, 1995

Page 2

demonstrates the placement and relationship of the individual autoinjector components and allows for better visualization of the autoinjector.

The acceptance controls for the autoinjector were described in Sections E.2.2.5.1 and E.2.2.5.2 (Vol.2, pp22-23) of the supplemental application. The acceptance specifications and testing of the autoinjector by Glaxo are hereby modified as follows:

<b>TEST</b>	<b>PROCEDURE</b>	<b>SPECIFICATION</b>
<b>Visual Inspection</b>	Examination for imperfections related to the manufacture and assembly quality of the autoinjector.	The defect level is noted during the examination and compared against agreed acceptable quality levels (AQL) before the consignment is approved for use.
<b>Dimensional Inspection</b>	Measurements are taken of key dimensions	Current drawing (Figure 70)
<b>Performance Standard</b>	Autoinjectors are tested for performance by qualitative and quantitative tests including: successful priming and firing, speed of delivery, cannula length and force to actuate.	

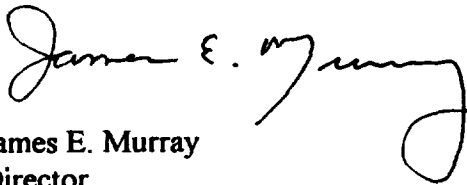


Paul D. Leber, M.D.  
June 16, 1995  
Page 3

We trust that these additional diagrams and details regarding the autoinjector components and controls satisfactorily address Dr. Blum's requests.

If there are any additional questions regarding this supplemental application, please contact me at (919)990-5119.

Sincerely,

A handwritten signature in black ink that reads "James E. Murray". The signature is written in a cursive style with a large, looping "M" at the end.

James E. Murray  
Director  
Regulatory Affairs

cc: Dr. Stan Blum, Supervisory Chemist, HFD-120, Woodmont II Bldg.

# HEMISTS REVIEW OF SUPPLEMENT

1. ORGANIZATION: HFD-120  
 2. NDA NUMBER: 20-080  
 3. SUPPLEMENT NUMBERS/DATES: S-005  
 LETTERDATE 03-MAR-93  
 STAMPDATE 04-MAR-93  
 4. AMENDMENTS/REPORTS/DATES:  
 (BC)LETTERDATE 20-JUN-95  
 (BC)STAMPDATE 21-JUN-95  
 5. REC'D BY CHM: 01-SEP-95

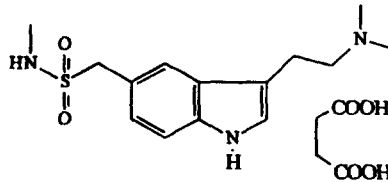
6. APPLICANT NAME AND ADDRESS:

GLAXO WELLCOME, Inc.  
 5 Moore Drive  
 Research Triangle Park, NC 27709

7. NAME OF DRUG:  
 8. NONPROPRIETARY NAME:  
 9. CHEMICAL NAME/STRUCTURE:

IMITREX® Injection  
 sumatriptan succinate

3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide, butane-1,4-dioate (1:1)



C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S · C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>  
 CAS # 103628-48-4

10. DOSAGE FORM(S):  
 11. POTENCY(IES):  
 12. PHARM. CATEGORY:  
 13. HOW DISPENSED:  
 14. RECORDS AND REPORTS CURRENT:  
 15. RELATED IND/NDA/DMF(S):

Injection, 0.5 mL syringe; 0.5 mL (2 mL vial)  
 12 mg/mL, 6 mg does / syringe  
 Antimigraine  
 XXX (Rx) \_\_\_ (OTC)  
 XXX (YES) \_\_\_ (NO)  
 NDA 20-132, IMITREX® Tablets

NDA 20-080, Y-002 IMITREX® Injection Annual Report

17. SUPPLEMENT PROVIDES FOR: STATDOSE® autoinjector system for subcutaneous injection.

sites.

18. COMMENTS: Supplement previously reviewed (SWB), approvable pending inspection o site. Applicant's withdrawal of this site eliminates need for inspection. Two-page letter of notification; no detailed review necessary for amendment.

