CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20626

Trade Name: IMITREX

Generic Name: Sumatriptan

Sponsor: Glaxo Wellcome

Approval Date: August 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20626

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20626

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-626

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

AUG 26 1997

Dear Mr. Murray:

Please refer to your August 29, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imitrex (sumatriptan) 5 mg, 10 mg, and 20 mg Intranasal Spray.

Reference is also made to an Agency approvable letter dated April 23, 1997. We also acknowledge receipt of your additional communications dated May 7, May 14, June 3, and June 11, 1997.

The User Fee goal date for this application is November 8, 1997.

This application provides for the use of Imitrex Intranasal Spray in the treatment of migraine headaches.

We have completed our review of this application, as amended, 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 draft labeling (see ATTACHMENT). Accordingly, this application is approved effective on the date of this letter.

Labeling

The labeling accompanying this letter should be used for marketing this drug product. This final labeling is based on your submissions dated May 7, May 14, June 3, and June 11, 1997, and on the Agency telefacsimile sent to you dated July 2, 1997.

Phase 4 Commitment

Please submit three copies of any 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

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the 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.

If you have any questions, please contact Ms. Lana Chen, Project Manager, at (301) 594-2777.

Sincerely yours,

Robert Temple

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20626

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-626

APR 23 1997

Glaxo Wellcome Inc.
ATTENTION: James E. Murray
Five Moore Drive
Research Triangle Park, North Carolina 27709

Dear Mr. Murray:

Please refer to your pending August 29, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Imitrex (sumatriptan) 5 mg, 10 mg, and 20 mg Intranasal Spray.

We also refer to an Agency not approvable letter dated August 28, 1996.

The User Fee goal date for this application is April 30, 1997.

We acknowledge receipt of your amendments dated October 29, 1996, December 20, 1996, January 17, 1997, January 23, 1997, February 06, 1997, March 3, 1997 and March 24, 1997.

We have completed our review of your new drug application as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

CLINICAL ISSUES

1. Labeling

Accompanying this letter (See Attachment) is the Agency's proposal for the labeling of Imitrex Nasal Spray. Our proposal is based on the Imitrex Injection labeling approved on December 23, 1996 under S-005.

Division staff would be happy to discuss any concerns that you might have with any part of the proposed labeling format or content.

It will be necessary for you to submit revised draft labeling or final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

2. Safety Update

Our review of the safety of Imitrex Nasal Spray in the treatment of migraine was based on data accumulated through August 1, 1996 for the integrated database for serious events. You will need to submit a final safety update including safety data

accumulated since this cutoff date. This safety update can focus on deaths, serious adverse events, and patients dropping out of clinical trials for adverse events. It should include a line listing, along with narrative summaries for patients who have died, had a serious adverse event or dropped out with other adverse events of particular interest. We may ask for copies of case report forms for selected patients from this list.

3. World Literature Update

This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conditions about the safety of Imitrex in this population. The report should also detail how the literature search was conducted, by whom, (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

5. Phase 4 Post-Marketing

6. Introductory Promotional Material

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

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

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

If you have any questions, please contact Mr. Merril J. Mille, Senior Regulatory Management Officer, at (301) 594-5528.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER : 20626

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20626 N(AZ)**
Sponsor:	**GlaxoWellcome**
Drug:	**Imitrex Nasal Spray**
Proposed Indication:	**migraine**
Material Submitted:	**Original Protocol**
Correspondence Date:	**10/29/96**
Date Received / Agency:	**10/30/96**
Date Review Completed	**11/29/96**

Introduction

GlaxoWellcome submitted this NDA on 8/29/95 for Imitrex Nasal Spray for the acute treatment of migraine. The agency responded with a non-approvable letter on 8/28/96 due to insufficient information on the long term safety of the product. This submission represents a full response from the sponsor. It includes additional preclinical and clinical data to support its long term safety.

The submission includes a final safety update, final printed labeling for containers and cartons, response to chemistry questions, and an update of patent information.

Background

The Division raised concerns regarding the presence of squamous metaplasia seen in rats and in one dog. The sponsor responds with the information that the pathology of the lesions are reflective of adaptive changes rather than proliferative or pre-neoplastic changes and that the most appropriate animal species for this route of administration is the dog and not the rat. In addition, they obtained an independent pathology assessment of the lesions by

This expert review is provided in the submission. Since this is a preclinical review, I don't include it here.

Based on the ICH guidelines of March 1995 regarding "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long Term Treatment of Non-Life Threatening Conditions," 300-600 patients should be followed for 6 months to assess delayed AE's that occur at a frequency of 0.5-5.0%, and that 100 patients should be followed for one year to assess AE's that may occur with increasing frequency or severity over time. A relevant long term exposure would reflect treatment of at least 2 headaches per month. These guidelines form the standards for evaluation of the long-term safety data.

The Division raised clinical concerns regarding the evidence for transient, local irritation following single doses of the drug. Although there were no acute

changes seen on routine examinations of the nose and throat, the long term experience is too limited to allow long term safety evaluation. Moreover, given the preclinical results, the long term safety concerns are heightened.

The sponsor submits a Final Safety Update in response to this clinical concern. The Update reports safety data from four clinical migraine studies (two active controlled and two uncontrolled studies) completed between 11/10/95 and 8/1/96. The final study reports for these four studies are included in this submission.

Of particular interest are the results of study S2BT51, "An Open Design Study to Evaluate the Efficacy and Tolerability of GR43175N Nasal Spray in the Acute Treatment of Migraine During a 12 Month Period." The current final study report evaluates the safety and tolerability of Imitrex Nasal Spray 20 mg plus an optional 20 mg administration for recurrence over a 12 month period. One hundred and eighty two (182) patients treated a total of 6382 migraine attacks in this study and 86 patients completed one year treatment with an average of four attacks per month. AE incidence were comparable though higher than those associated with single doses. No serious adverse events were reported.

Additional biopharmaceutical and chemistry concerns were raised which are not reviewed here.

Final Safety Update

This final safety update contains safety data from four clinical migraine studies: AMI-03, S2B-M12, SUMB3007, and S2B-T51. These were completed between 11/10/95 and 8/1/96. Final study reports are included in this submission. Serious Adverse Events between 11/10/95 and 8/1/96 are also included. Earlier reports were included in the Four Month Safety Updated previously submitted 12/20/95.

Description of the Studies

Table 1 summarizes the four clinical studies from which long-term safety data are drawn. The first two (AMI-03, S2B-M12) were controlled. The last two (SUMB3007, S2B-T51) were uncontrolled.

AMI-03 was a phase II double-blind study conducted in 44 centers in Japan. It evaluated the nasal spray at 5 mg, 10 mg, and 20 mg. A total of 260 entered the study and 198 patients received treatment. It began in 10/94 and ended in 12/95. No serious adverse events were reported since the 4 month safety update 11/95-8/96).

S2B-M12 was a randomized, double-blind, double-dummy, parallel group study conducted in Canada, Denmark, and the UK which compared the efficacy and safety of the nasal spray 20 mg vs. 100 mg tablet. It began 5/95 and ended 11/95. A total of 472 patients were treated. There are two serious adverse event

reports. One patient reported chest pain, shortness of breath, and arm pain lasting 15 minutes within three hours of receiving Imitrex Nasal Spray 20 mg. The second patient reported a gastrointestinal bleed that lasted for 6 days after administration of the Imitrex tablet 100 mg. Neither was withdrawn from the study.

Table 1: Source of Safety Data, Imitrex Nasal Spray

Study Type / No.	Title	Treatment [Optional Dose]	No. patients receiving at least 1 dose
Controlled Non-US AMI-03	Clinical Evaluation of Intranasal Sumatriptan in the Acute Treatment of Migraine Attack	A. Nasal 5 mg	61
		B. Nasal 10 mg	66
		C. Nasal 20 mg	71
		Total	**198**
Controlled Non-US S2B-M12	A Double-Blind, Double-Dummy, Parallel Group Study to Compare the Relative Efficacy and Safety Profiles of 20 mg Sumatriptan Nasal Spray and 100 mg Sumatriptan Tablet in the Acute Treatment of Migraine	A. Nasal 20 mg [+Oral 100 mg]	238
		B. Oral 100 mg [+Oral 20 mg]	234
		Total	**472**
Uncontrolled Non-US SUMB3007	An Open Parallel Group Study to Compare the Speed of Onset of Action of 20 mg Sumatriptan Nasal Spray with 100 mg Tablets	A. Nasal 20 mg	96
		B. Oral 200 mg	91
		Total	**107**
Uncontrolled Non-US S2B-T51	An Open Design Study to Evaluate Repeat Dose GR43175N Nasal Spray During a 12 month period	Nasal 20 mg [+Nasal 20 mg]	182
		Total	**182**

SUMB3007 was conducted in the UK at 40 centers between 9/95 and 4/96. It compared the nasal spray 20 mg with the tablet 100 mg. A total of 96 patients treated 223 attacks with nasal spray and 91 patients treated 222 attacks with tablets. No serious adverse events were reported since the four month safety update (11/95-4/96).

S2B-T51 assessed the safety and tolerability of repeat dosing with the nasal spray over a 12 month period at 20 centers in Canada, France, and Israel. A total of 182 patients treated 6382 migraine attacks. No serious adverse events were reported since the four month safety update (11/95-1/96).

Summary of Safety Results in Clinical Studies

AMI-03

A total of 260 patients enrolled, and 198 treated a single migraine attack. A total of 61, 66, and 71 patients treated with Imitrex Nasal Spray 5 mg, 10 mg, and 20

mg, respectively. Safety measures included incidence and nature of adverse events, screening and post-treatment ECG's, vital signs, and laboratory tests.

The overall incidence of AE's (excluding bitter taste) were 22%, 14%, and 26% for the 5 mg, 10 mg, and 15 mg dose, respectively. The most commonly reported AE across treatments were sleepiness (4), nose pain (5), hot feeling (4), and sore throat (4).

A bitter taste was reported by 87% (170/196). Seven percent (7%, 13/196) reported the taste as "unbearably bitter." A higher percentage of patients reported either slightly bitter, bitter but bearable, and unbearably bitter taste after 10 mg, and 20 mg doses compared with the 5 mg dose.

No serious adverse events, deaths, or pregnancies were reported and no patient withdrew from the study due to adverse events. There were no clinically significant changes in vital signs, or ECG's. Eight patients (2, 3, and 2, in the three dose groups, respectively) had abnormal laboratory abnormalities but none was considered clinically significant and none was reported as an adverse event by the investigators.

No patients withdrew due to adverse events or lack of efficacy. A total of 62 patients withdrew for "other" reasons: 49 had no opportunity to treat during the study, 8 failed to return or were lost to follow-up, and 5 withdrew consent.

S2B-M12

A total of 476 patients in Canada, Denmark, and the UK were randomized to treated up to 3 attacks, of whom 472 patients treated at least once with study medication. A total of 238 patients received nasal spray 20 mg and 234 patients received 234 received tablets 100 mg. Safety measures included the incidence and nature of adverse events, screening measurements of blood pressure and heart rate, and screening ECG". Post treatment vital signs and ECG" were not required but were performed if necessary.

The overall incidence of AE's was similar in the two treatment groups, with 53% receiving nasal spray 20 mg and 50% receiving tablets reporting AE's. The profile of AE's differed in that the most common AE was "odors and taste" (i.e., bad taste, foul taste, bitter taste, and bad smell) in the nasal spray group (21% of patients); and "nausea and vomiting" in the 100 mg tablet group (12%).

Two patients reported serious adverse events. One patient had chest pain, shortness of breath, angina pain, and pain in arms was reported in the Four Month Safety Update, dated 12/20/95. The other patient suffered a gastrointestinal bleed lasting six days. The time to onset of the SAE is unknown and the investigator felt this event was unrelated to treatment.

There were 12 withdrawals due to treatment (8, (3%) for nasal spray, and 4 (2%) for tablet). Six patients from the 20 mg nasal spray group and 3 from the tablet group experienced drug-related events as described by investigators. AE's which resulted in withdrawal from the nasal spray group include nausea and vomiting, severe migraine, tingling, unpleasant sensations, lightheadedness, sweating, burning sensation, bad taste, paresthesia. In the tablet group, AE's resulting in withdrawals included throat pain, malaise, dizziness, numbness, pain, stiffness, pressure sensation, nausea, vomiting, anxiety, fluttering of heart, and restlessness.

Blood pressures were taken at screening only. One patient had a systolic BP of 163 mm. This patient experience two unresolved and non-serious AE's (increased cholesterol and lumbar root pain). No follow-up measure of BP or heart rate was taken in this individual.

No follow-up ECG's were performed since no patient had an adverse event that clinically required one. No laboratory tests were collected.

SUMB3007

This was an open label study. A total of 219 patients were included in the intent to treat population, in which 111 were randomized to nasal spray 20 mg and 108 to tablet 100 mg. A total 96 and 91 patients in the UK were treated with nasal spray and tablet, respectively. The 96 patients on nasal spray treated a total of 223 attacks. All of the AE's reported are based on the intent to treat population. The measure of safety in this study was the incidence and nature of adverse events.

A total of 114 adverse events were reported, of which 66 events by 34 patients (31%) in the nasal spray 20 mg group, and 48 events by 30 patients (28%) in the tablet 100 mg group were reported. Of the 66 events in the nasal spray group, 27 (41%) were bad or bitter taste. Excluding these bad or bitter taste events, the percentage of patients reporting at least one adverse event decreases for 31% to 22% (24 patients) in the nasal spray group.

No serious adverse events were reported. There were no deaths. One patient reported pregnancy 6 days after using her first dose of tablet 100 mg. The outcome of this pregnancy is presently unknown.

Four (4) patients reported adverse events resulting in withdrawal. One patient reported heaviness in arms, legs, and head simply stated "family problems" as the reason for withdrawal. Other AE's resulting in withdrawals were vomiting/bad taste, blurred vision, severe migraine, sleepiness, and lethargy.

No vital signs or ECG's were measured or recorded. No laboratory tests were performed.

One hundred (100) patients withdrew after randomization: 12 (3%) withdrew due to adverse events, 10 (2%) withdrew due to lack of efficacy, 78 (17%) withdrew for "other" reasons (including 16 who failed to return, 43 failed to treat an attack at the appropriate time).

Four (2%) withdrew due to adverse events, 4 (2%) due to lack of efficacy, and 3 (2%) withdrew for "other" reasons. Of the 3 who withdrew due to adverse events, 1 was from the Nasal Spray 20 mg group.

S2B-T51

This was an open label, year long study. A total of 182 male and female patients treated at least one attack with nasal spray 20 mg. The population was predominantly female (85%). Of the initial 182, 116 patients completed the study. A total of 6382 attacks were treated by the 182 patients with a per-patient average monthly rate of 2.9 treated attacks. The per-patient monthly rate of attacks in the 86 patients who completed one year of treatment was 4 attacks. The majority of patients (72%) treated up to 50 attacks while in the study. Twenty patients (11%) treated over 70 attacks with study medication.

Safety measures included the incidence and nature of adverse events, measurements of BP and heart rate, hematological and biochemical laboratory tests, and brief physical examinations pre- and post-treatment. Since patients enrolled in this study were participants in a previous intranasal study, no ECG's were taken at screening unless the previous ECG was greater than 3 months from the screening dated. Post-treatment ECG's were performed if necessary at the discretion of the investigators.

Adverse events were reported following initial treatment of a migraine attack up to one year by 116 patients (74%). Investigators assessed AE's as drug related in 75 patients (41%). Overall, these percentages are higher than those noted in the single-attack studies due to patient's multiple exposure to the study drug during one year of treatment.

The most common AE's reported following initial dose and up to 1 year were disturbance of taste, reported mostly as a bad or bitter taste (34 patients, 19%), followed by nausea/vomiting (31 patients, 17%), disease of nasal cavity/sinuses (31 patients, 17%)[1], throat symptoms (11 patients, 6%)[2], headaches (9 patients, 5%), and influenza (9 patients, 5%). Other individual AE's occurred with an

[1] Includes acute nasopharyngitis, blood in nasal mucus, burning sensation in nasal mucosa, cold symptoms, crusting in nostrils, epistaxis, nasal blockage, nasal congestion, nasal discharge, nasal itching, nasopharyngitis, sinus pain, rhinitis, sinusitis, sneezing, stickiness or nasal mucosa, stinging sensation in nose, tender nostrils, and URI.

[2] Includes burning in pharynx, dryness of throat, irritation of pharynx, laryngitis, pharyngitis, foreign body sensation, sore throat, stenosis of laryngopharynx, throat infection, and throat pain.

incidence of 4% or less. When analyzed by time (in months) and by attacks, the overall combined incidence of diseases of the nasal cavity/sinuses declined with time. This could be due to the following factors: a) patients do not experience these AE's with continued use, b) patients become familiar with these events and no longer report them with continued use, or c) a combination of the above.

