

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20763

ADMINISTRATIVE DOCUMENTS

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **February 3, 1998**

FROM: **Paul Leber, M.D.**
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: **Amerge (naratriptan) Approval Recommendation**

TO: **File NDA 20-763**
 &
 Robert Temple, M.D.
 Director, Office of New Drug Evaluation 1

The reports submitted to Glaxo Wellcome's NDA for Amerge Tablets (naratriptan tablets) document, within the meaning of the Act, that naratriptan is, under the conditions of use recommended in the version of Amerge product labeling attached to the approval letter being forwarded to the Office for issuance, safe for use and effective in use in the management of acute migraine.

My conclusion that the application may be approved is based on the analyses of the sponsor's findings carried out by the Division's review team under the leadership of Dr. Randy Levin. An explication of my assessment of a number of substantive issues affecting the application's approvability was provided in an earlier memorandum to the file (i.e., approvable action memorandum of November 11, 1997).

The contemplated approvable action was not taken, however, because the firm made, during the last 3 months of the review cycle, a submission to the file intended to repair a number of deficiencies in the pending application about which they had been informed by the Division during the course of its review. Accordingly, the Office and Division agreed that it would be reasonable to forego the approvable action (that would have issued prior to 12/4/97) and move directly to an approval of the NDA within the first 2 months of 1998. This option was available because the timing of sponsor's supplemental submission allowed the PDUFA due date to be extended by 3 months (to 3/4/98).

The sponsor was informed of this decision. Subsequently, the review team worked with the firm to resolve the agency's outstanding questions and concerns.

At the time the approvable action was contemplated, residual concerns about the safety of naratriptan arose not from affirmative findings of risks known to be associated with the use of the drug, but from uncertainty about the precise nature, severity, and counts of the untoward clinical events reported in the application. The sponsor's efforts to repair the identified deficiencies in its initial reports were reviewed by the assigned safety medical reviewer, Dr. Sevka, (1/8/98), who works under the supervision of the Safety Team Leader, Dr. Burkhart. Based upon these reports, both Dr. Sevka and Burkhart now agree that the naratriptan has been shown to be safe for use.

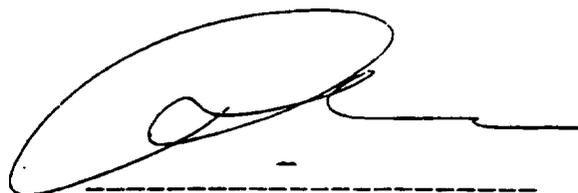
Labeling, incorporating the bulk of the recommendations made by the Office Director in the course of his review of the approvable action package, was developed by Dr. Levin in the course of a series of negotiations with the sponsor. Dr. Levin's memorandum of 1/15/98 describes his efforts, and notes where exceptions to the Office Director's labeling recommendations have been made.

Conclusion

Upon review, the reports contained within Glaxo Wellcome's NDA for Amerge have been found to document, within the meaning of the Act, that Amerge tablets are safe for use and effective for use under the conditions of use described in the version of product labeling attached to the approval action letter.

Recommendation

Issue the approval action letter.



Paul Leber, M.D.

2/3/98

cc: NDA 20-763

HFD-101

Temple

HFD-120

Katz

Levin

Burkhart

Sevka

Fitzgerald

Huff

Guzewska

Bates

Chen

HFD-710

Sahlroot

Choudhury

HFD-860

Sahajwalla

Mahmood

MEMORANDUM

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

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

Date: 1/15/98
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-763 (Naratriptan)
To: file

Background:

This is an addendum to my memo dated 11/14/97.

At the time of my 11/14/97 memo, I had concluded that the application was approvable pending the sponsor addressing issues raised by the review of the safety data and agreement to the draft labeling. In a memo dated November 20, 1997, Dr. Leber agreed with this conclusion. The draft labeling was forwarded to Dr. Temple who agreed with the division and provided comments on the division's draft labeling.

On October 22, 1997, Dr. Sevka and I communicated the safety issues to the sponsor and the sponsor initially responded to these issues on November 21, 1997. Because the NDA was amended with this information late in the review time, a 3 month extension was added to the original PDUFA date of 12/4/97.

During his review of the safety amendment, Dr. Sevka discovered problems in the data tables submitted by the sponsor and requested further clarification. On December 17, 1997, the sponsor provided the final response to the safety issues raised in October. The sponsor's response was reviewed by Dr. Sevka and Dr. Burkhart. They agreed that the sponsor had reasonably addressed our concerns and concluded that the drug was safe for use as described in the attached labeling.