19. CONCLUSIONS AND RECOMMENDATIONS: The supplement is directly approvable without inspection of th

20. REVIEWER NAME AND SIGNATURE

Doris J. Bates, Ph.D. *Doris J. Bates*

DATE COMPLETED

01-SEP-95 (orig. SWB)

Copies: ORIG: NDA 20-080

FD-120

rHFD-120/GrilleyD

HFD-120/BatesDJ/

Init: SWBlum

*SWB*  
 6/5/96

filename: N020080S.005

**Glaxo**

ORIGINAL

NDA SUPPL AMEND

June 20, 1995

Paul D. Leber, M.D., Director  
Division of Neuropharmacological Drug Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Food and Drug Administration  
HFD-120  
5600 Fishers Lane  
Rockville, MD 20857



**Re: NDA 20-080/S-005; Imitrex® (sumatriptan succinate) Injection  
Amendment to Pending Application  
Imitrex® STATdose System**

Dear Dr. Leber:

Reference is made to our supplemental application dated March 9, 1993 (S-005) which provided for the Imitrex® STATdose System, a new alternative subcutaneous injection delivery system for Imitrex Injection, also referred to in the submission as the Glaxo Autoinjector.

In order to expedite the approval of this supplemental application, we are hereby amending the application to delete the option for future stability testing of the Imitrex STATdose s,  
as noted in the original submission Vol. 2 p005.

A copy of this submission is being faxed to Dr. Stan Blum of the Agency to facilitate the completion of his review of this supplemental application.

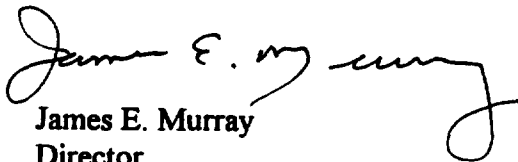
Paul D. Leber, M.D.

June 20, 1995

Page 2

Please contact me at (919)990-5119 if there are any comments or questions regarding this submission.

Sincerely,

A handwritten signature in cursive script that reads "James E. Murray". The signature is written in black ink and is positioned above the printed name and title.

James E. Murray  
Director  
Regulatory Affairs

cc: Dr. Stan Blum, HFD-120, Woodmont II Bldg.  
cc: Mr Don Grilley, HFD-120, Woodmont II Bldg.

17011

SEP 18 1996

# HEMISTS REVIEW OF SUPPLEMENT

1. ORGANIZATION: HFD-120  
 2. NDA NUMBER: 20-080  
 3. SUPPLEMENT NUMBERS/DATES: S-005  
 LETTERDATE 03-MAR-93  
 STAMPDATE 04-MAR-93  
 4. AMENDMENTS/REPORTS/DATES:  
 (AL)LETTERDATE 29-JUL-96  
 (AL)STAMPDATE 30-JUL-96  
 5. REC'D BY CHM: 06-AUG-96

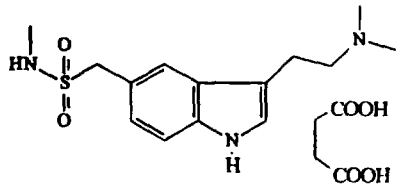
6. APPLICANT NAME AND ADDRESS:

GLAXO WELLCOME, Inc.  
5 Moore Drive  
Research Triangle Park, NC 27709

7. NAME OF DRUG:  
8. NONPROPRIETARY NAME:  
9. CHEMICAL NAME/STRUCTURE:

IMITREX® Injection  
sumatriptan succinate

3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide, butane-1,4-dioate (1:1)



C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S · C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>  
CAS # 103628-48-4

10. DOSAGE FORM(S):  
11. POTENCY(IES):  
12. PHARM. CATEGORY:  
13. HOW DISPENSED:  
14. RECORDS AND REPORTS CURRENT:  
15. RELATED IND/NDA/DMF(S):

Injection, 0.5 mL syringe; 0.5 mL (2 mL vial)  
12 mg/mL, 6 mg dose / syringe  
Antimigraine  
XXX (Rx) \_\_\_ (OTC)  
XXX (YES) \_\_\_ (NO)  
NDA 20-132, IMITREX® Tablets

NDA 20-080, Y-002 IMITREX® Injection Annual Report

17. SUPPLEMENT PROVIDES FOR: STATdose® autoinjector system for subcutaneous injection. *This amendment:* Provides revised labeling in accordance with the FDA approvable letter of 03JUN96.