There were no reports of serious adverse events, deaths, or pregnancies since the last Safety Update (11/10/95 - 8/1/96), however 6 patients reported SAE's (not considered drug related by the investigators) and one reported pregnancy during the previous interim period, details of which were already submitted to the Division in the NDA 20-626 submission of 8/29/95.

Eight patients withdrew due to adverse events. Three of these were previously reported in the 8/29/95 submission. Of the remaining 5 patients, 2 withdrew as a result of AE's not considered drug related by investigators. On patient had a calculus of the gall-bladder associated with elevated liver enzymes, and one patient had depression. Two others withdrew due to events considered unlikely to be related to treatment: an exacerbation of migraine and an elevation of BP without a diagnosis of hypertension. The remaining patient withdrew due to dizziness, syncope, and vertigo, which was considered to be drug-related by the principal investigator.

Vital signs were recorded at entry and were performed at follow-up if clinically indicated. There was one recorded AE of hypertension, and this event was not considered drug related by the investigator.

Screening ECG's were obtained, but no follow-up ECG's were done unless clinically indicated. Five (5) patients had follow-up ECG's:

1. one had reported chest heaviness, ECG was normal
2. one had mild chest tenderness 30 minutes after nasal spray 20 mg and continued for 11 days. Pre and post-ECG were normal.
3. one had shoulder and neck strain on one occasion after nasal spray. ECG were normal before and after treatment
4. one reported "hot flushes" four days after treatment and had multiple ECG's which were all normal
5. one had several ECG's recorded due to abnormalities noted in the previous studies. The ECG showed flat ST segments and T wave inversion before receiving sumatriptan. This was assessed as a possible normal variant. The patient continued in the study and similar abnormalities were noted at subsequent visits.

Twenty-four patients had laboratory tests performed both before and after treatments. None had a laboratory test value which exceeded the Sponsor's defined threshold criteria and none were reported as AE's.

Sixty-four (64) withdrew from the study: 8 (4%) withdrew due to adverse events, 31 (17%) withdrew due to lack of efficacy, 25 (14%) withdrew for "other" reasons (11 failed to return, and one became pregnant). All those who withdrew due to adverse events or pregnancy received Nasal Spray 20 mg.

Table 2: Imitrex Nasal Spray: Long Term Exposure Summary

Study	N	With-drawals	N treating ≥1 attack	N receiving NS	N of attacks	total attacks per patient	N treated 1 year	Rate of Attack (per mo)	N treated 6 mos	Rate of Attack (per mo)
AMI-03	260	62	198	198	198	1.0	n/a	n/a	n/a	n/a
S2B-M12	476	100	472	238	569	2.4	n/a	n/a	n/a	n/a
(Sub-total for controlled studies)	(736)	(162)	(670)	(436)	(767)					
SUMB3007	219	11	187	96	223	2.3	n/a	n/a	n/a	n/a
S2B-T51	182	64	182	182	6382	35.1	86	4	116	4
(Sub-total for uncontrolled studies)	(401)	(75)	(369)	(178)						
TOTAL	1137	237	1039	714	7372	10.3	86	4	116	4

Comments

1. The first three studies (AMI-03, S2B-M12, and SUMB3007) are single attack studies (maximum 3 attacks) and the overall long-term exposures are too small to assess long-term safety.
2. The fourth study (S2B-T51) treated 86 patients for one year with an average of 4 attacks per month, and 116 patients for six months with an average of 4 attacks per month. The absolute number of patients exposed does not meet ICH guidelines to demonstrate long-term safety. However, the attack frequency of 4 per month in both groups is double the 2 per month minimum. Therefore, the lower numbers of patients is partially offset by the increased exposure per patient.
3. Furthermore, Imitrex is a known, marketed drug with known systemic side effects. There is no evidence to suggest that long-term systemic side effects are any different with the nasal spray. The only unique concern is the potential long-term effect on the nasopharynx. The nasal spray has a widely-reported unpleasant bitter taste, but there is no evidence from the available data to suggest that the nasal spray is not safe. The sole remaining question is whether the numbers of patients exposed are sufficient to assess long-term safety.
4. I believe that the current long-term safety data support approval, with proper labeling to reflect that long term safety data are still preliminary. Additional post-marketing is recommended.

A Oliva

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. (see my memo)

ao 11/29/96
cc:
HFD-120
NDA 20626 N(AZ)
HFD-120/Leber/Katz
electronic copy-Levin

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:----------	**20-626**
SPONSOR:----------	**Glaxo**
DRUG:----------	**Imitrex Nasal Spray**
INDICATION:----------	**Migraine**
MATERIAL SUBMITTED:---	**NDA application**
CORRESPONDENCE DATE:-	**8/29/95**
DATE RECEIVED:----------	**8/31/96**
DATE REVIEWED:----------	**4/29/96**

Overview:

The sponsor has investigated the use of sumatriptan in various formulations for the acute treatment of migraine headaches. Sumatriptan subcutaneous injection has been approved for the acute treatment of migraine and cluster headaches (NDA 20-080) and sumatriptan tablets have been approved for the acute treatment of migraine headaches (NDA 20-132). Suppository and intranasal formulations were evaluated to provide patients with more convenient routes of administration. The sponsor submitted an NDA for the use of sumatriptan suppositories (NDA 20-598) but subsequently withdrew deciding that this route was not going to used by patients in the US. The current NDA is for an intranasal route of administration.

To support this application, the sponsor has provided data from 4,489 healthy volunteers and patients enrolled in 23 studies. The sponsor has included data from 10 clinical pharmacology studies, 8 placebo controlled migraine studies, one active controlled migraine study (vs DHE 45), two uncontrolled migraine studies, one ongoing, uncontrolled migraine study and one uncontrolled cluster headache study. The sponsor has also included summary data from 1 clinical pharmacology study investigating the effect of nasal xylometazoline on the PK of the nasal spray, four phase 1 studies conducted in Japan on 27 healthy male volunteers (2 with the gel formulation of sumatriptan and two phase 1 studies with the nasal spray), one ongoing migraine study being performed in Europe and one ongoing phase 2 migraine study underway in Japan. (Note: phase 2 or 3 studies with the letter T or P in their name were conducted outside the US.)

The objective of the ten clinical pharmacology studies conducted in healthy volunteers was to find a nasal formulation that was well absorbed and well tolerated. Study WHP 88 16, WHP 87 16, WHP 86 34 evaluated the nasal spray. Study WHP 87 28 evaluated nasal drops and spray. Study WHP 87 13 evaluated nasal drops. Study WHP 88 14 evaluated a dry powder preparation. Studies C93-053, C93-065, S2B-125 evaluated an unpreserved, buffered aqueous nasal spray of sumatriptan delivered as the hemisulphate salt. Study WHP 90 04 showed that preservatives did not effect the PK of the drug. From the results, the sponsor concluded that the unpreserved, buffered aqueous nasal spray of sumatriptan as the hemisulphate salt delivered as a single dose produced adequate absorption and was equally or better tolerated that the other nasal formulations.

The sponsor looked for a dose that was both tolerated and effective in three, well controlled, dose ranging studies. These studies, S2B-T35, S2B-T39 and S2B-T47, evaluated doses of 1, 2.5, 5, 10, 20 and 40 mg. Study S2B-T47 used the marketed formulation while studies T35 and T39 used a preserved buffered formulation. The sponsor concluded from these studies that there was no benefit from administering the dose into two nostrils instead of one. They also concluded that a dose less than 5 mg was not effective and that 40 mg was no more effective than 20 mg.

The sponsor performed five, well controlled, pivotal, efficacy and safety studies comparing 0, 5, 10 and 20 mg of the formulation proposed for marketing. Two studies, S2B-340, S2B-341 and S2B-342, were conducted in the US while studies S2B-T50 and S2B-T05 were conducted outside the US. In study T05, patients treated a single attack in the clinic and all patients received two doses separated by 15 minutes. Patients in studies T50, 340 and 341 treated a single attack at home. A second dose was allowed if the patients continued to have pain 2 hours after the initial treatment. In study 342, patients were allowed to treat up to 3 attacks at home. A second dose was allowed if patients continued to have pain.

One active controlled cross over study, S2B-T60, compared 1 mg of intranasal DHE with an option for a second dose, with 20 mg of sumatriptan. A single open label study was conducted in 5 patients with cluster headaches.

To provide additional safety experience, the sponsor conducted three uncontrolled studies. Study S2B-P12 evaluated 10, 20, 30 and 40 mg. Patients were allowed to use a second dose if there was no relief after 20 minutes. Study S2B-P25 was an open label follow up for patients in study S2B-T05. Patients use two doses of 20 mg separated by 15 minutes. Study S2B-T51 was a 12 month, open label extension of study S2B-T47. Patients took 20 mg with an optional

second dose for headache recurrence. Study S2B-T51 was ongoing at the time of the submission and a 6 month interim analysis was provided.

Other studies included 4 clinical pharmacology studies conducted in Japan. The only information from these studies, AMI-01, AMI-02, AMN-01 and AMN-02, was that no serious AEs or withdrawals were reported from the 27 subjects studied.

The safety data base included all information from studies completed by 5/22/95 plus additional information from a 4 month safety update. This included the 10 PK studies, 5 placebo controlled studies, one active controlled study, three open label studies and the single study in patients with cluster headaches and the serious adverse events from the 4 PK studies conducted in Japan. A total of 3,767 subjects were involved in the controlled clinical trails, with 3,026 subjects receiving at least a single dose of the sumatriptan and 741 exposed to placebo. 1,007 were treated with 10 mg, 1249 received 20 mg and 77 received 40 mg.

Efficacy:

Clinical Program:

Eight randomized, double blind, placebo controlled, parallel studies provided the basis of the sponsor claims for efficacy. The studies are summarized briefly as follows:

Efficacy studies (part 1 of 2)			
Study number	Design	Treatment Groups	Number of patients
S2B-T35	Treatment of a single migraine	0 mg 1 mg 5 mg 10 mg 20 mg 40 mg	40 39 42 39 40 42
S2B-T39	Treatment of a single migraine (two nostrils)	0 mg 1 mg 5 mg 10 mg 20 mg 40 mg	31 34 33 35 39 34
S2B-T47	Treatment of a single migraine	0 mg 2.5 mg 5 mg 10 mg 20 mg	63 122 122 115 119
S2B-T05	Treatment of a single migraine	0 mg 20 mg	37 36
S2B-T50	Treatment of a single migraine	0 mg 10 mg 20 mg	151 288 292
S2B-340	Treatment of a single migraine	0 mg 10 mg 20 mg	100 106 202

Efficacy studies (part 2 of 2)			
S2B-341	Treatment of a single migraine	0 mg 10 mg 20 mg	112 109 215
S2B-342	Treatment of a three migraine attacks	0 mg 5 mg 10 mg 20 mg	198 297 294 288

Study design:

Definitions:

The following definitions were used in all of the efficacy studies:

- Headache severity was rated as severe (3), moderate (2), mild (1) or none (0).
- Clinical disability was rated as requiring bed rest (3), function severely impaired (2), function impaired to some degree (1), no disability (0)
- Headache relief was defined as no headache or mild pain.
- Headache recurrence was defined as complete or almost complete headache relief (no pain or mild pain) at 120 minutes and no rescue medication and subsequent significant worsening between 120 minutes and 24 hours after dosing.
- A new attack was any migraine occurring after a 24 hour pain free interval.
- Meaningful relief of headache was a subjective rating by the patient that relates to the achievement of a worth while degree of relief from migraine symptoms.

Selection criteria:

For the three US based pivotal studies, 340, 341 and 342, the selection criteria were nearly identical. Patients were from 18 to 65 years old. They all had a

diagnosis of migraine with or without an aura using the IHS criteria with a headache frequency ranging from 1 to 6 migraines a month (2 to 8 in study 342). Patients with basilar or hemiplegic migraines were excluded. Patients with ischemic heart disease, uncontrolled hypertension, Raynaud's syndrome, a history suggestive of cerebrovascular disease, a history consistent with unrecognized coronary disease and other concurrent medical problems that may otherwise effect the results of the study were excluded. Women who were not using adequate contraceptive methods and women who were breast feeding or pregnant were also excluded. In these studies, patients were not allowed to use MAOIs, SSRIs or lithium within 2 weeks of the study treatment (study 342 only excluded the use of MAOI). Imitrex and ergotamine containing medication were not allowed 24 hours before and after study treatment (in study 342, Imitrex could be used 4 hours after treatment). Analgesics or antiemetics were not allowed within 6 hours of the study treatment. Patient selection criteria were similar for the dose ranging, open and active control studies.

Dose:

In the initial dose ranging studies, T35 and T39, a preserved buffered formulation of the nasal spray was used. In all other studies, the proposed formulation for marketing was used. In study, T39, the dose was divided and given into each nostril. In all other studies, the dose was given in one nostril. Patients were instructed in the use of the nasal applicator. After blowing the nose, the applicator was to be inserted into the nostril about 1 cm. The opposite nostril was covered and the patient was instructed to breathe through the nose at the same time the plunger was pushed.

Except for the dose ranging studies, all patients were allowed to take a second dose of the study treatment if the migraine pain worsened between 2 and 24 hours after the initial treatment. In study T05, all patients took a second dose after 15 minutes.

Study procedures:

After using the study treatment, the patients started a stopwatch and filled out a migraine assessment/Diary card which recorded (the time period for study T49 was 240 minutes):

1. the date and start time of the attack, the date and time of taking the study treatment.

2. severity of the pain at 0,15,30,60,90 and 120 minutes post dosing.
3. Presence or absence of associated symptoms (nausea, vomiting, photophobia and phonophobia) at 0,15,30,60,90 and 120 minutes post dosing

4. Overall Clinical Disability at 0,30,60,90 and 120 minutes post dosing.

5. Time to meaningful relief of headache

6. Any medication taken within 24 hours of the treatment dosing.

Study outcome:

Patients were instructed to treat migraine headaches with a severity of moderate to severe. The primary outcome was the headache relief rate 120 minutes after receiving the study treatment except in study 342 where the primary outcome was the headache relief rate at 60 minutes. Secondary outcome measures were defined as headache relief at 15, 30, 60 and 90 minutes post dose, pain free rates at 120 minutes, meaningful headache relief at 120 minutes post dose, number of patients with normal or mild clinical disability at 120 minutes post dose, absence of associated symptoms (nausea, vomiting, photophobia and phonophobia) at 120 minutes post dose, number of patients with headache relief at 120 minutes and rescue free for 24 hours.

Analysis:

All studies were powered to detect a difference between placebo and either dose of the drug. All patients who received treatment and returned the dairy card were included in the intent to treat population. Only patients with a baseline headache severity of moderate to severe were included in the assessments of headache relief.

Results:

Dose Ranging studies:

Study S2B-T05:

Design:

This was a pilot, multicenter, multinational, randomized, double blind, placebo

controlled, parallel study conducted in Finland from 8/88 to 2/89 evaluating sumatriptan nasal spray for the acute treatment of migraine attacks. Patients received one dose of 20 mg followed 15 minutes later by a second 20 mg dose in a clinic. Patients were allowed to use rescue treatment 2 hours after receiving the first dose of the drug. Assessments of the headache severity were measured at 0, 30, 60 and 120 minutes.

Disposition:

76 patients were enrolled at 6 centers with 74 randomized and treating at least one migraine with the study treatment. One patient in the active group, who did not receive both doses of the drug because the headache resolved before 15 minutes, was excluded from the efficacy analysis. The disposition of patients is summarized in the following table.

Study S2B-T05: Patient Disposition			
	Placebo	Drug	Total
Patients randomized	37	37	74
Patients treated with two doses	37	36	73

Demographics:

85% of the patients were female with a mean age of 39 years. 99% of the patients were white. 74% of the patients did not have an aura with their migraine. There was an imbalance between group for the type of migraine. 13 patients in the active group and 6 in the placebo group had classical migraines. There were no other major differences between groups for any of the demographic parameters. The baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for drug group when compared to placebo.

Subgroup analyses were not performed.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting and photophobia) are summarized in the following table.

Study S2B-T05: Initial efficacy results		
Outcome	Placebo (N=37)	Drug (N=36)
Headache relief		
at 30 minutes	30%	42%
at 60 minutes	30%	64%*
at 120 minutes	32%	75%*
Presence of nausea at 120 minutes	38%	14%*
Presence of Vomiting at 120 minutes	14%	0%
Presence of photophobia at 120 minutes	51%	19%*
No disability at 120 minutes	11%	56%*
Rescue free for 24 hours	16%	68%*

*Nominal p value < 0.05 in a comparison with the placebo group

Study S2B-T35

Design:

This was a multicenter, multinational, randomized, double blind, placebo controlled, parallel, dose ranging study conducted from 8/12/90 to 3/91 in France Germany and Norway evaluating sumatriptan nasal spray for the acute treatment of migraine attacks. The buffered solution was used. Patients were randomized to 0, 1, 5, 10, 20 or 40 mg. Patients were treated in a clinic setting. Patients were allowed to use rescue treatment 3 hours after receiving the study treatment. Assessments of the headache severity were measured at 0, 30, 60, 90, 120 and 180 minutes.