The labeling was revised addressing Dr. Temple's comments. Dr. Temple suggested changes to parts of the safety portion of labeling, mostly to make the labeling consistent with the ZOMIG labeling. Some of these differences were requested by the sponsor. As these changes strengthened the labeling and were not false and misleading, I left them in the labeling. Dr. Temple suggested the addition of a statement that if naratriptan is used in the elderly, the initial dose should be 1 mg. I think that we should not recommend dosing for the elderly to be consistent with the labeling of the other drugs in this class. The labeling includes a description of why the elderly may have more adverse events if treated with the drug. Dr. Temple asked if we needed to add information about the results for the treatment of the second and third headache. Since only one study evaluated patients treating more than one headache with the same dose and since we did not include this information in labeling for other migraine drugs with similar results, I did not add this information into the labeling.

Dr. Sevka added additional changes to the labeling following review of the safety amendment.

After all of the changes were made, the labeling was sent to the sponsor for final revisions. They have no outstanding issues or concerns regarding the draft labeling.

Recommendation:

I recommend that the application be approved with the attached labeling. There are no outstanding issues for the NDA from the review team or from the sponsor.



Randy Levin, M.D.
Neurology Team Leader
rl/January 15, 1998

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-763 Naratriptan Tablets

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126[©] for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

- 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.
- 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Pediatric studies were done and the drug was ~~not~~ found ~~to~~ not to
be effective. The draft labeling describes the study results

Rdy Li
Signature of Preparer

10/27/97
Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

Temple

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 20, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Amerge (naratriptan)

TO: File NDA 20-763
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the Division's Review Team's recommendation that Glaxo Wellcome's NDA 20-763, which allows for the use of Amerge (naratriptan) tablets (2.5 mg) in the management of acute migraine attacks, be declared approvable. This recommendation is conditioned upon the firm's capacity to satisfy and its willingness to agree to the requirements enumerated in the approvable action letter, including its attached draft labeling, being forwarded to the Office for issuance.

A systematic exposition and review of the information and argument that support the proposed approvable action is presented in the approvable action memorandum provided (11/14/97) by Dr. Levin, the Team Leader of the Division's Neurology subunit responsible for anti-migraine drug products.

Dr. Levin led the negotiations with Glaxo regarding the form and content of product labeling. The labeling attached to the approvable action letter was provided to the sponsor (11/14/97), but as of the date of issuance of this memorandum, I am uncertain as to their views on its acceptability.

The PDUFA Goal date for the NDA is December 4, 1997

Background

Naratriptan is one of several 5HT 1d /1b agonists that have been developed for use in the management of acute migraine attacks. Although Imitrex (sumatriptan), another Glaxo product, was the first of a number of relatively selective members of the product class to be developed (marketed as an injection in 1992), a number of long marketed ergot derivatives (e.g., dihydroergotamine), also presumably exert their anti-migrainous effects through these receptors.

The Division has determined¹ that there is sufficient preclinical and clinical evidence and supporting theory to support a conclusion that anti-migraine "drugs with similar affinities for and actions at 5HT1d and 5HT1b receptors belong to a common pharmacologic/therapeutic class," and, accordingly, that there is sufficient justification to require that all "anti-migraine drug product with these [pharmacologic] attributes ... carry a number of generic statements²

¹ See arguments developed in my memorandum on Zomig (11/12/97), another 5HT1d/ 1b antimigraine drug product.

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The Division's position vis a vis labeling is provided in my 11/12/97 Zomig memo: "... an anti-migraine drug product of the kind identified [5HT-2 agonist] would...be unsafe for use if it were marketed under product labeling that fails to provide generic statements warning and/or cautioning about the untoward events that are known to be, or are likely to be, associated with the use of drugs within the putative class.

Because of the potential for the numerical values reported in clinical investigations of anti-migraine drug effects (e.g., percent subjects pain free, etc.) to be misunderstood and/or misrepresented, the Division takes the view that an anti-migraine drug product will be misbranded if its labeling fails to advise that the data adduced in controlled clinical investigations of the drug product cannot be validly compared with that adduced in trials of other anti-migraine drug products. "

Product Specific Issues.

Effectiveness in Use

The Division's affirmative conclusions regarding the efficacy of naratriptan as an oral anti-migraine treatment derive from the reviews of Dr. Levin (10/6/97;11/14/97) and Dr. Choudhury (9/16/97) of reports made to the NDA.