18. COMMENTS: Supplement previously reviewed (SWB), one prior amendment withdrawing a stability test site. Changes in the package insert are in the PRECAUTIONS, ADVERSE REACTIONS, Postmarketing Experience, Information for the Consumer, and HOW SUPPLIED sections of the labeling. Changes have been made in the patient leaflet "How to Use the IMITREX® STATdose System™" which is also enclosed. The requisite number of copies of labeling were provided.

19. CONCLUSIONS AND RECOMMENDATIONS: minor typographical error in HOW SUPPLIED section. No other CMC deficiencies. Applicant has been informed of the error and agrees to correct. MAY BE APPROVED for chemistry.

20. REVIEWER NAME AND SIGNATURE

Doris J. Bates, Ph.D. *[Signature]*

DATE COMPLETED  
11-SEP-96 (orig. SWB)

Copies: ORIG: NDA 20-080  
HFD-120  
HFD-120/DavidP/ChenL  
HFD-120/BatesDJ/  
Init: SWBlum

*AMB 9/17/96*

20080\_05.02

**MEMORANDUM**

**DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration**

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**Division of Neuropharmacological Drug Products (HFD-120)  
Center for Drug Evaluation and Research**

**Date: December 11, 1996  
From: Randy Levin, M.D., Neurology Team Leader  
Subject: NDA 20-080 supplement 005  
To: file**

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**Introduction:**

An approvable letter for supplement 005 was sent on 6/3/96 with two requests:

1. provide a description of the STAT dose autoinjector in the How Supplied section of labeling and
2. Use pictures of the new autoinjector in the Patient Instruction Sheets.

In addition to this request, the sponsor has included three additional proposed changes to the labeling.

This submission has been reviewed by chemistry, biopharm and clinical reviewers and labeling changes have been suggested.

**How supplied:**

The sponsor has added the following statement to labeling to describe the Imitrex STAT dose:

(NDC-0173-0479-00) Imitrex® STAT dose System TM containing two prefilled single-dose syringe cartridges, one Imitrex® STAT dose Pen TM, and instructions for use.

The chemist found this statement acceptable.

**Consumer information section:**

The sponsor has replaced the pictures in the consumer information section to show the STAT dose unit.

**Nursing Mothers:**

The sponsor conducted a study in 5 nursing mothers to evaluate the sumatriptan levels in breast milk following a single 6 mg subcutaneous dose. The levels were measured hourly for 8 hours following the dose. The T<sub>max</sub> was about 2.6 hours with a C<sub>max</sub> of 87 µg/L. The half life was 2.2 hours with a range of 1.2 to 3.1 hours. At 8 hours, the concentration was 1.7 µg/L with a range of 9 to 20.6 µg/L. With the low levels along with a likely reduced bioavailability for the oral dose in infants, the sponsor concluded that continued breast feeding following a single dose of the drug would result in a very small dose for the infant. They proposed recommending in labeling that nursing mothers avoid breast feeding for 24 hours following a dose to minimize the exposure to the infant.

The sponsor's proposed labeling assumes that there is little or no drug in breast milk 24 hours after the mother has received a single dose of the drug. Our biopharm consultant noted the low levels at 8 hours and the half life of the drug and stated that the data supported the sponsor's statement that breast feeding be avoided for at least 24 hours following administration of sumatriptan. A factor not consider is the frequency of milk expression by the mother. In this study, the women expressed milk every hour. Feeding of infants may be every couple of hours at first but as the child gets older, milk is expressed at longer intervals. This changes the amount of drug in the breast milk at any one time. I would prefer knowing that no drug was in the breast milk at 24 hours prior to recommending that children can be exposed to the breast milk. I suggest that the

sponsor determine when no drug is being excreted into the breast milk prior to telling the patient when it is safe to resume breast feeding.