Disposition:

245 patients were enrolled at 21 centers with 245 randomized and treating at least one migraine with the study treatment. Three patients were excluded for treating

a mild headache. The disposition of patients is summarized in the following table.

Study S2B-T35: Patient disposition						
	Plb	1 mg	5 mg	10 mg	20 mg	40 mg
Patients enrolled	40	40	42	40	41	42
Patients included in analysis	40	39	42	39	40	42

Demographics:

78% of the patients were female. The mean ages ranged from 38 to 41. 99% of the patients were white. About 76% of the patients did not have an aura. There were no major differences between groups for any of the demographic parameters. The baseline headache type ranged from classical migraine in 3% in the placebo group to 20% in the 20 mg group. 38% of the patients in the placebo group and 54% of the patients in the 20 mg group treated their headache within 4 hours. Otherwise, the baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for all drug groups when compared to placebo except for 1 mg.

Subgroup analyses were not performed.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting and photophobia) are summarized in the following table.

Study S2B-T35: Initial efficacy of sumatriptan						
	PLB	1 mg	5 mg	10 mg	20 mg	40 mg
Outcome						
Headache relief						
at 30 minutes	10%	13%	29%*	18%	45%*	33%*
at 60 minutes	28%	26%	50%*	51%*	60%*	52%*
at 120 minutes	35%	38%	67%*	67%*	78%*	60%*
at 180 minutes	48%	44%**	69%*	64%	85%*	67%*
Pain free rates at 120 minutes[1]	13%	13%	36%	33%	41%	40%
Presence of nausea at 120 minutes	25%	25%	10%	18%	17%	17%
Presence of Vomiting at 120 minutes	3%	3%	2%	5%	2%	5%
Presence of photophobia/phonophobia at 120 minutes	45%	55%	31%	35%	20%*	32%
No disability at 120 minutes[1]	10%	15%	43%	35%	44%	48%
Rescue free for 24 hours						

*Nominal p value < 0.05 in a comparison with the placebo group
[1] No statistical analyses were performed

Study S2B-T39

Design:

This was a multicenter, multinational, randomized, double blind, placebo controlled, parallel, dose ranging study conducted in Sweden, Finland and Eire evaluating sumatriptan nasal spray for the treatment of a acute migraine attacks. Patients were randomized to 0, 1, 5, 10, 20 or 40 mg. The patient received the dose as two nasal insufflation, one in each nostril. A buffered solution was used. Patients were allowed to use rescue treatment 3 hours after receiving the study treatment. Assessments of the headache severity were measured at 0, 30, 60, 90, 120, 150 and 180 minutes.

Disposition:

210 patients were enrolled at 17 centers. Four patients were excluded for treating a mild headache. The disposition of patients is summarized in the following table.

Study S2B-T39: Patient disposition						
	Plb	1 mg	5 mg	10 mg	20 mg	40 mg
Patients enrolled	32	34	33	36	40	35
Patients included in analysis	31	34	33	35	39	34

Demographics:

82% of the patients were female. The mean ages ranged from 41 to 44. 100% of the patients were white. 65 to 75% of the patients did not have an aura. There were no major differences between groups for any of the demographic parameters. The baseline headache type ranged from classical migraine in 3% in the placebo group to 20% in the 20 mg group. 38% of the patients in the placebo group and 54% of the patients in the 20 mg group treated their headache within 4 hours. Otherwise, the baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for the 10, 20 and 40 mg groups.

Subgroup analyses were not performed.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting and photophobia) are summarized in the following table.

Study S2B-T39: Initial efficacy of sumatriptan						
	PLB	1 mg	5 mg	10 mg	20 mg	40 mg
Outcome						
Headache relief						
at 30 minutes	19%	24%	27%	20%	38%*	29%
at 60 minutes	42%	29%	45%	46%	59%	62%
at 90 minutes	48%	35%	52%	66%	72%*	71%
at 120 minutes	46%	38%	47%	67%*	73%*	70%*
at 180 minutes	35%	35%	36%	69%*	74%*	71%*
Presence of nausea at 120 minutes	38%	26%	33%	17%	13%*	21%
Presence of Vomiting at 120 minutes	6%	0%	6%	3%	0%	6%
Presence of photophobia/phonophobia at 120 minutes	53%	56%	45%	39%	38%	31%
No disability at 120 minutes[1]	19%	15%	24%	31%	45%	29%

*Nominal p value < 0.05 in a comparison with the placebo group
[1] No statistical analyses were performed

Study S2B-T47:

Design:

This was a multicenter, randomized, double blind, placebo controlled, parallel study in Canada, Finland, France, Germany, Holland, Israel, Norway and Sweden evaluating 2.5, 5, 10 and 20 mg nasal spray for the treatment of a single, acute migraine attacks. Patients were treated in a clinic setting. Patients were randomized with a 2:2:2:2:1 ratio of 20 mg to 10 mg to 5 mg to 2.5 mg to placebo. Efficacy was assessed at 0, 15, 30, 60, 90, 120 minutes and 3, 4, 6, 8, 12 and 24 hours after treatment.

Disposition:

855 patients were randomized at 68 centers with 544 treating at least one migraine with the study treatment. One patient on placebo did not submit the diary. The group assignments are as follows:

Study S2B-T47: Patient Disposition					
	Placebo	2.5 mg	5 mg	10 mg	20 mg
Patients randomized	64	123	122	115	120
Patients treated	63	123	122	115	120

Demographics:

85% of the patients were female with a mean age of about 41 years. 99% of the patients were white. 71% of the patients did not have an aura. There were no major differences between groups for any of the demographic parameters. The baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for the 5, 10 and 20 mg when compared to placebo. At 120 minutes, the response rate was greater in the 20 mg when compared to the 5 and 10 mg group.

No subgroup analyses were performed.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting, photophobia and phonophobia) are summarized in the following table.

Study S2B-T47: Initial efficacy of sumatriptan					
Outcome	Placebo (N=63)	2.5 mg (N=123)	5 mg (N=122)	10 mg (N=115)	20 mg (N=120)
Headache relief					
at 15 minutes	6%	6%	7%	9%	18%*
at 30 minutes	19%	16%	16%	21%	38%*
at 60 minutes	27%	29%	32%	37%	53%*
at 90 minutes	27%	34%	44%*	45%*	63%*
at 120 minutes	25%	37%	49%*	46%*	64%*
Pain free rates at 120 min [1]	11%	14%	21%	24%	42%
Nausea at 120 min	42%	41%	30%	28%	18%*
Vomiting at 120 minutes	3%	6%	5%	2%	3%
Photophobia/phonophobia at 120 minutes	68%	58%	44%*	50%*	34%*
No disability at 120 minutes [1]	16%	14%	18%	21%	36%
Relief and rescue free for 24 hours [1]	7%	9%	15%	16%	25%

*Nominal p value < 0.05 in a comparison with the placebo group
[1]Statistical analysis not performed

Pivotal studies:

Study S2B-340:

Design:

This was a multicenter, randomized, double blind, placebo controlled, parallel study evaluating 10 and 20 mg nasal spray for the treatment of a single acute migraine attack. Patients were treated at home. Patients were randomized with a 2:1:1 ratio of 20 mg to 10 mg to placebo.

Disposition:

458 patients were randomized with 409 treating a migraine with the study treatment. Patient 2339 on placebo failed to return the diary after treating a migraine.The group assignments are as follows:

Study S2B-340: Patient Disposition				
	Placebo	10 mg	20 mg	Total
Patients randomized	116	114	228	458
Patients treated	100*	106	202	408

*One patient was treated and did not return the diary

Demographics and baseline characteristics:

86% of the patients were female with a mean age of 40 years. 90% of the patients were white. 60% of the patients did not have an aura. 52% of the patients had a prior exposure to sumatriptan with 34% having used it on a regular basis. There were no major differences between groups for any of the demographic parameters. The baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for both 10 and 20 mg when compared to placebo.

Subgroup analyses for sex, age, race and migraine characteristics were performed. The number of males and non white patients were small but the direction of improvement favored 20 mg over placebo. The result of the age subgroup analysis did not suggest a difference. There did not appear to be a difference in the subgroup analyses of the migraine characteristics duration of attack prior to treatment and use of prophylaxis. Placebo patients with an aura had a higher response rate than patients without an aura.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting, photophobia and phonophobia) are summarized in the following table.

Study S2B-340: Initial efficacy of sumatriptan			
Outcome	Placebo (N=100)	10 mg (N=106)	20 mg (N=202)
Headache relief			
at 15 minutes	17%	9%	12%
at 30 minutes	26%	21%	29%
at 60 minutes	32%	31%	46%*
at 90 minutes	33%	46%*	56%*
at 120 minutes	35%	54%*	63%*
Pain free rates at 120 minutes	20%	20%	31%
Presence of nausea at 120 minutes	50%	35%*	29%*
Presence of Vomiting at 120 minutes	6%	8%	3%
Presence of photophobia at 120 minutes	65%	60%	44%*
Presence of phonophobia at 120 minutes	57%	46%	39%*
No disability at 120 minutes	26%	27%	42%*
Relief and rescue free for 24 hours	18%	19%	35%*

*Nominal p value < 0.05 in a comparison with the placebo group

Duration of effect:

All patients were allowed to take rescue therapy after 2 hours. A second dose of study treatment could be taken if the headache returned. The pattern of response to the second dose was similar to the first dose with the greatest effect seen with the 20 mg dose.

Study S2B-340: Duration of effect			
Outcome variable	Placebo (N=101)	10 mg (N=106)	20 mg (N= 202)
Headache relief after 2 hours	35%	54%	63%
Headache relief at 2 hours and no further treatment	18%	19%	34%
Requiring rescue treatment	69%	77%	59%
Mean time to rescue (hrs)	4.3	4.9	7.2

Study S2B-341:

Design:

This was a multicenter, randomized, double blind, placebo controlled, parallel study evaluating 10 and 20 mg nasal spray for the treatment of a single acute migraine attack. Patients were treated at home. Patients were randomized with a 2:1:1 ratio of 20 mg to 10 mg to placebo.

Disposition:

468 patients were randomized with 436 treating a migraine with the study treatment. The group assignments are as follows:

Study S2B-341: Patient Disposition				
	Placebo	10 mg	20 mg	Total
Patients randomized	119	116	233	468
Patients treated	112	109	215	436

Demographics and baseline characteristics:

86% of the patients were female with a mean age of 41 years. 94% of the patients were white. 70% of the patients did not have an aura. 52% of the patients had a prior exposure to sumatriptan with 30% having used it on a regular basis. There

were no major differences between groups for any of the demographic parameters. The baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for only the 20 mg when compared to placebo. The 10 mg group had a reduction in headache compared to placebo group at a p value of 0.063

Subgroup analyses for sex, age, race and migraine characteristics were performed. The number of males and non white patients were small but the direction of improvement favored 20 mg over placebo. The result of the age subgroup analysis did not suggest a difference. There did not appear to be a difference in the subgroup analyses of the migraine characteristics duration of attack prior to treatment and use of prophylaxis. Placebo patients with an aura had a higher response rate than patients without an aura.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting, photophobia and phonophobia) are summarized in the following table.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Study S2B-341: Initial efficacy of sumatriptan			
Outcome	Placebo (N=112)	10 mg (N=109)	20 mg (N=215)
Headache relief			
at 15 minutes	4%	9%	34%*
at 30 minutes	13%	21%	35%*
at 60 minutes	19%	34%*	47%*
at 90 minutes	24%	43%*	57%*
at 120 minutes	29%	43%	62%*
Pain free rates at 120 minutes	4%	23%*	32%*
Presence of nausea at 120 minutes	53%	42%	27%*
Presence of Vomiting at 120 minutes	11%	4%	3%*
Presence of photophobia at 120 minutes	75%	65%	48%*
Presence of phonophobia at 120 minutes	65%	61%	40%*
No disability at 120 minutes	13%	29%*	46%*
Relief and rescue free for 24 hours	10%	19%	33%*

*Nominal p value < 0.05 in a comparison with the placebo group

Duration of effect:

All patients were allowed to take rescue therapy after 2 hours. A second dose of study treatment could be taken if the headache returned. The pattern of response to the second dose was similar to the first dose with the higher rates seen in the active treatment groups.

Study S2B-341: Duration of effect			
Outcome variable	Placebo (N=112)	10 mg (N=109)	20 mg (N= 215)
Headache relief after 2 hours	29%	43%	62%
Headache relief at 2 hours and no further treatment	10%	19%	33%
Requiring rescue treatment (including 2nd dose)	83%	72%	60%
Mean time to rescue (hrs)	3.8	4.9	6.6

Study S2B-342:

Design:

This was a multicenter, randomized, double blind, placebo controlled, parallel study evaluating 5, 10 and 20 mg nasal spray for the treatment of a acute migraine attacks. Three migraine attacks were treated with the assigned treatment. Patients were treated at home. Patients were randomized with a 3:3:3:2 ratio of 20 mg to 10 mg to 5 mg to placebo.

Disposition:

1196 patients were randomized at 56 centers with 1086 treating at least one migraine with the study treatment. 13 patients had no pain or mild headache prior to taking the study treatment. These patients were excluded from the efficacy evaluation. 15 attacks had missing diaries entries. The group assignments are as follows:

Study S2B-342: Patient Disposition					
	Placebo	5 mg	10 mg	20 mg	Total
Patients randomized	218	328	326	324	1196
Patients treated	199	299	296	292	1086
Attack 1	198	297	294	288	1077
Attack 2	175	246	240	239	900
Attack 3	130	190	186	190	696
Total attacks	503	733	720	717	2673
Attacks for analysis	502	731	714	713	2660

The sponsor terminated the study early and 326 patients received treatment but did not complete the final visit. The reason for withdrawal are summarized in the following table.

Study S2B-342: Reasons for withdrawal					
	Placebo	5 mg	10 mg	20 mg	Total
Adverse event	1	0	3	4	4
Lack of efficacy	7	3	3	5	18
Failed to return	6	6	4	4	20
Study terminated	54	93	98	81	326
other	1	8	7	10	26
total	69	110	112	103	394

Demographics:

88% of the patients were female with a mean age of 41 years. 93% of the patients were white. 70% of the patients did not have an aura. There were no major differences between groups for any of the demographic parameters. The baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 60 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 60 minutes for the 5, 10 and 20 mg when compared to placebo. The rates did not appear to change in the three attacks. The 10 and 20 mg groups had a significantly higher response rate than the 5 mg group. At 120 minutes, the response rate was greater in the 20 mg compared to the 10 mg group (p=0.05).

Subgroup analyses for sex, age, race and migraine characteristics were performed. The number of males and non white patients were small but the direction of improvement favored 20 mg over placebo. The result of the age subgroup analysis showed less difference between groups for the younger age group. There did not appear to be a difference in the subgroup analyses of the migraine characteristics duration of attack prior to treatment and use of prophylaxis. Placebo patients with an aura had a higher response rate than patients without an aura. Patients in the placebo group who had used sumatriptan before had a lower rate than those who did not use the drug. The opposite was true for the 10 mg group. Patients weighing over 85 kg had similar relief rates in all groups.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting, photophobia and phonophobia) are summarized in the following table.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Study S2B-342: Initial efficacy of sumatriptan				
Outcome	Placebo (N=502)	5 mg (N=731)	10 mg (N=714)	20 mg (N=713)
Headache relief				
at 15 minutes	5%	8%	7%	5%
at 30 minutes	13%	18%	19%*	16%
at 45 minutes	19%	26%*	31%*	30%*
at 60 minutes	25%	34%*	40%*	42%*
at 90 minutes	29%	41%*	48%*	52%*
at 120 minutes	32%	44%*	54%*	60%*
age 18-35 (N)	50%(48)	45% (87)	47% (76)	55% (77)
age 36-50 (N)	33%(38)	33%(162)	55%(166)	61%(171)
age 51-65 (N)	26%(34)	35% (48)	52% (52)	65% (40)
Pain free rates at 120 minutes	12%	17%*	23%*	27%*
Nausea at 120 minutes	47%	36%*	32%*	31%*
Vomiting at 120 minutes	6%	4%	4%	3%*
Photophobia at 120 minutes	70%	58%*	54%*	47%*
Phonophobia at 120 minutes	58%	51%	45%*	41%*
No disability at 120 minutes	18%*	27%*	30%*	38%*
Relief and rescue free for 24 hours	13%	20%*	27%*	29%*

*Nominal p value < 0.05 in a comparison with the placebo group

Duration of effect:

All patients were allowed to take rescue therapy after 2 hours. A second dose of study treatment could be taken if the headache returned. At 120 minutes the relief rates in the placebo groups were similar to the rates for the 5 and 10 mg groups for the treatment of the first and second attack. The relief rates for second dose in the 20 mg group was consistently higher than the placebo group.