### **Adverse reactions:**

From post marketing experience, the sponsor has noted reactions at the injection site. The sponsor proposed describing the reactions as including pain, redness, stinging, contusions and subcutaneous bleeding. Dr. Oliva noted in his review that there were reports of swelling and induration as well and I agree that this should also be added to labeling.

### **How to use Imitrex injection:**

The sponsor evaluated the adequacy of the injection site in a study of 20 cluster headache patients (19 males and 1 female). The patients were asked to evaluate the differences between randomized injections in the thigh and gluteal region. The sponsor noted that the thigh injections were associated with greater local side effects (bleeding and local pain) as well as systemic side effects (head, neck and chest pressure). In the males tested, the thickness of the fatty tissue of thigh was 2 to 5 mm. Since the needle length is 5 to 6 mm, the sponsor concluded that some of these effects may be related to intramuscular injection rather than a subcutaneous injection. The sponsor suggested the addition of a statement noting that "Before injecting, identify an area with an adequate fatty tissue layer".

The use of an autoinjector is different from manual administration of a subcutaneous dose. With manual injections, the patient sees the needle and can direct the injection into the subcutaneous area. When using an autoinjector, the patient is not aware of the length of the needle. Placing the needle in a position where there is less distance between the skin and the muscle may result in an intramuscular injection. While this study did not prove that these patients were giving intramuscular injections, it increased my awareness that this is a definite possibility. Intramuscular injections may lead to different local effects and since an intramuscular injection may change the PK of the drug, it may also lead to changes in systemic effects.

Since the choice of injection site may result in intramuscular rather than subcutaneous delivery of the drug, I recommend that prescribers and patients be made aware of this possibility and that this information be added to the Precautions and Dosage and Administration section as well as in the information to patients section. Prescribers and patients should be aware of not only how to select an area adequate for injection but also the possible consequences of



choosing the wrong site. They should know that for the auto injectors, the needle penetrates 5 to 6 mm and that in order to avoid intramuscular delivery of the drug that may be associated with a greater incidence of local and systemic adverse event, patients should be directed to use injection sites with adequate skin and subcutaneous thickness to accommodate the needle length. Patients should be instructed on which injection sites are acceptable.

**Recommendations:**

I recommend that the supplement be approved with the following changes to the drug labeling and patient instruction sheet.

In the **PRECAUTION** section:

**Change:**     **Information for Patients:** See **PATIENT INFORMATION** at the end of this labeling for the text of the separate leaflet provided for patients.

**To:**           **Information for Patients:** With the autoinjector, the needle penetrates 1/4 of an inch (5 to 6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle. See **PATIENT INFORMATION** at the end of this labeling for the text of the separate leaflet provided for patients.

**No change:** **Nursing Mothers:** Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of **IMITREX Injection** to a nursing woman.

In the **ADVERSE REACTIONS** section under **Postmarketing Experience**:

**Change:**     Rarely, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) has been reported following subcutaneous administration of sumatriptan.

**To:**           Following subcutaneous administration of sumatriptan, pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding and on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) have been reported.

In the **DOSAGE AND ADMINISTRATION** section:

**Change:** An autoinjection device is available for use with 6-mg prefilled syringes to facilitate self-administration in patients in whom this dose is deemed necessary.

**To:** An autoinjection device is available for use with 6-mg prefilled syringes to facilitate self-administration in patients in whom this dose is deemed necessary. With this device, the needle penetrates 1/4 inch (5 to 6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.


In the **How Supplied** section:

**Add:** (NDC-0173-0479-00) Imitrex® STAT dose System TM containing two prefilled single-dose syringe cartridges, one Imitrex® STAT dose Pen TM , and instructions for use.

In the **Information for the Consumer** section:

**Change:** Before using the autoinjector, see the enclosed instruction pamphlet on loading your autoinjector and discarding the empty syringes.

**To:** Before using the autoinjector, check with your doctor on acceptable injection sites and see the enclosed instruction pamphlet on loading your autoinjector and discarding the empty syringes.

  
Randy Levin, M.D.  
Neurology Team Leader

cc:  
Original IND  
HFD-120  
HFD-120//Chen  
rl/December 11, 1996

Review and Evaluation of Clinical Data

AUG - 8 1996

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<b>NDA</b>	<b>20-080 / S-005</b>
<b>Sponsor:</b>	<b>GlaxoWellcome</b>
<b>Drug:</b>	<b>sumatriptan STAT-dose</b>
<b>Proposed Indication:</b>	<b>migraine, cluster</b>
<b>Material Submitted:</b>	<b>various</b>
<b>Correspondence Date:</b>	<b>July 29, 1996</b>
<b>Date Received / Agency:</b>	<b>July 30, 1996</b>
<b>Date Received / Reviewer:</b>	<b>August 2, 1996</b>
<b>Date Review Completed</b>	<b>August 8, 1996</b>

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**Introduction:**

This submission is in response to the Agency's approvable letter dated 6/3/96 for the supplemental application S-005 for Imitrex® (sumatriptan succinate) STATdose System™. This is a new alternative subcutaneous delivery system.

The agency letter requested draft labeling that includes a description of the STATdose autoinjector system in the How Supplied section. This description is included in the submission.

In addition, the submission includes changes to the Precautions, Adverse Reactions, and Post-marketing experience sections of the labeling.

Four attachments are included. There are four main items for review:

1. Description and revised labeling of the STATdose Autoinjector system.
2. Changes to the Precautions section to nursing mothers.
3. Changes to the Adverse Reactions section, under Postmarketing Experience regarding local, injection site irritation.
4. Changes to the Information for the Consumer section regarding selection of injection site.

I use each number in the review to refer to these items.

**Attachment 1:**

This contains the revised labeling for Imitrex® (sumatriptan succinate) Injection.

1. How Supplied: The following statement describes the Imitrex STATdose System:

*(NDC-0173-0479-0) Imitrex® STATdose System™ containing two prefilled single-dose syringe cartridges, one Imitrex® STATdose Pen™, and instructions for use.*

2. Precautions: Under the subheading *Nursing Mothers* the following sentence has been added to the end of the paragraph. Justification for the revision is in Attachment 3 (see below):

*"It is recommended that breast-feeding be avoided for 24 hours following administration of sumatriptan."*

3. Adverse Reactions: Under the *Postmarketing Experience* subheading, the following sentence has been added to the end of the paragraph. Justification for the revision is in Attachment 4.

*"Pain, redness, stinging, contusion, and subcutaneous bleeding at the injection site have been reported."*

4. Information for the Consumer: Under the section 4. *How to Use Imitrex Injection* the phrase *"in an area that has an adequate fatty tissue layer"* has been added to the second paragraph, which now reads:

*"For adults, the usual dose is a single injection just below the skin, in an area that has an adequate fatty tissue layer."*

Justification is also in Attachment 4.

#### **Attachment 2:**

This contains copies of final cartons and labels for the Imitrex STATdose System™.

The following changes to the draft labeling have been made to the *"How to Use the Imitrex® STATdose System™"* leaflet:

*"Do not load the Imitrex STATdose Pen until you are ready to give an injection."* and *"Keep the Imitrex STATdose System out of the reach of children"* have been moved to page 1 of the instruction leaflet.

*"Note: Do not use a syringe cartridge if the tamper-evident seal is broken or missing."* Has been added to page 4 of the leaflet and the paragraph has been changed so this it now reads: *"Remove the tamper-evident seal from one container of the cartridge pack. Discard the seal and open the cartridge lid (see Figure 4)."*

*"Grasp the Imitrex STATdose Pen by the ridges at the top (See Figure 5)"* has been added to the top of page 5. Also on page 5 the sentences *"If the white plunger rod is sticking out from the lower end of the Imitrex STATdose Pen, put the Imitrex STATdose Pen back into the carrying case and press down firmly"*

*until you feel it click. Remove from carrying case.*" have been added to the second paragraph.