Study S2B-342: Duration of effect				
Outcome variable	Placebo (N=502)	5 mg (N=731)	10 mg (N=714)	20 mg (N=713)
Headache relief after 2 hours	32%	44%	54%	60%
Headache relief at 2 hours and no further treatment	13%	20%	27%	29%
Requiring rescue treatment (including 2nd dose)	80%	74%	65%	65%
Mean time to rescue (hrs)[1]	4.6	N/A	5.8	6.6

[1]From the electronic database

Study S2B-T50:

Design:

This was a multicenter, multinational, randomized, double blind, placebo controlled, parallel study evaluating 10 and 20 mg nasal spray for the treatment of a acute migraine attacks. One migraine attack was treated by the patient at home. Patients were allowed to use a second dose of the drug if significant worsening of the headache occurred between 2 and 24 hours of the first dose. Patients were randomized with a 2:2:1 ratio of 20 mg to 10 mg to placebo. Assessments of the headache severity were measured at 0, 15, 30, 60, 90 and 120 minutes.

Disposition:

1024 patients were randomized at 101 centers with 763 treating at least one migraine with the study treatment. Only two patients, one assigned to 20 mg and one assigned to the 10 mg group were not included in the efficacy analysis because they did not include their diary card information. 29 patients treated a mild headache. The disposition of patients is summarized in the following table.

Study S2B-T50: Patient Disposition				
	Placebo	10 mg	20 mg	Total
Patients randomized				1024
Patients treated	156	305	302	763
Patients treating a moderate to severe headache with diary card	151	289	292	732

Other protocol violations:

3 patients on placebo, 6 patients on 10 mg and 6 patients on 20 mg took rescue prior to the 2 hour assessment.

Demographics:

84% of the patients were female with a mean age of 40 years. 99% of the patients were white. 72% of the patients did not have an aura. There were no major differences between groups for any of the demographic parameters. The baseline characteristics for the headaches were similar between groups.

Efficacy:

The primary outcome measure was the percentage of patients with headache relief at 120 minutes after dosing. A statistically significant greater percentage of patients reduced their headache severity from moderate or severe to no or mild headache pain at 120 minutes for the 10 and 20 mg when compared to placebo. At 120 minutes, the response rate was greater in the 20 mg compared to the 10 mg group (p=0.008).

Only subgroup analyses for sex were performed. The number of males patients were small but the direction of improvement favored 10 mg and 20 mg over placebo.

The results of the headache relief rates at all time points and the rate of patients with clinical disability and associated clinical symptoms (nausea, vomiting, photophobia and phonophobia) are summarized in the following table.

Study S2B-T50: Initial efficacy of sumatriptan			
Outcome	Placebo (N=151)	10 mg (N=288)	20 mg (N=292)
Headache relief			
at 15 minutes	4%	8%	9%*
at 30 minutes	9%	19%*	20%*
at 60 minutes	14%	32%*	35%*
at 90 minutes	22%	42%*	47%*
at 120 minutes	25%	44%*	55%*
age 18-35 (N)	32% (12)	47% (41)	58% (57)
age 36-50 (N)	23% (20)	45% (69) (45)	50% (68)
age 51-65 (N)	13% (2)	33% (10)	65% (28)
Pain free rates at 120 minutes	5%	24%	26%
Presence of nausea at 120 minutes	45%	38%	35%*
Presence of Vomiting at 120 minutes	6%	6%	3%
Presence of photo/phonophobia at 120 minutes	67%	49%	44%
Relief and rescue free for 24 hours	9%	23%	33%

*Nominal p value < 0.05 in a comparison with the placebo group

Duration of effect:

All patients were allowed to take rescue therapy after 2 hours. A second dose of study treatment could be taken if the headache returned. The relief rates for second dose in the 10 and 20 mg group was consistently higher than the placebo group.

Study S2B-T50: Duration of effect			
Outcome variable	Placebo (N=151)	10 mg (N=288)	20 mg (N=292)
Headache relief after 2 hours	25%	44%	55%
Headache relief at 2 hours and no further treatment	9%	23%	33%
Requiring rescue treatment (including 2nd dose)[1]	13%	20%	20%
Mean time to rescue (hrs)[1]	4.0	5.9	5.3

[1]From the electronic database

Comments regarding efficacy data:

The sponsor has reported on 9 controlled efficacy studies. Four of these studies, S2B-T35, S2B-T39, S2B-T60 and S2B-T05, were not adequate to provide definitive evidence for efficacy. Two of these studies, S2B-T35 and S2B-T39, did not use the formulation of nasal spray to be marketed. One study, S2B-T60, did not have a placebo control group and one study, S2B-T05, did not use the recommended dosing regimen.

Evidence of efficacy of Imitrex Nasal Spray in the acute treatment of migraines comes from the remaining five adequate and well controlled studies. In these studies, migraine patients, age 18 to 65, with a moderate or severe headache were randomized in a double blind fashion to receive either a single dose of Imitrex Nasal Spray or placebo. Two hours after receiving their initial treatment, patients were generally allowed to take rescue treatments and/or a second dose of the study treatment. Patients rated their headache severity over 24 hours. The primary outcome measure was the headache relief rate 120 minutes after treatment. Headache relief was defined as a moderate or severe headache improving to a mild headache or no headache. This outcome measure has been used by the sponsor and accepted by the division as adequate to provide evidence for efficacy for sumatriptan tablets and subcutaneous injection.

In all five studies, a statistically significant increase in the headache relief rate was seen for a single dose of 20 mg of the Imitrex Nasal Spray when compared to placebo. In 4 of 5 studies, a similar result was found for the comparison of the 10 mg dose and placebo. In 2 of the 2 studies in which the 5 mg dose was assessed, a

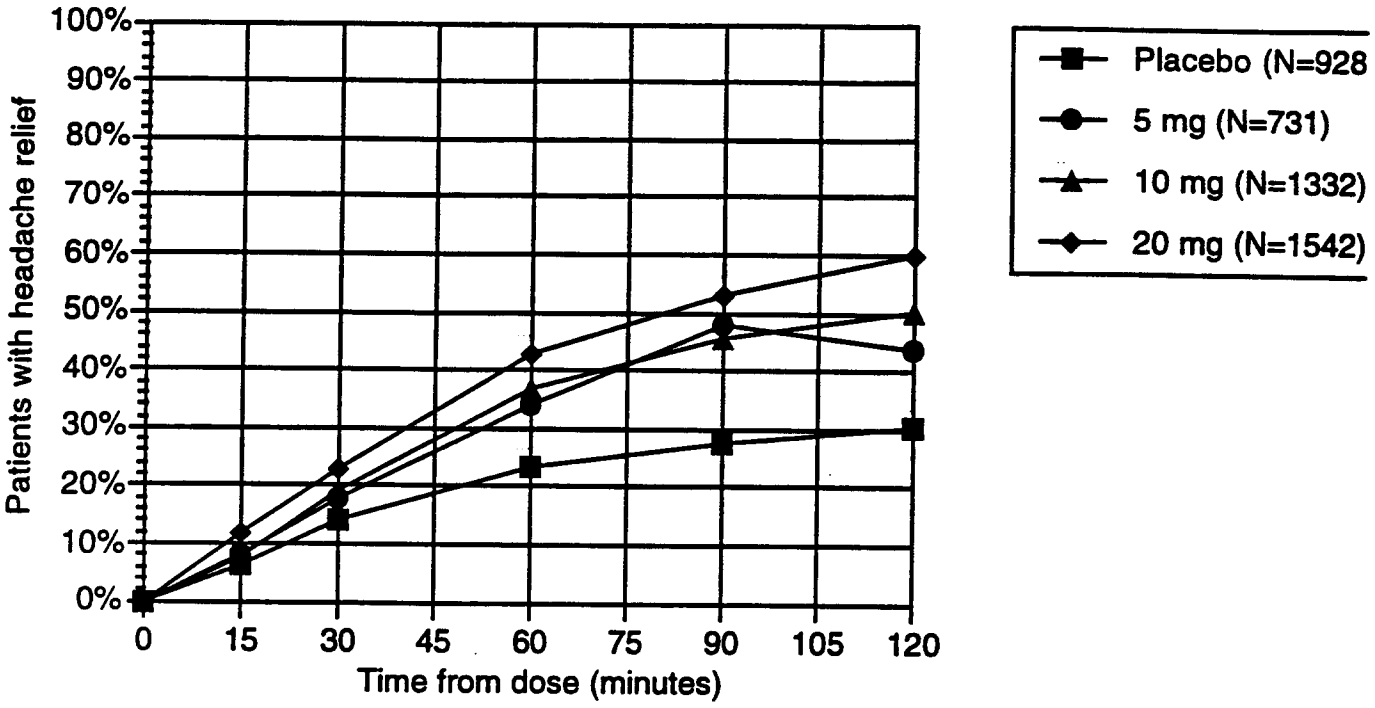
single dose provided for a statistically significant increase in headache relief when compared to placebo. In general, the headache relief rate was higher in patients treated with 20 mg when compared to either 5 or 10 mg. These comparisons were associated with a nominal p value of ≤ 0.05. The following table summarizes the comparison of the different doses.

Comparison of the headache relief rates at 120 minutes post dose			
Study	5 mg	10 mg	20 mg
S2B-T47	49%	46%	64%**#
S2B-T50	n/a	44%	55%**
340	n/a	54%	63%
341	n/a	43%	62%**
342	44%	54%	60%*###

*P≤ 0.05 vs 10 mg; **p<0.01 vs. 10 mg; ***p<0.001 vs 10 mg
#p≤ 0.05 vs 5 mg; ##p<0.01 vs 5 mg; ###p< 0.001 vs 5 mg

The time to relief and duration of relief of the migraine headaches were not part of the primary statistical evaluation. In regards to time to initial relief, at the first time point for measurement, 15 minutes after treatment, the headache relief rate was increased in the group of patients treated with Imitrex compared to those receiving placebo. The differences between the patients receiving 20 mg and those receiving placebo were associated with a nominal p value of ≤ 0.05 in three of six studies. 60 minutes after treatment, differences in the headache relief rate in favor of patients receiving 20 mg were associated with a nominal p value of ≤ 0.5. For descriptive purposes, I have combined the results of the five studies and plotted the percentage of patients with headache relief at each time point during the initial 2 hours following study treatment. This provides some indication of the time course of headache relief. See the following figure.

Percentage of patients with headache relief
(N=number of migraine headaches treated)



In the trials, the efficacy of Imitrex was only determined for the initial few hours of a migraine attack while the duration of a migraine is usually much longer. A simple look at the data reveals that many patients had a return of their headaches after initial improvement suggesting that Imitrex may only provide temporarily relief from the pain of a migraine and not cure the migraine. The efficacy of the drug after 2 hours is difficult to assess as patients were generally allowed to take either an additional study treatment or rescue medication 2 hours after receiving the initial study treatment. Without re randomization, the efficacy of the second dose of study treatment cannot be determined and any conclusions drawn from outcome variables measured after a patient took an additional treatments is confounded by the effect of the additional treatment. Outcome measurements that may provide some insight into the duration of effect of the drug that are not confounded by the use of rescue treatment include the percentage of patients who have had headache relief without the need of additional treatments, the rate of rescue treatments use including a second dose of study treatment and the time to use of additional treatments. See the table below for additional information.

Duration of effect	Placebo (N=865)	10 mg (N=1217)	20 mg (N=1422)
Proportion of patients with headache relief 2 hours following initial treatment	31%	51%	60%
Proportion of patients using additional treatments	69%	56%	54%
Proportion of patients with headache relief without the need for additional treatments	12%	25%	31%
Mean time to use of additional treatments following initial treatment	4.4 hrs	5.7 hrs	6.4 hrs

Describing the experience in the clinical trials as to the use of additional treatments may be helpful to the prescriber when they discuss the use of Imitrex with patients. For example, about one half of patients who had improvement of their headaches 2 hours after treatment with a single dose of 20 mg of Imitrex used additional medication to treat their migraine attack.

Recommendations:

I recommend that Imitrex Nasal Spray be approved for the acute treatment of migraine headaches. I suggest that instead of recommending a single dose, that a description of the results of the studies be provided showing that doses of 5, 10 and 20 mg are effective and that a higher percentage of patients on 20 mg will have relief compared to 5 and 10 mg. I would also suggest that labeling provide some description for the duration of effect. I suggest that safety labeling should generally follow the recommendations and descriptions established for the subcutaneous and tablet formulations.

Randy Levin, M.D.
Medical Reviewer

cc:
Original IND
HFD-120
HFD-120/Leber/Katz/Levin/Grilley
rl/April 29, 1996

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	**20-626**
SPONSOR:	**Glaxo**
DRUG:	**Imitrex Nasal Spray**
INDICATION:	**Migraine**
MATERIAL SUBMITTED:	**NDA application**
CORRESPONDENCE DATE:	**8/29/95**
DATE RECEIVED:	**8/31/96**
DATE REVIEWED:	**4/29/96**

Safety:

Overview:

In the sponsor's proposed labeling, the recommended dose is a single 20 mg spray in one nostril that can be repeated after 2 hours for a total of 40 mg daily. The drug will also be available in a 5 and 10 mg dose.

In the NDA and 4 month safety update, the sponsor has provided information from 29 studies involving intranasal sumatriptan to support the recommended use. All safety data from 23 studies,10 PK studies, 8 placebo controlled studies, one active controlled study, three open label studies and a single study in patients with cluster headaches, was included. The cut off date for the safety data was 5/22/95. Only information regarding serious AEs and withdrawals due to AEs are available from 6 studies. These studies included 4 PK studies conducted in Japan, one phase 2 study ongoing in Japan and one active control study ongoing in Canada and Europe.

A total of 3,767 subjects were involved in the placebo controlled clinical trails, with 3,026 subjects receiving at least a single dose of intranasal sumatriptan and 741 exposed to placebo. 1,007 received 10 mg, 1249 received 20 mg and 77 received 40 mg.

Studies in the safety data base:

The safety database includes PK studies in healthy subjects, controlled and uncontrolled clinical trials in patients with migraine headaches and a single trial in 5 patients with cluster headaches.

PK studies in healthy subjects:

121 healthy subjects were exposed to intranasal sumatriptan in 13 PK studies including 4 studies conducted in Japan. Another PK study C95-028 was completed after the NDA cut off data and the final study report was submitted in the 4 month safety update which is reviewed at the end of this report. In the 4 PK studies conducted in Japan, only serious AEs and withdrawals due to AEs were included in the NDA. There were no serious AEs or withdrawals due to AEs reported for the 24 subjects exposed to intranasal sumatriptan in these studies. The 13 studies are summarized in the following table.

Clinical Pharmacology studies		
Study	**Doses**	**Number of Patients (M/F)**
C93-053	5, 10, 20 mg	20 (0/20)
C93-065	25 pr, 6 sc, 25 po, 20 in	24 (24/0)
S2B-125	0, 20 mg tid for 3.5 days	12 (10/2)
WHP:87:28	5, 10 (spray and drops)	2 (2/0)
WHP:88:16	10, 20 mg in each nostril	6 (0/6)
WHP:86:34	0,5,10,20,40 mg	6 (6/0)
WHP:87:16	2.5,5,10 mg	4 (4/0)
WHP:90:04	20 mg (±preservatives)	16 (8/8)
WHP:87:13	10,20,40 mg	3 (3/0)
WHP:88:14	10,20 mg	4 (4/0)
AMI-01#	10, 20 mg	6 (6/0)
AMI-02#	20 mg	6 (6/0)
AMN-01#	5,10,20 mg	6 (6,0)
AMN-02#	5,10,20 mg	6 (6/0)
Total	**0 to 40 mg**	**121 (85/36)**

#Not included in the database

Controlled Clinical Trials In Patients With Migraines:

There were 8 placebo controlled, randomized, double blind, parallel, clinical trails evaluating intranasal sumatriptan. The studies differed in the location that the patients received treatment (home or at a clinic), the number of headache attacks treated (one or multiple),the number of doses used (one dose or two doses separated by 2 hours (in study S2B-T05 and S2B-P25 doses were separated by 15 to 20 minutes)). Studies conducted outside the US are designated by the letter T or P in the study name. One active control study was performed, S2B-T60, comparing 1 mg of intranasal DHE with 20 mg of intranasal sumatriptan with a cross over design. 389 patients were treated in the study. The 8 placebo controlled studies are summarized in the following table:

Placebo controlled studies: Number of patients enrolled							
Study	Location/attacks/doses	Doses (mg)					
		0	1-2.5	5	10	20	40
S2B-T35	Clinic/one attack/one dose	40	40	42	40	41	42
S2B-T39	Clinic/one attack/one dose	32	34	33	36	40	35
S2B-T47	Clinic/one attack/one dose	64	123	122	115	120	n/a
S2B-T05	Clinic/one attack/two doses	37	n/a	n/a	n/a	37	n/a
S2B-340	Home/one attack/two doses	101	n/a	n/a	106	202	n/a
S2B-341	Home/one attack/two doses	112	n/a	n/a	109	215	n/a
S2B-T50	Home/one attack/two doses	156	n/a	n/a	305	302	n/a
S2B-342	Home/three attacks/2 doses	199	n/a	299	296	292	n/a
Total		741	197	496	1,007	1,249	77

Uncontrolled trials in patients with migraines:

Study S2B-P12 was a pilot efficacy study. Study S2B-P25 was the open label extension to study S2B-T05. Study S2B-T51 was a 12 months open label study ongoing at the time of the NDA submission. A 6 month interim report was included in the original submission. Follow up information was included in the 4 months safety update which is reviewed at the end of this report. Serious AEs and

withdrawals due to AEs as of 5/22/95 were reported.