On page 6 the phrase "*Grasping the ridges*" has been added to the first sentence.

On page 8 the first sentence now read "*Before injecting, identify an area with an adequate fatty tissue layer. Clean the skin area to be injected.*"

The instructions on page 11 have been modified so that the second paragraph now reads "*Put the Imitrex STATdose Pen back into the carrying case and press down firmly until you feel it click. Close the carrying case lid. If the lid will not close, you have not primed the device for the next use. Push the pen down until you feel it click, and then close the lid (see Figure 14).*" The last sentence has been changed so that it now read "*After both cartridges have been used, remove the cartridge pack and discard.*"

### **Attachment 3:**

Report No GCP/95/049: "A Study to Evaluate the Excretion of a 6 mg Subcutaneous Dose of Sumatriptan in Breast Milk", is submitted.

Five lactating females (mean age 27.2 yrs, range 24-32, mean weight 75 kg) took part in an open, single dose study to investigate the excretion of sumatriptan (6 mg s.c.) into breast milk. Sumatriptan concentrations in both plasma and breast milk were measured for 8 hours after dosing.

Blood samples for plasma concentrations of sumatriptan were taken pre-dose, at 5, 10, 15, 20, 30, 45 minutes and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 hours after dosing.

Total milk volume from both breasts was collected pre-dose and at hourly intervals after dosing, and analyzed for sumatriptan concentrations. Mean milk volumes at each collection were: 48.6, 49.6, 21.4, 41.0, and 21.6 mL for subjects 1-5 respectively.

The mean milk-plasma ratio estimated from the areas under the milk and plasma concentration-time curves was 4.9 (95% CI 4.1-5.7). This indicates significant transfer of sumatriptan to the breast milk compartment.

The mean total recovery of sumatriptan in milk was 14.4  $\mu\text{g}$  (95% CI 6.1-22.7  $\mu\text{g}$ ) or 0.24% of the 6 mg dose. On a weight-adjusted basis, this is equivalent to a mean infant exposure of 3.5% (95% CI 0.3-6.7%) of the maternal dose.

The sponsor states that if oral bioavailability in the infant is similar to that in adults, the infant exposure would be reduced further. For example, oral

bioavailability in the adult is approximately 14%. Assuming similar in infants, then the weight-adjusted theoretical exposure in the child would be 0.49% of the maternal dose.

They conclude sumatriptan's low excretion in breast milk suggests that continued breast feeding after administration would result in a very small dose reaching the infant. The sponsor recommends to avoid breast feeding for twenty four hours after taking sumatriptan since this would minimize the exposure. This change appears in the Precautions section of the labeling.

**Results:**

Parameter	Plasma Data Mean (95% CI)	Milk Data Mean (95% CI)
$C_{max}$ ( $\mu\text{g L}^{-1}$ )	80.2 (62.4 - 98.1)	87.2 (61.9 - 112.5)
$T_{max}$ (h)	0.23 (0.13 - 0.31)	2.6 (1.7-3.4)
$T_{1/2}$ (h)	1.3 (0.75 - 1.85)	2.22 (1.16 - 3.1)
MRT (h)	1.47 (1.12 - 1.82)	4.33 (3.25 - 5.41)
Cl ( $\text{L h}^{-1} \text{ kg}^{-1}$ )*	0.91 (0.84 - 1.01)	-
$V_z$ ( $\text{L kg}^{-1}$ )	1.69 (1.34 - 2.34)	-
AUC ( $\mu\text{g L}^{-1} \text{ h}$ )	89.1 (79.3 - 98.8)	432 (372 - 493)

\*assuming bioavailability is complete

**Attachment 4:**

Submitted for review is a prepublication manuscript entitled "The gluteal area compared to thigh as injection site in patients with cluster headache treated with sumatriptan self-injections." In addition, MedWatch reports of injection site reactions are included.