Uncontrolled studies in migraines: Number of patients enrolled					
Study	Location/duration/doses	Doses (mg)			
		10	20	30	40
S2B-P12	Clinic/one attack/two doses	22	17	18	8
S2B-P25	Clinic/one dose	n/a	16	n/a	n/a
S2B-T51	Home/12 months/one dose	n/a	137	n/a	n/a
Total		22	170	18	8

Other studies:

Study S2B-M12 was a double blind study comparing 20 mg nasal spray with the 100 mg tablets. The study was being conducted outside the US and was scheduled to enroll 480 patients by the end of October of 1995. Study S2B-P14 was an open, pilot study in 5 patients with cluster headache. Study AMI-03 was a Japanese randomized, placebo controlled study comparing 0, 5, 10 and 20 mg in the treatment of migraines. 70 patients per group were to be enrolled. The study was to be completed by 10/95.

Demographics:

Only 2 patients over the age of 65 were treated. No patients were under the age of 18 were treated. Demographics for the patients in the safety database are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

Demographics of subjects in the safety database: Number of patients							
Type of study	Total N	Age		Sex		Race	Aura
		18-35	35-65	Male	Female	White	No Aura
PK	97	62	35	61	36	54	n/a
Placebo controlled	3767	1099	2668	554	3213	3598	2301
Active controlled	405	144	260	65	340	393	292
Uncontrolled	220	74	145	46	174	215	154
Total	4,489	1,379	3,108	726	3,763	4,260	2,747

Extent of Exposure:

All studies:

The exposure to sumatriptan nasal spray by dose in all studies in the safety database is summarized in the following table:

All studies: Number of patients exposure to sumatriptan nasal spray by dose								
Type of study	Plb	1 mg	2.5 mg	5 mg	10 mg	20 mg	30 mg	40 mg
Clinical Pharmacology	38	n/a	2	29	36	87	n/a	12
Placebo controlled efficacy studies	741	74	123	496	1007	1249	n/a	77
Uncontrolled studies	n/a	n/a	n/a	n/a	22	170	18	8
Active controlled	n/a	n/a	n/a	n/a	n/a	389	n/a	n/a
Total	779	74	125	525	1065	1895	18	97

Placebo controlled migraine studies:

In some studies, patients were able to use more than one dose of drug to treat a single headache attack and in some studies, patients were able to treat more than one headache attack. The number of patients exposed to the drug, the number of

attacks treated with one or two doses, the number of patients treating more than one attack and the time between attacks are summarized in the following table:

Placebo controlled studies: Number of patients exposure to sumatriptan nasal spray by dose and duration				
	5 mg	10 mg	20 mg	Total[1]
Number of patients exposed	496	1007	1249	3026
Number of attacks treated	933	1434	1681	4322
with 1 dose	756	1064	1238	3332
with 2 doses	177	370	442	989
Total number of doses given	1110	1804	2124	5312
Number of patients treating				
only 1 attack	249	766	1008	2297
>1 but <3 attacks	57	55	50	162
3-5 attacks	190	186	191	567
>5 attacks	0	0	0	0
Average time between attacks (days)	23.7	25.2	23.4	24.1

[1]Includes patients receiving 1, 2.5 and 40 mg doses

APPEARS THIS WAY
ON ORIGINAL

Open label migraine studies:

Open label studies: Exposure to sumatriptan nasal spray by dose and duration			
	10 mg	20 mg	Total[1]
Number of patients exposed	22	170	215
Number of attacks treated	22	2570	2619
with 1 dose	5	1640	1658
with 2 doses	17	929	960
Total number of doses given	39	3501	3581
Number of patients treating			
≤ 1 attack	22	33	75
>1 but < 3 attacks	0	8	10
3-5 attacks	0	16	17
>5 attacks	0	113	113
Average time between attacks	n/a	10.7	10.9

[1] Includes patients receiving 30 and 40 mg doses

Disposition of patients:

In the single dose studies, very few patients withdrew. In the studies where patients were treating many attacks, most withdrawals were related to the inability of the patient to treat three headaches during the specified time period. The number of patients who withdrew from the studies are summarized in the following table:

Disposition of patients			
Study	Number of patients treated	Reason for withdrawal	
		AE	Other[1]
Clinical Pharmacology	97	2	0
Placebo controlled studies			
single attack			
placebo	369	0	0
sumatriptan	1239	0	0
Multiple attacks			
placebo	199	1	68
sumatriptan	887	3	322
Uncontrolled studies			
Single attacks	78	1	0
Multiple attacks	137	4	38

[1]Lack of efficacy or did not treat three headaches

APPEARS THIS WAY
ON ORIGINAL

The AEs that led to discontinuation of the patients are as follows:

Adverse events leading to discontinuation of patients		
Study/investigator/patient	Dose	AE
W88-014/1322/30	20 mg	Nasal tingling, bitter taste
W88-014/1619/31	10 mg	Nasal tingling, epistaxis
S2B-342/6242/4154	20 mg	Forgetfulness, vomiting
S2B-342/4383/4358	20 mg	Nausea/vomiting
S2B-342/2564/4910	20 mg	Depression
S2B-342/6241/5413	plb	Exacerbation of migraines
S2B-P12/398/78	20 mg	Bad taste, increased BP
S2B-T51/K332/3856	20 mg	Chest pressure, sore throat
S2B-T51/P327/3999	20 mg	Nausea
S2B-T51/M779/3835	20 mg	Pituitary neoplasm
S2B-T51/M779/3851	20 mg	Acute nasopharyngitis

Deaths:

There were no deaths reported.

Serious AEs:

16 subjects reported serious AEs. Two were on placebo, 1 on 10 mg, one on 40 mg and 12 on 20 mg. Only three events were thought by the investigators to be related to the drug. These events are summarized as follows:

Cardiovascular: One involved a cardiovascular event. A 41 year old female (CGS01587) enrolled in study S2B-T39 had T wave inversion noted 2 hours after use of 20 mg of the intranasal spray. The patient was asymptomatic. A stress test

showed ST depression. An evaluation with a thallium scan showed an anteroseptal defect interpreted as an MI. An angiogram showed normal coronary arteries. The diagnosis was vasospasm due to sumatriptan treatment.

Psychiatric:A 50 year old patient (A0006512) was enrolled in study S2B-342 and three days after receiving 2 doses of intranasal sumatriptan, the patient developed acute depression. The patient had a history of depression and she was on lithium and chlorpromazine. While being treated for the depression, the patient received a 6 mg of sumatriptan sc and had a worsening of her depression.

Skin: A 41 year old female in study S2B-T47 (B0003347) developed severe urticaria 105 minutes after receiving a dose of sumatriptan.

Other events classified as serious were determined to be unrelated to the drug and include; five patients noted an increase in migraines (all had received sumatriptan), one patient had asthma 10 days after taking sumatriptan and another had a lobar pneumonia 43 days after dosing, one patient with back pain after a fall 30 days after sumatriptan, one patient on placebo with a bleeding peptic ulcer, one patient with a small bowel obstruction 47 days after sumatriptan, one patient with labyrinthitis 1 day after receiving a 20 mg dose and one patient with pituitary hyperplasia diagnosed.

AEs possibly associated with local irritation:

Disturbance of taste, described as unusually bad or bitter or unpleasant, was seen in 2% of patients receiving placebo, 15% of patients receiving 5 mg, 20% in patients receiving 10 mg and 25% in patients receiving 20 mg. The onset was typically within 15 minutes of receiving. The median duration was 30 minutes with 86 to 99% of patients having resolution within 120 minutes.

Aside from taste disturbance, there were a number of symptoms suggestive of local irritation in the nose, sinuses and throat. These include burning, numbness, paresthesia, discharge, pain or soreness. In the controlled clinical trials, 11 of about 1200 patients dosed with 20 mg and 3 of about 1000 had a severe reaction. These reactions occur within minutes of dosing (range seconds to 20 minutes) and usually resolve within an hour (range 10 minutes to 1.75 hours).

Treatment Emergent Adverse Events:

Placebo controlled trials:

Studies S2B-T35, T39, T47, T05, T50, 340, 341 and 342 were included in this analysis. The following rules were used to analyze AEs:

AEs were counted by patient rather than event. If a patient had more than one specific AE, it was counted only once.

Any event after treatment was counted even if it occurred more than 24 hours after dosing.

If a patient used a second dose of treatment, it was counted as the second dose for the first attack even if the dose was used to treat an attack that occurred more than 24 hours after the first attack.

Analysis of the "Dose at Event" presents the incidence of AEs that (1) occurred anytime after the first dose whether or not they took a second dose or (2) occurred only after the patient took a second dose.

Analysis of "Total Dose" presents the incidence of AEs that (1) occurred in patients who took only one dose of treatment or (2) occurred in patients who took two doses. The AE could occur after the first or second dose. The second rate would provide an estimate of the AE incidence rate for the maximum recommended dose.

Whether looking at the Dose at Event or the Total Dose, the pattern of AEs were similar. The frequency of AEs occurring in the placebo controlled trials with an incidence ≥1% and more frequent in the active group compared to placebo is summarized in the following table. The overall incidence used is for all AEs reported at anytime after a single dose (Dose at Event) and the incidence of events occurring in patients taking two doses (Total Dose).

Treatment emergent adverse events that occurred any time after dosing or in patients taking two doses [1,2]				
	Placebo (N=741)	5 mg (N=496)	10 mg (N=1007)	20 mg (N=1249)
Warm/Hot sensation	<1%	1%	<1%	<1%
Burning sensation	<1%	<1%	<1%	1%
Disease of nasal cavity (2nd dose)	1% (<1%)	2% (2%)	1% (3%)	2% (2%)
Throat symptoms	<1%	<1%	1%	2%
Nausea and vomiting (2nd dose)	5% (7%)	8% (9%)	9% (5%)	10% (8%)
Disorder of mouth and teeth	0%	1%	<1%	<1%
Disturbance of taste (2nd dose)	2% (2%)	15% (14%)	20% (18%)	25% (28%)
migraine	1%	2%	<1%	<1%
malaise /fatigue	<1%	1%	<1%	<1%
dizziness /vertigo	<1%	1%	1%	1%

[1]Only includes AEs that are ≥ 1% and more frequent in the active group compared to placebo

[2] Patients taking two doses: placebo (N=223), 5 mg (N=122), 10 mg (N=312) and 20 mg (N=377)

The frequency of AEs were similar for the following subgroups: patients treated

in the clinic, patients treated at home, patients receiving 1 dose for an attack, patients receiving 2 doses for an attack, patients treating more than one attack, patients treating only one attack, patients treated in US studies, patients treated in non US studies.

Other studies:

The frequency of AEs in the open label studies in patients with migraines who were allowed to treat multiple attacks, the single active controlled study and the single open study in patients with cluster headache (n=5) were similar to the pattern seen in the placebo controlled studies.

Package insert:

The sponsor used the frequency of AEs in the placebo controlled studies excluding study S2B-T05 where patients received 2 doses 15 minutes apart. They included all AEs which were ≥ 1% and of higher frequency in the 20 mg group compared to the placebo group.

Treatment emergent AEs with an incidence of ≥ 1% and greater in the 20 mg group compared to placebo in the placebo controlled trials (excluding study S2B-T05)

Adverse events				
	Placebo (n=704)	5 mg (n=496)	10 mg (n=1007)	20 mg (n=1212)
Burning sensation	0.1	0.4	0.6	1.4
Discomfort nasal cavity	2.4	2.8	2.5	3.8
Nausea /vomiting	11.3	12.2	11.0	13.5
Bad/unusual taste	1.7	13.5	19.3	24.5
Dizziness /vertigo	0.9	1.0	1.7	1.4

Adverse events with a frequency of ≥ 0.1% and < 1% and of higher frequency in the 20 mg group compared to placebo are: atypical sensations (tingling, warm/hot sensation, numbness, pressure sensation, felling strange, feeling heaviness, felling tightness, paresthesia, tight feeling in head), cardiovascular disorders (flushing, hypertension, tachycardia, arrhythmias, chest tightness, chest pressure), Endocrine (thirst), eye disorders (irritation of the eye, visual disturbance), GI (diarrhea, dysphagia, gastric symptoms), Miscellaneous (injury, cough, infection), Mouth and teeth disorders, Musculoskeletal disorders (neck pain/stiffness, backache, joint symptoms, myalgia), Neurological disorders (headache, drowsiness, sedation, anxiety, sleep disturbance, tremors, syncope, shivers, difficulty concentrating, mental confusion), respiratory (influenza, dyspnea, disease of the lower respiratory tract), skin (erythema), urogenital disorders (disorder of breasts, dysmenorrhea).

Laboratory abnormalities:

Few abnormalities were noted in the lab tests that exceeded the sponsor's defined critical levels. In the clinical pharm studies elevated potassium, elevated calcium, decrease hematocrit, decrease lymphocytes and increased eosinophils were noted though none of the changes were categorized as an adverse event. Each abnormality occurred in a single subject except for the increased eosinophils which occurred in two subjects. In the trials involving patients, there were few lab values that were beyond the critical levels and in general the abnormalities were more frequent in the placebo group. There were no dose related abnormalities noted.

Vital signs and physical examination:

While vital signs were checked in all controlled studies, they were only followed closely after a dose in three single dose, clinic based studies (S2B-T35, T39 and T47) and one multiple dose, clinic based study (S2B-T05). The criteria for a significant change in blood pressure is summarized in the following table:

Criteria for significant changes in vital signs		
	Increase	Decrease
Systolic BP	≥ 180 mmHg and 20 point increase	≤ 90 mmhg and 20 point decrease
Diastolic BP	≥ 105 mmhg and 15 point increase	≤ 50 mmhg and 15 point decrease
Heart rate	≥ 120 and 15 beats/minute increase	≤ 50 and 15 beats/minute decrease

In study S2B-T05, two patients had an elevation of the diastolic BP. Patient H0012's diastolic BP rose from 94 to 109 mmHg at 20 minutes post a 20 mg dose. Patient H0082's diastolic BP had the same increase 120 minutes following a 20 mg dose.

In the single dose, clinic based studies, there was an increase in the diastolic BP in 1/135 patients on placebo, 4/197 patients on 5 mg, 2/191 patients on 10 mg and 1/201 patients on 20 mg.

There did not appear to be any dose related changes noted on follow up physical examinations including ENT and respiratory assessments.

ECG assessments:

In the US studies, all patients had an ECG at baseline and as needed, as determined by the investigator. In study S2B-342, all patients also had a post study ECG. In study S2B-340, 2 of 308 patients had a follow up ECG, one for palpitations, chest pain and SOB which occurred 17 hours after dosing. The second patient had an ECG for complaints of pressure in the left shoulder. Neither ECG showed any changes. In study S2B-342, 4 ECG changes were reported as adverse events. The events were non specific ST-T abnormalities after a dose of 5 mg, frequent PVC after a second dose of 5 mg, tachycardia after 20 mg and ST-T wave changes on a routine exit ECG.

In clinical pharmacology studies, 2 of 10 subjects with post treatment ECGs had changes. One subject had prolongation of the PR interval at baseline which became marked after treatment. This change occurred after one dose of 10 mg but did not occur after 2 doses of 5 mg or a repeat dose of 10 mg. Another subject, number 05 in study WHP:86:34, had non specific T wave changes in

leads III and AVF 5 minutes after administration of sumatriptan 40 mg. No ECG changes were noted on rechallenge.