20 cluster headache patients (19 male, 1 female) underwent an open label and questionnaire study to evaluate differences between injection sites in thigh and gluteal areas, regarding depth of fat tissue, local and general side effects and overall patient preference associated with self-injection of sumatriptan 6 mg.

Fat tissue depths were measured using a 3.5 MHz ultrasound probe and in the thigh was 2-5 mm in men, 12 mm in the one female patient. Fat tissue depth in the upper lateral gluteal region was 34-68 mm. The needle of the self injector protrudes 5-6 mm. A total of 40 thigh and 39 gluteal injections were recorded.

Results: There was no difference in sites regarding symptomatic headache relief. The thigh injections were associated with a significantly increased incidence of bleeding ( $p < 0.001$ ), local pain ( $p < 0.05$ ) and "oppression of the head, neck and chest area" ( $p < 0.05$ ) compared with gluteal injections. 15 patients preferred the gluteal injection site, 2 had no preference, 3 preferred the thigh injection site.

Conclusion: Thigh injections, particularly in the male, are more likely to occur intramuscularly and may explain the differences in local and general side effects seen. They conclude that the upper lateral gluteal region is a more suitable injection site when injecting sumatriptan.

This attachment also contains numerous (> 200) MedWatch forms describing many instances of the adverse reactions described above. In addition, swelling and induration were often reported.

**Conclusions:**

1. The draft labeling and description of the STATdose autoinjector included in this submission is complete. In particular, the photographs have been changed to accurately display the new autoinjector system.
2. Concerning the breast milk excretion study, no data were collected after eight hours. The sponsor recommends avoiding breast feeding for 24 hours after sumatriptan administration but presents no data about the sumatriptan milk concentration at 24 hours. The data presented do indicate low and declining levels at 8 hours. The measured levels at 8 hours ( $\pm$  15 min) are:

Patient	Milk Concentration ( $\mu$ g/L)
1	
2	
3	
4	
5	
Mean	

3. Concerning the changes in Adverse Reactions describing local site irritation, there are multiple reports of those reactions described by the sponsor above, in addition, swelling, and induration at the site are also numerous reported.
4. The open label questionnaire study of 20 patients and 79 injections seem to support the advantage of selecting a site with an adequate fatty layer, such as the upper lateral gluteal region.

**Recommendation:**

1. I recommend approval of the STATdose Autoinjector System. Chemistry also concurs.
2. Since no breast milk concentration data are available at 24 hours, the recommendation to avoid breast-feeding for 24 hours should not be made. Pending Biopharm review and agreement, the following statement in the

Precautions section, subheading *Nursing Mothers*, of the labeling should be considered:

*Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of IMITREX Injection to a nursing woman. In a small study of 5 lactating women, low and declining concentrations of sumatriptan (mean = 17 µg/L) were still detectable in breast milk at 8 hours after a single 6 mg subcutaneous dose.*

3. In addition to the changes proposed to the Adverse Reactions section under Postmarketing experience, I would add *swelling*, and *induration*. The sentence should therefore read:

*"Pain, redness, swelling, induration, stinging, contusion, and subcutaneous bleeding at the injection site have been reported."*

4. In the proposed labeling, under Information for the Consumer: , section 4. *How to Use Imitrex Injection* the sentence *"For adults, the usual dose is a single injection just below the skin, in an area that has an adequate fatty tissue layer"* should be amended explain why this is necessary. For example, *"For adults, the usual dose is a single injection just below the skin. An area with an adequate fatty tissue layer should be selected in order to minimize local and generalized adverse reactions."*

**Comments to Sponsor:**

In order to make the recommendation that breast-feeding should be avoided for 24 hours, then pharmacokinetic data at 24 hours should be collected showing undetectable breast milk concentration.



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Armando Oliva, M.D.  
Medical Reviewer

R. Levin, M.D. 

ao  
cc:  
HFD-120  
NDA 20080  
HFD-120/Leber/Katz  
electronic copy-Levin