In study S2B-T35, 2 of 205 patients had ECG changes possibly indicative of myocardial ischemia. Patient H0367, 60 minutes after a 5 mg dose, had ST depression noted. Patient H0988 had t wave inversion 30 minutes after treatment which were not accompanied by any symptoms. In study S2B-T39, clinically significant ECG changes occurred in 1 of 178 patients. Patient H0859, who was described in the section on serious AEs had asymptomatic T wave inversions in the anterior chest leads 120 minutes following treatment with no changes noted at 90 minutes. An exercise stress test showed ST depression with a anteroseptal defect in the Thallium scan and normal coronary arteries on angiogram. A diagnosis of sumatriptan induced vasospasm with possible MI was made.

In study S2B-T47, 12 of 480 patients had significant ECG changes most consisting of changes in rate or conduction (PR or QT prolongation) which were not considered to be of clinical concern. Patient H2737 was a 39 year old male who was found to have tachycardia with flattening of the T wave with depression of the ST segment in the anterolateral leads 90 to 120 minutes following a dose of 5 mg. The patient was asymptomatic. Patient H2915 had ventricular extrasystoles immediately after receiving 20 mg of sumatriptan.

In study S2B-T50, one of 36 patients had a significant change in the ECG. Patient H2101 had bradycardia (rate 43) on the exit ECG.

In study S2B-P12, one of 67 patients had a significant change in the ECG. Patient D0020, a 34 year old male had diphasic t waves 40 minutes after dosing but had an abnormal baseline ECG.

Interactions:

The sponsor compared the incidence of AEs in patients on a concomitant medication to those patients not on the medication. There were no differences in the incidence of AEs. No specific syndromes were reported by the sponsor. The sponsor did not find evidence for differences in the incidence of AEs in various subgroups including sex of the patient, race, age, aura, weight, pretreatment headache duration.

Overdose:

There were no reported overdoses. In studies, 97 subjects received a single dose

of 40 mg. Reported AEs were similar to those seen with lower doses. In study S2B-T05, 36 patients were given two 20 mg doses 15 minutes apart without serious AEs reported. In study S2B-125, 12 subjects were given a dose of 20 mg three times a day for 10 doses without serious AEs. Reported events were similar to those reported with single doses.

Long Term Experience:

Study S2B-T51 is an open label study evaluating the dose of 20 mg with an optional 20 mg dose for headache recurrence. 137 patients had received one or more doses as of 7/94. The sponsor reports that the nature and frequency of the AEs were similar to the short term studies.

Sponsor's conclusions:

There were no unexpected and serious AEs or safety concerns for the nasal spray.

Treatment emergent AEs that were of greater incidence in the active treatment group by at least 2 percentage points include disturbance of taste, disease of the nasal cavity/sinus, throat symptoms, nausea, vomiting and phonophobia.

Serious AEs were infrequent with only 16 (< 1%) reported. The incidence of withdrawals from the controlled clinical trials was < 0.1%. There were no apparent drug related or dose related changes in the clinical lab tests. Changes seen in vital signs were similar to those observed with placebo.The over all incidence of ECG changes was 0 to 2.8%. ECG changes indicative of ischemia occurred at a frequency < 0.1%.

Risk/Benefit:

The AEs reported with the intranasal dosing are similar to those seen with the oral and subcutaneous dosing with the exception of the disturbance of taste. The incidence of AEs are lower than seen with the oral and subcutaneous injections. The efficacy of the drug has been demonstrated in 9 clinical trials which were of similar design to the oral and subcutaneous studies.

Safety Update:

Methods:

A 4 month safety update was submitted 12/21/95. This report covered a period from 11/22/95 to 11/10/95. There were 4 clinical migraine studies ongoing and 1 clinical PK study completed in this time period. Serious AEs for all studies reported between 5/22/95 and 11/10/95 were also reported.

Clinical pharmacology studies:

There was one clinical pharmacology study, C95-028, completed during the time frame of the safety update.The final study report for study C95-028, a clinical pharmacology study which evaluated the effects of xylometazoline nasal drops on the PK and tolerability of 20 mg of Imitrex nasal spray in 12 patients, was included in the submission. In this cross over study, patients received 3 drops of either placebo or xylometazoline drops and 20 mg of sumatriptan nasal spray. In regards to safety, there were no serious AEs reported. None of the 12 patients withdrew from the study. No adverse changes were observed on anterior rhinoscopy in patients receiving either treatment. There were no changes in any of the lab tests that were reported as AEs or attributed to the drug by the investigator. No clinically significant changes were noted in vital signs. There was no evidence to suggest an interaction with the nasal drops and sumatriptan spray.

Placebo controlled clinical trials:

A single controlled study, S2B-M12, was included in the safety update. This was a double blind, double dummy study comparing the efficacy and safety of 20 mg of the nasal spray and 100 mg tablet. The study was completed in 11/95 with 469 patients treated. The data analysis was ongoing at the time of the submission. One serious AE was reported. A 48 year old female complained of chest pain with SOB three hours after a dose of nasal spray to treat the second migraine attack during the study. The event resolved after 15 minutes. The first attack and a third attack treated with oral sumatriptan were not associated with chest pain.

Uncontrolled clinical trials:

Three uncontrolled studies, S2B-T51, AMI-03 and SUMB3007, were ongoing or recently completed. The analysis of data was ongoing at the time of the

submission. In study S2B-T51, patients treated migraines over the course of 12 months with 20 mg of sumatriptan nasal spray with a repeat dose of 20 mg for a recurrence. The 6 month interim results were presented with the NDA. Analysis continues for this study and there is no update except that there have been no new serious AEs to report. Study AMI-03 evaluated 5, 10 and 20 mg spray in a double blind study conducted in Japan. The study was completed in 10/95 with 158 patients receiving treatment. The analysis is ongoing and no information was provided except that there were no serious AEs reported from 5/22/95 to 11/10/95. Study SUMB3007 compared the speed of onset for the 20 mg spray and the 100 mg tablets. 10 of 232 patients had been enrolled at the time of the submission. No serious AEs were reported.

Sponsor's conclusions:

The 4 month safety update doses not reveal any serious or unexpected AEs or safety concerns.

Comments regarding safety:

Aside from the local effects of the nasal spray, the safety data do not suggest that the nasal spray will have a different safety profile when compared to the oral and subcutaneous formulations. I would suggest that the labeling carry the contraindications, warning and precautions noted in the labeling for the subcutaneous and oral formulations. In regards to the local irritation effects, no local changes were noted on exam with an acute dose but the long term effects after repeated use were not studied. Preliminary comments from the preclinical reviewer, suggest that preclinical evaluation of the local irritation were limited. Final recommendations are pending the final review of the preclinical information.

Randy Levin, M.D.
Medical Reviewer

cc:
Original IND
HFD-120
HFD-120/Leber/Katz/Levin/Grilley
rl/April 29, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20626

CHEMISTRY REVIEW(S)

mille

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-626

CHEMISTRY REVIEW: # 4 **REVIEW COMPLETED: 07FEB97**

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	29AUG95	29AUG95	06SEP95
Amendment	03JAN96	05JAN96	05FEB96
Amendment	20JUN96	21JUN96	21JUN96
Amendment	29OCT96	30OCT96	05NOV96
Amendment	18NOV96	20NOV96	27NOV96
Amendment	20DEC96	23DEC96	30DEC96
Amendment	17JAN97	21JAN97	24JAN97

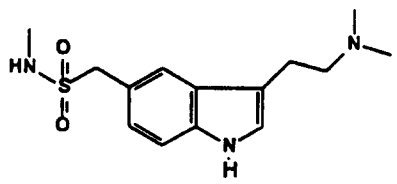
NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME:
Proprietary: IMITREX®
Nonproprietary/Established/USAN: sumatriptan
Code Name/#: GR43175X
Chem. Type/Ther. Class: 3S

DESI / Patent Status: No DESI issues.
Patent expires 28 DEC 2006; extension from 28 MAR 2006

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: nasal spray
STRENGTHS: 5, 10, 20 mg / 100 µl (unit dose single spray)
ROUTE OF ADMINISTRATION: intranasal
DISPENSED: **XXX** Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:



3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulfonamide
$C_{14}H_{21}N_3O_2S$ Mol. Weight: 295.4

(the hemisulfate is present *in situ* in the spray formulation)

CONCLUSIONS & RECOMMENDATIONS:

cc: Orig. NDA
HFD-120/Division File
HFD-120/DJBates/07FEB97
HFD-120/MMille/
HFD-120/SBlum/Init.: 2/10/97

Doris J. Bates, Ph.D., Review Chemist
Filename: N020626.004

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-626

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 01-JUL-96

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	29AUG95	29AUG95	06SEP95
Amendment	03JAN96	05JAN96	05FEB96
Amendment	20JUN96	21JUN96	21JUN96

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

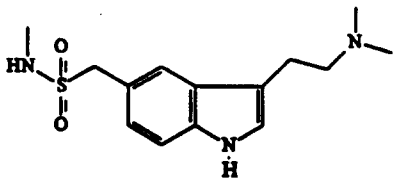
JUL 3 1996

DRUG PRODUCT NAME:
Proprietary: IMITREX®
Nonproprietary/Established/USAN: sumatriptan
Code Name/#: GR43175X
Chem. Type/Ther. Class: 3S

DESI / Patent Status: No DESI issues.
Patent expires 28 DEC 2006; extension from 28 MAR 2006

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: nasal spray
STRENGTHS: 5, 10, 20 mg / 100 µl (unit dose single spray)
ROUTE OF ADMINISTRATION: intranasal
DISPENSED: XXX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:



3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulfonamide
$C_{14}H_{21}N_3O_2S$ Mol. Weight: 295.4

(the hemisulfate is present *in situ* in the spray formulation)

CONCLUSIONS & RECOMMENDATIONS:

cc: Orig. NDA
HFD-120/Division File
HFD-120/DJBates/01JUL96
HFD-120/DGrilley/
HFD-120/SBlum/Init.:

7/2/96

Doris J. Bates, Ph.D., Review Chemist
Filename: N020626.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-626

CHEMISTRY REVIEW: # 1,2

DATE REVIEWED: 01FEB96, 14FEB96

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	29AUG95	29AUG95	06SEP95
Amendment	03JAN96	05JAN96	05FEB96

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME:

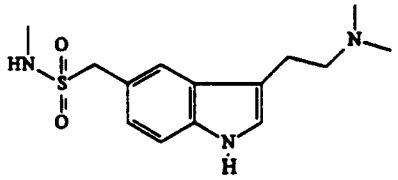
Proprietary:	IMITREX®
Nonproprietary/Established/USAN:	sumatriptan
Code Name/#:	GR43175X
Chem. Type/Ther. Class:	3S

DESI / Patent Status: No DESI issues.
Patent expires 28 DEC 2006; extension from 28 MAR 2006

PHARMACOLOGICAL CATEGORY/INDICATION: antimigraine
DOSAGE FORM: nasal spray
STRENGTHS: 5, 10, 20 mg / 100 µl (unit dose single spray)

ROUTE OF ADMINISTRATION: intranasal
DISPENSED: XXX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:



3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulfonamide

$C_{14}H_{21}N_3O_2S$

Mol. Weight: 295.4

(the hemisulfate is present *in situ* in the spray formulation)

CONCLUSIONS & RECOMMENDATIONS:

cc:NDA 20-626
HFD-120/Division File
HFD-120/DJBates/19FEB96
HFD-120/DGrilley
HFD-120/SBlum/Init.: SMB 4/15/96

Doris J. Bates 4 Mar 96
Doris J. Bates, Ph.D., Review Chemist
Filename: N0020626.001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20626

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

IMITREX®

(sumatriptan)

NASAL SPRAY, 5 AND 20 MG

NDA 20-626

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL

DRUG PRODUCTS

ODE-1 / HFD-120

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-626

IMITREX®

(sumatriptan)

Nasal Spray

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 Imitrex® Nasal Spray, Glaxo Wellcome, Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Sumatriptan is a synthetically manufactured drug which is administered as a nasal spray in the treatment of acute migraine. The drug substance will be manufactured by Glaxo Wellcome, Inc., in Montrose, Scotland; the drug product will be manufactured by Glaxo S.p.A., in Parma, Italy. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

The drug substance will enter the environment from effluent wastewater during manufacture and formulation. Chemical and physical test results indicate that the drug substance and its principal metabolites will most likely be restricted to the aquatic environment ~~and will biodegrade~~ without significant bioaccumulation.

As the drug substance is expected to persist in the aquatic environment for some time, the toxicity of sumatriptan to aquatic organisms was characterized. Acute static toxicity studies found the drug to be essentially nontoxic to water fleas (Daphnia magna) at concentrations at least three orders of magnitude greater than the maximum expected environmental concentration (MEEC). The drug is non-inhibitive to environmental microorganisms at concentrations at least four orders of magnitude greater than the maximum expected environmental concentration (MEEC).

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. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. 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.

19/2/96 Doris J. Bates
DATE PREPARED BY
Doris J. Bates, Ph.D.
Review Chemist
Office of New Drug Chemistry

3/5/96 Stanley W. Blum
DATE DIVISION CONCURRENCE
Stanley W. Blum
Supervisory Chemist
Office of New Drug Chemistry - 1

3/9/96 Nancy Sager
DATE APPROVED
Nancy Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

CC:
HFD-120/Division file NDA 20-626
HFD-120/D. Grilley NDA 20-626
HFD-004/C. Good
HFD-004/FONSI File NDA 20-626
HFD-004/Docket File NDA 20-626
HFD-019/FOI COPY

ENVIRONMENTAL ASSESSMENT

Freedom of Information (FOI) Releasable Copy

NAME OF APPLICANT

GLAXO WELLCOME INC.
Five Moore Drive
Research Triangle Park, NC 27709

NAME OF NEW DRUG

Imitrex® (sumatriptan) Nasal Spray

TABLE OF CONTENTS

1.0 DATE

June 1, 1995

2.0 APPLICANT

Glaxo Wellcome Inc.

3.0 ADDRESS

Five Moore Drive
Research Triangle Park, NC 27709

4.0 DESCRIPTION OF THE PROPOSED ACTION

4.1 Description of Requested Approval

Glaxo Wellcome Inc. is requesting the approval to formulate, package and market Imitrex® Nasal Spray, an alternative dosage form for sumatriptan. The drug substance for sumatriptan nasal spray (sumatriptan) is prepared from and has the same source of manufacture as that in the currently marketed injection formulation (sumatriptan succinate) which has been described in NDA 20-080 (Imitrex® Injection) dated June 29, 1990, amended April 30, 1992 and approved December 28, 1992.

4.2 Need for the Action

Sumatriptan nasal spray is indicated for the acute treatment of migraine attacks, with or without aura.

4.3 Locations where Products will be Produced

Sumatriptan will be manufactured in bulk form at Glaxo Operations (UK) Limited in Montrose, Scotland. The drug product will be formulated into final dosage form and packaged at the Glaxo S.p.A. facility located in Parma, Italy.

The environmental assessment for drug substance manufacture is unchanged from the Environmental Assessment submitted for NDA 20-080 (Imitrex® Injection) dated June 29, 1990, amended April 30, 1992 and approved December 28, 1992.

Drug Product Manufacturing and Packaging

Glaxo S.p.A.
Strada Asolana Km 11
43056 San Polo di Torrile
Parma
Italy

Glaxo S.p.A.'s Parma factory is located in an industrial area of the Village of San Polo di Torrile, a small town about 13 km north of Parma, in Emilia Romagna Region, Italy. Linate and Malpensa airports in Milan are the nearest major international airports (130 and 170 km away, respectively) to the Parma site. The San Polo di Torrile municipal territory covers 37.3 square kilometers, has a population of 5,012. The Glaxo factory is located in an industrial area in the vicinity of the village. The site has a total area of about 155,800 square meters of which approximately half is open space and the remainder is developed. The production facility covers 23,500 square meters and consists of a main building including manufacturing departments, laboratories, offices, warehouse and general services. Other separate buildings are dedicated to boiler house, workshop and stores and electrical substation.

4.4 Sites of Product Use

Sumatriptan nasal spray will be dispensed by prescription and used in private residences, hospitals, and clinics throughout the United States.

4.5 Sites of Disposal

Product that is introduced into the patient will be excreted in the urine and feces and distributed into wastewater treatment systems throughout the United States.

Returned product disposal will occur at high-temperature commercial incinerator facilities that are permitted to dispose of such wastes by appropriate local, state and federal regulatory agencies. Currently, disposal of return product is contracted to:

Chambers Medical Technologies, Inc.
100 Nix Street
Hampton, South Carolina 29924

Chambers Medical Technologies, Inc. holds permit number 1280-0021, issued on July 29, 1986 by the South Carolina Department of Health and Environmental Control (DHEC). The permit has an expiration date of March 31, 1991. DHEC confirms that Chambers Medical Technologies, Inc. applied for a permit renewal as required and is operating under the existing permit until DHEC issues a new permit.

An alternative solid waste incineration facility under consideration for the disposal of returned product is:

BFI - Medical Waste Systems
1168 Porter Avenue
Haw River, North Carolina 27258

BFI - Medical Waste Systems holds air permit number 5896R7 issued June 18, 1994 by the North Carolina Department of Environment, Health and Natural Resources (DEHNR). The permit has an expiration date of July 1, 1996.

Rejected drug substance and drug product produced at manufacturing sites is disposed of via high temperature incineration either on site or at off-site facilities approved by the respective governments for this purpose. Information on incineration facilities used to destroy rejects can be found in Section 6.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES

The chemical substances that are the subject of the proposed action can be divided into five categories: (1) drug substance, (2) drug substance impurities and degradants, (3) drug product excipients, (4) drug substance and drug product manufacturing waste products, and (5) packaging materials. Information of the chemical substances identified in each of the categories is discussed in Sections 5.1 through 5.5. A Material Safety Data Sheet for the drug substance is included as Appendix 1.

5.1 Drug Substance Information

Description: - White to pale yellow powder

Name: - Sumatriptan

Chemical Name - 3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide

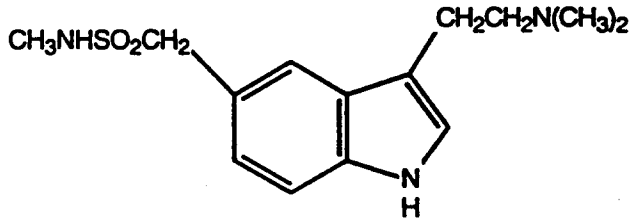
CAS Number: - 103628-46-2

Molecular Weight: - 295.4

Molecular Formula: - $C_{14}H_{21}N_3O_2S$

Water Solubility: - >100 mg/ml at 20°C

Structure:



5.2 Drug Substance Impurities and Degradants

A confidential list of impurities and degradants has been supplied to FDA in NDA 20-080 (Imitrex® Injection) dated June 29, 1990, amended April 30, 1992 and approved December 28, 1992.

5.3 Drug Product Excipients

A confidential list of drug product excipients has been supplied to FDA.

5.4 Manufacturing Waste Products

Confidential information on drug substance and drug product manufacturing wastes has been supplied to FDA.

5.5 Packaging Materials

The following materials will be used in packaging of the drug product:

glass vials
polypropylene cups
paper labels
medical paper
product insert
chlorobutyl rubber stoppers
polypropylene/metal adapters
PET blister packing
cardboard cartons

These packaging materials will enter the waste stream as a result of product use, and when rejected or expired materials are returned. Information on chemical names, CAS numbers and chemical structures is not available for these widely used commercial packaging materials.

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and other substances associated with its manufacture can potentially enter the environment from four main sources: (1) the sites associated with the manufacture of the drug substance, sumatriptan or its intermediates; (2) the sites associated with the manufacture and packaging of the drug product; (3) the sites of use by patients; and (4) waste disposal sites for discarded or rejected product and packaging materials. Sections 6.1 through 6.4 discuss potential emissions from each of these sources.

6.1 Introductions of Substances from Drug Substance Production

Confidential information on the substances expected to be emitted, emission controls, and compliance with relevant environmental and occupational laws for the manufacturing site associated with the production of sumatriptan has been supplied to FDA.

6.1.1 Effect of requested approval on compliance

The requested approval is not anticipated to have a detrimental effect on compliance at Glaxo Operations (UK) Limited, Montrose as only 4% of production would be required to support the predicted annual requirements for the drug product.

6.2 Introductions of Substances from Drug Product Manufacturing and Packaging

The drug product sumatriptan nasal spray will be manufactured and packaged at Glaxo S.p.A. in Parma, Italy. The substances expected to be emitted, emission controls, and compliance with relevant environmental and occupational laws for the Parma facility are discussed below.

6.2.1 Substances expected to be emitted

Confidential information on the substances expected to be emitted, emission controls, and compliance with relevant environmental and occupational laws has been supplied to FDA.

6.2.2 Controls on emissions

The site effluent stream comprises mainly process related effluent from manufacturing operations and other flows from utilities. The wastewater is collected and conveyed to an equalization basin, combined with wastewater coming from canteen and toilets, and it is discharged to the San Polo di Torrile sewer, where it is treated prior to discharge to surface waters.

The manufacture of sumatriptan nasal spray does not generate air emissions; nevertheless all air from production area passes into abatement systems. The extracted air is filtered before discharge to the atmosphere. The filters are monitored by pressure drop and are replaced when a pre-set level is reached. Spent filters are removed from the housing and bagged.

There are no on-site facilities for the disposal of solid or liquid wastes. The site operates a thorough segregation scheme for pharmaceutical waste, small quantities of rejected product, hazardous chemical waste, office waste and canteen waste. Each waste stream is treated securely, marked and labeled prior to secure and safe disposal or for recycling as appropriate.

Hazardous or pharmaceutical contaminated waste is stored, transported off-site and disposed by a contract waste handling company via high temperature incineration.

The waste handling company currently contracted to incinerate hazardous and pharmaceutical waste from Glaxo's Parma facility is the following:

Chimet S.p.A.
Via dei Laghi, 31/32
Civitella Val di Chiana
Arezzo - Italy

The Chimet Incinerator operates under permit n.01689 issued 22 June 1995 by the Toscana Region local authority. The permit expires 30 June 1996.

The facility currently used to dispose of non-contaminated packaging waste from the site is:

A.M.N.U.
Strada Baganzola, 36/a
Locality Cornocchio
Parma - Italy

A.M.N.U. holds the permit n.74 issued by the Province of Parma on 23 December 1993. The permit expires 31 December 1998.

6.2.3 Regulatory Controls and Compliance

This Section contains discussions of environmental regulatory requirements and compliance associated with the manufacture of sumatriptan nasal spray. Summaries of wastewater, air, solid waste and occupational requirements are included below. Table 1 contains a list of environmental regulations applicable to the Parma manufacturing site.

Table 1. Environmental and Occupational laws Applicable to the Parma facility.

Act	Summary	Manufacturing Site Permit
Water Protection Acts	Regulations concerning the safeguarding of water from contamination (L.319/76 and L.650/79)	Nr. 12 of 3 January 1995 issued by Mayor of Torrile
	Emilia Romagna regional regulations concerning the discharge c sewers	Nr. 12 of 3 January 1995 issued by Mayor of Torrile
Air Protection Acts	Not Applicable	Not Applicable
Solid and Hazardous Waste Acts	Implementation of EEC directives 75/442 concerning waste disposal, 76/403 concerning disposal of polychorodiphenils and polychlorotriphenils, and 78/319 concerning toxic and harmful waste (DPR 915/82)	Nr. 48 of 13 March 1993 issued by Province of Parma
	Regional measures concerning waste disposal, implementing Decree DPR 915 of 10 September 1982. Administrative delegation to the Provinces and to the local authority for Rimini (R.L. 6/86).	Nr. 48 of 13 March 1993 issued by Province of Parma
	Regulations concerning temporary storage of toxic and harmful waste by their producers - Further modifications and integration of regional law, 27 January 1986, nr. 6 (R.L. 5/92).	Nr. 48 of 13 March 1993 issued by Province of Parma.
Occupational Health and Safety Acts	Regulations for prevention of the accidents at work (DPR 547/55)	Not required
	General regulations for hygiene in the place of work (DPR 303/56)	Not required
	Implementation of EEC Directives 80/1107, 82/605, 83/477, 86/188 and 88/642 concerning protection of workers against risks deriving from exposure to chemical, physical and biological agents during work (D.Lgs. 277/91)	Not required
	Implementation of EEC Directives 89/391, 89/654, 89/655, 89/656, 90/269, 90/270, 90/394 and 90/679 concerning the improvement of health and safety of workers in the place of work (D.Lgs. 626/94).	Not required

Glaxo's wastewater is discharged to the San Polo di Torrile public sewer. The discharge of effluent comes under the jurisdiction of the Mayor of Torrile. The Law 10 May 1976 nr. 319 (L.319/76) allows the discharge of effluent under condition of an authorization that specifies limits on the quality of the effluent.

No specific laws or regulations on air emissions apply to the manufacturing process for sumatriptan nasal spray.

Waste disposal is controlled by local authorities under governmental laws and subsequently regional regulations. The article 16 of the Decree of the President of the Republic 10 September 1982, nr. 915 (DPR 915/82) establishes a permitting requirement for the storage of toxic-harmful wastes. In addition, the authority Emilia Romagna Region has promulgated the Laws 27 January 1986 n. 6 and 5 February 1992 n. 5, where the respective articles n. 18 and n. 2 define in detail the rules regarding the storage of toxic-harmful wastes.

The requirements specific to Glaxo have been specified in the waste permit nr. 48 issued by local authority Province of Parma on 13 March 1993, expiring on 31 December 1998.

Occupational emissions are regulated under the following laws: Decree of the President of the Republic 27 April 1955, nr. 547; Decree of the President of the Republic 19 March 1956, nr. 303; Legislative Decree 15 August 1991, nr. 277; Legislative Decree 19 September 1994, nr. 626. Compliance with the general regulations is required and no specific permits are issued.

Appropriate preventative, containment and protective measures are taken to minimize the risk of exposure. Containment is the primary control in the use of the hazardous substances associated with sumatriptan nasal spray production. In addition, the use of personal protective equipment is seen as a secondary control in addition to containment or where containment is not a feasible option.

6.2.4 Effect of requested approval on compliance

There are no specific air, wastewater, solid waste or occupational emission limits on sumatriptan or the other substances which are expected to be emitted from the manufacturing process. There is therefore no expected effect on compliance.

6.3 Statement of Compliance

By signing this Environmental Assessment report, Glaxo Wellcome Inc. states that it is in compliance, or on an enforceable schedule to be in compliance, with all environmental laws and regulations applicable to the production of sumatriptan drug substance and sumatriptan nasal spray at the Montrose and Parma manufacturing facilities.

6.4 Introductions from Product Use

Administered sumatriptan will enter the environment primarily through wastewater treatment facilities. The Maximum Expected Emitted Concentration of sumatriptan from product use is estimated to be 0.07 mg/L. This estimate is based on an estimated 150 gallons (568 liters) per capita daily wastewater discharge (PMA 1991) and the following worst case scenario:

1. all the people discharging to a wastewater treatment system are being treated with the maximum recommended 40 milligram daily dose of sumatriptan, and

2. 100% of the drug substance passes though the patient into the wastewater.

Using this scenario provides an MEEC estimate which is independent of market volume. The MEEC was calculated as follows:

$$\frac{\text{Daily Application}}{\text{Daily Water Usage}} = \text{MEEC}$$

$$\frac{\text{40 milligrams}}{\text{568 liters}} = 0.07 \text{ mg/l}$$

6.5 Introductions from Product Disposal

It is estimated that there will be no emission to the environment from product disposal. All product in the United States that is returned is disposed of by high-temperature incineration at an off site facility operated by a contract waste disposal firm. All of the drug substance, excipients, and packaging materials are destroyed in the incineration process.

The contractor used to dispose of returned pharmaceuticals is:

Chambers Medical Technologies of South Carolina, Inc.
100 Nix Street
Hampton, SC 29924

The contractor holds permit number 1280-0021, issued by the South Carolina Department of Health and Environmental Control (DHEC). The permit was issued on July 29, 1986 and expired on March 31, 1991. However, the contractor has applied for their permit renewal as required and is operating under the existing permit until DHEC issues a new permit. An alternative solid waste incineration facility under consideration for the disposal of returned product is:

BFI - Medical Waste Systems
1168 Porter Avenue
Haw River, North Carolina 27258

BFI - Medical Waste Systems holds air permit number 5896R7 issued June 18, 1994 by the North Carolina Department of Environment, Health and Natural Resources (DEHNR). The permit has an expiration date of July 1, 1996.

7.0 FATE OF SUBSTANCES IN THE ENVIRONMENT

For sumatriptan nasal spray production and use, information presented in Section 6 of this Environmental Assessment report indicates that only the fate of sumatriptan need be considered. Other compounds potentially emitted in production of the drug substance and in the production or use of the drug product are introduced into the environment from a wide variety of sources other than those associated with the proposed action. The amounts of these compounds expected to enter the environment as a result of approval of the proposed action are negligible by comparison, and are not expected to result in any adverse environmental effects. Furthermore, the manufacturing facilities all are in compliance with applicable environmental or occupational health and safety regulations.

The major route of drug substance emission into the environment is via excretion in the urine and feces following product use and subsequent release into wastewater collection and treatment systems. As discussed in Section 6 of this Environmental Assessment report, all sumatriptan manufacturing losses will be disposed of using procedures in compliance with the

applicable national environmental laws and regulations. All returned and rejected drug product will be disposed of via high-temperature incineration. This process destroys all drug substance and excipients prior to emission. Therefore, the environmental fate of drug substance emitted as a result of losses from manufacturing processes or disposal is not considered in this section of the Environmental Assessment report.

7.1 Metabolism

When administered to humans, the principal route of excretion of sumatriptan is in the urine. Available data indicate that the drug is, to a great extent, excreted unchanged. The only metabolite identified was GR49336 which is more polar than the drug substance and accounted for 53-61.6% of the dose. Thus sumatriptan metabolites are not expected to be more environmentally persistent than the drug substance. Accordingly, these compounds are not considered significant for the purposes of this environmental assessment and will not be further evaluated.

7.2 Fate Studies

The fate and effects of chemical substances in the environment are predominately determined by their physical, chemical, and biological characteristics. To determine the environmental fate and effects of sumatriptan, several laboratory studies were carried out in accordance with guidelines provided in the Food and Drug Administration (FDA) Environmental Assessment Technical Assistance Handbook. The results of these studies are summarized in Table 2. The complete environmental fate and effects study reports for sumatriptan (tested as the succinate) have been provided in NDA 20-080 (Imitrex® Injection) dated June 29, 1990, amended April 30, 1992 and approved December 28, 1992. These studies are relevant to the current NDA since in an aqueous solution sumatriptan will exist in the form of its base rather than as a salt.

Supplementary fate and effects study reports on the physico-chemical properties (which could differ for the base or succinate salt) and soil biodegradation studies conducted for the first time on sumatriptan base have been provided to FDA.

As noted above, the major route of drug substance emission into the environment is via excretion in the urine following product use and subsequent release into wastewater collection and treatment systems. Sumatriptan was found to be hydrolytically stable over all pH ranges tested; thus, hydrolysis cannot be considered an important removal process. Based on consideration of the Pharmaceutical Manufacturers Association/Food and Drug Administration (PMA/FDA) Environmental Assessment Technical Test Matrix, the results of the minimum data base fate tests indicate that sumatriptan will localize primarily into the aquatic environmental compartment.

Because of the high water solubility ($>3.4 \times 10^{-4}$M) it is likely that the drug substance will be distributed into the aquatic environmental compartment. Upon entry into the aquatic compartment the drug substance should not bioaccumulate (log $P<0.5$). Although the vapor pressure is above 10^{-7} Torr, the drug substance is not expected to partition into the atmosphere, because the drug substance does not readily evaporate from the aquatic compartment. The very low value for the Henry's law constant ($<9 \times 10^{-13}$) would indicate a theoretical half life in water of many thousands of years. Transport of sumatriptan into the terrestrial and atmospheric compartments are expected to be negligible by comparison with its distribution into the aquatic environment.

7.3 Fate In Aquatic Ecosystems

A major determinant of the fate of sumatriptan in the aquatic compartment is its rate of degradation. Thus, a determination of its aerobic biodegradation in water was carried out in accordance with the FDA Environmental Assessment Technical Handbook, 3.11. The results of this test indicated less than 1% degradation to CO_2 occurred over the 28-day test period. Thus, sumatriptan does not meet the current FDA criteria for ready biodegradability (i.e., half-life less than approximately 8 hours for aerobic biodegradation). According to the PMA/FDA Guidelines for preparing environmental assessments, the relatively low octanol/water partition coefficient, indicates that sumatriptan is unlikely to bioaccumulate in the tissues of aquatic organisms.

For the aquatic compartment, the worst case estimate of the drug substance's environmental concentration from product use would be equal to the MEEC (0.07 mg/l). This worst case estimate assumes no removal through the wastewater treatment process and discharge into a zero flow stream.

Table 2. Summary of Environmental Fate and Effects Studies Conducted on Sumatriptan

STUDY NAME	RESULTS OF STUDY		
Hydrolysis Rate	Hydrolytically stable over all pH ranges.		
Vapor Pressure	2×10^{-7} Torr at 20 C		
	Absorbance Range	Molar Extinction Coefficient	
Ultraviolet-Visible Adsorption Spectra	277 - 294 nm	4660 - 3670 L/mol-cm	
	pH	Mean $P_{(ow)}$	Log P(mean)
$P_{(ow)}$ Octanol/Water Partition Coefficient	5	0.038	-1.42
	7	0.012	-1.91
	9	2.45	0.389
Aerobic Biodegradation- Water - Soil	Did not degrade under laboratory conditions in 28 days <50% mineralization in 64 days (3 soil types)		
Dissociation Constant	$pK_a = 9.51$		
	Soil Type	K_d	K_{oc}
Soil Sorption/Desorption	Iowa	85.2	3721
	Ohio	35.0	3302
	California	53.1	3340
Activated Sludge Respiration Inhibition	EC_{50} > 720 mg/L		
Acute Toxicity to Daphnids	48 hr EC_{50} = 290 mg/l		

* Activated Sludge Respiration Inhibition Test (ASRIT) reflects microbial inhibition in wastewater treatment facilities

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Environmental Hazard Assessment

No published studies evaluating the potential environmental toxicity of sumatriptan were identified. Therefore, two studies were carried out to evaluate the acute effects of sumatriptan on potential environmental receptors: (1) the Activated Sludge Respiration Inhibition Test (ASRIT) Study, and (2) a test of acute toxicity to *Daphnia magna*. The results of these studies are summarized in Table 2. These tests were determined to be most appropriate for evaluating the effects of sumatriptan in the environment. Emissions to the environment are expected to occur primarily following use of the drug product and would result in release to wastewater treatment plants and, ultimately, to surface water.

The ASRIT Study determined the toxicity to activated sludge microorganisms, typical of those found in municipal sewage treatment facilities, by a respirometric method. The test was carried out according to Organization for Economic Cooperation and Development (OECD) Test Guideline 209 under conditions sufficient to satisfy the requirements of the FDA Good Laboratory Practice Regulations (21 CFR 58). No inhibition of microbial growth was observed under the conditions of the test, the Minimum Inhibitory Concentration was >720 mg/l.

The acute toxicity to *Daphnia magna* was evaluated according to procedures identified in FDA Technical Assistance Document 4.08. The test determines a median effect concentration (EC_{50}), defined as the concentration resulting in 50% immobilization of the *Daphnia* in the specified time period. The *Daphnia* acute aquatic toxicity study identified the 24-hour EC_{50} to be 500 mg/L and the 48-hour EC_{50}s to be 290 mg/L sumatriptan. The no observed effect concentration at 48 hours was 200 mg/L sumatriptan.

8.2 Evaluation of Environmental Effects

Small amounts of sumatriptan may be excreted by individuals using sumatriptan nasal spray which ultimately may enter the aquatic environment through wastewater treatment plants. Based upon the estimated maximum release of sumatriptan to the aquatic compartment and the assumptions set forth in Section 6, a Maximum Expected Emitted Concentration (MEEC) of 0.07 mg/L for the aquatic compartment was calculated for this environmental pathway. This MEEC is less than 1/100 of the EC_{50} for microbial inhibition and the EC_{50} for acute *Daphnia* toxicity. Under 21 CFR 25.15(b), the estimated maximum concentration of sumatriptan in the aquatic compartment would be considered non toxic because the MEEC is less than the no observed effect concentrations and less than 1/100 of the median effect concentrations (median lethal concentrations were not identified) determined in environmental effects testing.

Based on consideration of the information presented above, sumatriptan, at maximum expected environmental concentrations, is not expected to adversely affect sensitive environmental receptors in the aquatic environmental compartment.

No adverse environmental effects are expected to occur as a result of emissions associated with the sumatriptan nasal spray manufacturing processes. Emissions of all substances are within regulatory limits or are collected and disposed of using appropriate, approved procedures.

9.0. USE OF RESOURCES AND ENERGY

The raw materials used in the production of sumatriptan and sumatriptan nasal spray, including the substances used as excipients in the final dosage form, are readily available. The production of this drug product will not cause significant depletion of any natural resources, including energy, minerals/chemicals, and land.

Energy use estimates expected to occur as a result of approval of the requested action are based upon the estimated percentage of total facility usage for the manufacture of sumatriptan nasal spray or its chemical precursors. A review of the manufacturing processes considered in this environmental assessment indicates that the energy resources required to produce sumatriptan nasal spray are in a range which is considered normal for production and distribution of a pharmaceutical product.

9.1 Energy and Land Use

For all manufacturing sites considered in this assessment, the proposed action will be performed within existing facilities and with the present work force. No additional buildings, equipment, landscaping, or construction will be necessary. Therefore, approval of the request to manufacture sumatriptan nasal spray will not affect existing land use in Montrose or Parma.

Information on resource and energy consumption associated with the manufacture of the drug substance has been provided to FDA in NDA 20-080 (Imitrex® Injection) dated June 29, 1990, amended April 30, 1992 and approved December 28, 1992.

The total annual energy for the formulation and packaging of sumatriptan nasal spray at Parma has been calculated using the information from the site specific data. The energy use information has been adjusted to show only the amounts needed to support the fifth year production estimate for the requested approval. The total annual use of electricity and natural gas is expected to be 61,044 kilowatt hours and 13,362 cubic meters respectively.

9.2 Water Use

Total water use associated with the manufacture of sumatriptan nasal spray at Parma is estimated to be 1,662 cubic meters. This estimate is based on manufacturing site water use information adjusted to show only the water needed to support fifth year forecasts for the requested approval.

9.3 Effects on Endangered or Threatened Species

The requested approval is not expected to affect rare, endangered, or threatened species. Effects associated with obtaining raw materials are not a concern because manufacture of the drug substance and drug product do not involve any biological or natural extractions. Effects from loss of habitat will not occur because all manufacturing will be done at existing facilities. Adverse effects on endangered species or local ecosystems from manufacturing emissions are not expected to occur because emission levels are minimal and well below any levels that might cause toxicity (see Section 6 of this environmental assessment report). It is also unlikely that emissions after use will have any adverse environmental effects because resulting environmental concentrations are expected to be minimal and significantly below any observed toxicity levels.

9.4 Effects on Property Listed in the National Register of Historic Places

The production, use, and disposal of substances associated with the requested approval will have no effect on property listed or eligible for listing in the National Register of Historic Places.

10.0. MITIGATION MEASURES

For all manufacturing sites it is projected that no additional structural controls will be needed in order to comply with applicable environmental regulations and permits. However, many non-structural environmental controls which are implemented at the facilities as standard procedures will have the effect of being mitigation measures for the proposed action. Furthermore, standard emergency response procedures will have the effect of being mitigation measures for the proposed action.

Information on mitigation measures at the site associated with the manufacture of the drug substance and drug product has been provided to FDA.

11.0. ALTERNATIVES TO THE PROPOSED ACTION

The only alternative action is no action. The alternative would deny an alternate dosage form of a safe and effective drug to some segments of the public that could benefit from its use.

12.0. LIST OF PREPARERS

Alan R. Beckham

-Environmental Engineer, Glaxo Wellcome Inc., 1994 - present
-Environmental Scientist, Glaxochem Ltd, 1987 - 1994
-Scientific Officer, Glaxo Operations (UK) Ltd, 1981 - 1987
- Bachelor of Science in Microbiology
University of Newcastle upon Tyne, 1980

13.0. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Glaxo Wellcome Inc.

Thomas F. Cecich — JUNE 5, 1995

Thomas F. Cecich — Date

Vice President, Safety & Environmental Affairs
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

14.0. REFERENCES

Council On Environmental Quality, " Regulations On Implementing National Environmental Policy Act Procedures," Federal Register, Vol. 43, November 29, 1978, p. 55990.

Pharmaceutical Manufacturers Association, "Interim Guidance To The Pharmaceutical Industry For Environmental Assessment Compliance Requirements For The FDA v7," Seminar on Environmental Assessments, Rockville, Md., July 29-30, 1991.

U.S. FDA, "Environmental Assessment Technical Assistance Handbook, U.S. FDA, March 1987

U.S. FDA, "National Environmental Policy Act; Policies and Procedures; Final Rule," Federal Register, Vol. 50, April 26, 1985

15.0. APPENDIXES

Appendix 1 Material Safety Data Sheet

ATTACHMENT 1

DRUG SUBSTANCE MATERIAL SAFETY DATA SHEET

SUMATRIPTAN BASE MSDS FORM

ACCESSION NUMBER: 360

SHEET STATUS: Amended

FILE CODE: Authorised

CONFIDENTIALITY: Restricted

NAME: SUMATRIPTAN BASE

SYNONYMS:
3-(2-(Dimethylamino)ethyl)-N-methyl-1H-indole-5-methanesulphonamide;
1H-indole-5-methanesulphonamide, 3-(2-(dimethylamino)ethyl)-N-methyl-; GR 43175X

MOLECULAR FORMULA: C14H21N3O2S

CAS REGISTRY NUMBER: 103628-46-2

RELATED REGISTRY NUMBER(S):
Not applicable

ITEM CODE: Not available

EINECS/ELINCS NUMBER: Not applicable

SUBSTANCE IDENTIFICATION NO. (UN NO.): Not applicable

SUBSTANCE CLASS: Intermediate

DESCRIPTION

Sumatriptan base is a white or off-white solid, insoluble in water but soluble in dilute acid.

MELTING POINT (deg.C): Approximately 172

BOILING POINT (deg.C): Not applicable

FLASH POINT (deg.C):	Not applicable
AUTOIGNITION TEMPERATURE (deg.C):	Not applicable
UPPER EXPLOSIVE LIMIT (%):	Not available
LOWER EXPLOSIVE LIMIT (%):	0.001
CONDUCTIVITY (pS/m):	0.167 to 0.4147
RESISTIVITY (ohm.cm):	2.4 to 6.0 x 10(exp14)
VAPOUR DENSITY (air=1.0):	Not applicable
SPECIFIC GRAVITY/DENSITY:	0.41 g/ ml (tapped bulk density)
WATER SOLUBILITY/MISCIBILITY (%w/v):	Less than 0.1 at 20 deg.C (Insoluble)
PARTITION COEFFICIENT:	Not available
GAS GROUP:	Not applicable

CHEMICAL AND THERMAL

Sumatriptan base decomposes on heating in air (0.5 deg.C/min) with no detectable exotherm.

FIRE

Sumatriptan base is a combustible solid. It will burn on strong heating but flame is not readily transmitted. However, toxic and flammable vapours may be emitted when the substance is heated strongly.

The minimum ignition energy is dependent upon the physical characteristics of the powder. Several values in the range 1-4 mJ to 7-8 mJ have been obtained.

CORROSION

No information is available.

BIOLOGICAL EFFECTS

Sumatriptan is a pharmacologically active base usually administered as the succinate salt. The succinate has proven efficacy in the treatment of migraine, believed to be mediated by its action on the blood vessels of the brain.

Most toxicological tests have been performed using sumatriptan succinate but any systemic effects seen in these tests would have been due to the pharmacologically active base, sumatriptan.

NO ACTIVITY

Sumatriptan base has been shown to have no activity in animal and laboratory tests to demonstrate:
Skin sensitisation
Skin irritancy on intact skin

Sumatriptan succinate has been shown to have no activity in animal and laboratory tests to demonstrate:
Reproductive dysfunction
Birth defects
Mutagenicity
Oncogenicity

Sumatriptan base can be assumed to share this lack of activity.

Sumatriptan base is not irritant to the sensitive tissues of the respiratory and nasal passages of the monkey, and is therefore assumed to have no significant irritancy by eye contact.

ACTIVITY

Sumatriptan base is slightly irritant to abraded skin.

Adverse effects in animals have only been seen following excessive exposure to sumatriptan succinate, considerably above therapeutic levels. At these high doses, the following clinical effects were observed: tremor, incoordination, mydriasis, vasodilatation, salivation, increased respiration and increased heart rate. All the effects were transient, and animals tolerated the excess dose well for periods of 12-18 months.

The oral LD50 of sumatriptan succinate in rats is in excess of 2g/kg.

Information from large numbers of patients and volunteers indicates that sumatriptan succinate is well tolerated following subcutaneous doses of up to 16mg and oral doses of up to 400mg.

Minor but distinctive side effects have been reported following therapeutic doses of sumatriptan succinate. These include sensations of heaviness or pressure, tingling and warmth. Less commonly, visual disturbances, sensations of pressure and tightness of the chest have been experienced, and rare cases of coronary vasospasm, cardiac arrhythmias and ECG changes have been reported.

ENVIRONMENTAL EFFECTS

No information is available.

Emissions and discharges must be kept to a minimum, complying with any requirements laid down by regulatory bodies.

OCCUPATIONAL EXPOSURE

No Occupational Exposure Level (Glaxo) has been established. However, the value for sumatriptan succinate is:
TWA (8 hr) 0.15 mg/m3

OCCUPATIONAL HYGIENE MONITORING

Reference should be made to the Group Occupational Health and Hygiene Manual.

Airborne concentrations may be determined by collecting samples on a suitable filter e.g. PTFE membrane or glass fibre filter.

The sample should be analysed by chromatographic techniques.

HEALTH SURVEILLANCE

Any symptoms apparently due to exposure to sumatriptan base must be reported to the Occupational Health Department/Occupational Health Physician and Line Management without delay.

Health surveillance should be appropriate to the risk and must be determined only after a risk assessment has been carried out.

PERSONAL PROTECTIVE EQUIPMENT

The selection of protective equipment should be based on an assessment of the potential levels of exposure. Reference should be made to the Group Occupational Health and Hygiene Manual.

Overalls, boots, chemical resistant gloves and goggles should be worn to prevent skin or eye contact. Any respiratory protection must also provide skin and eye protection. An air suit may be required when handling the bulk material.

HANDLING AND STORAGE

Store at ambient temperature in clearly labelled, tightly closed, sealed containers (e.g. double polythene bags inside closed and labelled kegs).

Wherever possible, sumatriptan base should be used in enclosed plant fitted with exhaust ventilation.

DISPOSAL

Consideration must be given to recovery operations. However, if disposal is necessary this may best be effected by dissolving the compound in a suitable solvent and burning the solution in a licensed incinerator.

Disposals must conform to relevant legislation.

FIRST AID

Never attempt to give any solid or liquid by mouth to an unconscious person. No attempt should be made to induce vomiting in unconscious or semi-conscious persons.

Eye contact
Wash immediately with water for at least 15 minutes. Obtain medical attention.

Skin contact
Thoroughly wash all affected areas with soap and water, removing contaminated clothing. Obtain medical attention. Thoroughly wash contaminated clothing.

Inhalation
Remove the casualty to fresh air, and if breathing is difficult or ceases, give oxygen or mouth to mouth resuscitation. The casualty should be kept warm and at rest. Obtain medical attention.

Ingestion
Wash out the mouth and give water to drink. Obtain medical attention.

EMERGENCY MEDICAL TREATMENT

Treat symptomatically.

EMERGENCY ACTION CODE (HAZCHEM CODE): None assigned

FIRE FIGHTING

Wear breathing apparatus and clothing designed to give full skin and eye protection.

Use dry powder, foam or carbon dioxide.

LEAKAGE/SPILLAGE

Wear an air suit, gloves and boots or respiratory protection and protective clothing designed to give full skin and eye protection. Unprotected personnel must not be permitted to enter the spillage area. If possible stop the spillage. Avoid raising dust.

Solid Spillage
Collect the spillage by vacuum. Transfer to a suitably labelled, sealable, container e.g. a double polythene bag.

Solution Spillage
Remove all possible sources of ignition. Contain the spillage by improvising dams with sand or other inert material. If possible, transfer liquid to a sealable, labelled container for recovery or disposal. Otherwise absorb on sand or other inert material and remove for disposal in a safe place.

For both solid and solution spillages, flush the site of spillage with copious quantities of water and detergent to an effluent drain only after as much as possible of the spilled material has been collected. Thoroughly ventilate and test the area before allowing re-entry of unprotected personnel and the resumption of normal working practices.

UK CLASSIFICATION, PACKAGING AND LABELLING:

Sumatriptan base is not listed under the Classification, Packaging and Labelling of Dangerous Substances Regulations 1984.

It is non-hazardous for conveyance and supply and so has not been designated risk phrases or safety precautions as they are not applicable.

INTERNATIONAL TRANSPORT CLASSIFICATION:

Non-hazardous in transit.

AUTHORISING PERSON(S): Dr SJ Burge, Glaxochem Ltd.

DATE: Jul 22, 1993