The sponsor's clinical development program for naratriptan is comprised of 7 clinical trials. (enumerated in the following table [Chart 3, taken from the sponsor's ISE):

Chart 3: List of Study Numbers and Protocol Titles

List of Study Numbers and Protocol Titles for the Adequacy and Safety of the Clinical Studies	
S2WB2003	A Double-Blind, Placebo-Controlled, Randomized, Parallel Group Study to Evaluate the Safety and Efficacy of Oral Naratriptan (5mg and 10mg) Following Dosing during a Migraine Attack
S2WB2004	A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study to Compare the Efficacy and Safety of Oral Naratriptan with that of Oral Sumatriptan and Placebo in the Acute Treatment of Migraine Headache
S2WA3001	A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Four Doses of Oral Naratriptan in the Acute Treatment of a Single Migraine Attack
S2WB3002	A Randomized, Double-Blind, Placebo-Controlled, Oral Sumatriptan-Controlled (100mg), Three Attack, Parallel Group Study to Determine the Efficacy, Safety and Tolerability of Oral Naratriptan (0.1mg, 0.25mg, 1.0mg and 2.5mg) in the Acute Treatment of Migraine Headache
S2WA3003	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Oral Naratriptan in the Acute Treatment of Four Migraine Attacks
S2WB3011	A Randomized, Double-Blind, Two Attack, Crossover Study to Compare the Efficacy, Safety and Tolerability of Oral Naratriptan (2.5mg) with Oral Sumatriptan (100mg) in the Acute Treatment of Migraine in Patients Susceptible to Headache Recurrence
S2WA3012	A Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Efficacy, Safety and Tolerability of Oral Naratriptan in an Adolescent Migraine Population

Source: ISE Table 2

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Among these studies, Dr. Levin identifies four³, all conducted with the “to be marketed formulation” as adequate and well controlled clinical investigations capable of providing “substantial evidence” of naratriptan’s effectiveness as an acute anti-migraine treatment. Three of these four studies (i.e., 3001,3002 and 3003), each conducted in samples of adult migraineurs, provide statistically significant findings documenting naratriptan’s effectiveness in use. The 4th study, 3012, conducted in adolescents finds no statistically significant between treatment difference, a result attributed to the “high” rate of response among patients assigned to placebo.

In all studies, patients evaluated pain on a 4 point scale. The proportion of patients attaining Headache relief, defined as a score of 0 or 1 (no or mild pain) among patients with an initial score of moderate to severe pain (2 or 3 points), 240 minutes following treatment administration was the primary outcome measure used in these trials.

A reasonably wide range of doses were explored in the development program as the following table (Chart 4, taken from the sponsor’s ISE) reveals.

Chart 4: Summary of Patients Treated in Controlled Clinical Studies

Summary of Patients Treated with Blinded Study (Placebo or Naratriptan) in the Seven Adequate and Well-Controlled Clinical Studies									
	Placebo		Naratriptan (100mg)					Active control ¹	
Placebo-Control									
Adult Studies ²	947	350	638	1024	1016	122	93	129	341
Adol. Studies ³	74		78	78	70				
Active-Control									
Adult Study ⁴					239				239
Total	1021	350	1016	1102	1325	122	93	129	580

1 active control agent = Sumatriptan Tablets 100mg
 2 adult placebo-controlled studies: S2WB2003, S2WB2004, S2WA3001, S2WB3002, S2WA3008
 3 adolescent placebo-controlled study: S2WA3012
 4 active-controlled study (adult): S2WB3011
 Source: ISE Table 4

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³ Studies 3001,3002, 3003 and 3012.

The results of several studies document that an oral dose of 1 mg of naratriptan can consistently be distinguished at a statistically significant level from placebo while lower doses cannot. The more difficult question of identifying the dose at which the asymptote of maximum response begins is less easily answered. Evidently, the sponsor considers 2.5 mg a dose superior to the 1 mg dose for a substantive proportion of migraineurs, and, presumably a dose that is well onto the asymptote. This view is supported by the findings of Studies 3001, 3002, and 3003, in which the percent of patients attaining relief at 4 hours is greater among those treated with 2.5 mg than with 1.0 mg⁴.

Naratriptan also improves other dysphoric phenomena that comprise the constellation of signs and symptoms of an acute migraine attack. Although not assessed as a primary measure of treatment outcome, the intensity and duration of these signs and symptoms were also lessened by naratriptan treatment. The beneficial effects on these phenomena is very similar to that obtained with other effective 5HT 1d/1b agonists.

In sum, there is more than sufficient evidence to support a regulatory conclusion that the sponsor has provided "substantial evidence" of naratriptan's effectiveness in use as an acute treatment for migraine headaches.

Biopharmacokinetics

The OCPB finds the application approvable (see 6/24/97 Review by Dr. Mahmood). Dr. Levin provides a succinct summary of the drug's PK profile in tabular form on page 3 of his 11/14/97 memorandum. No feature or finding described presents a regulatory concern.

⁴ The between dose difference is "statistically significant" in Studies 3002 and 3003 (see tables for rates by time post Rx, pages 13-14 in Dr. Levin's 11/14/97 memorandum)

Safety for use -

Generic Safety Issues

Within the meaning of the Act, Amerge has been shown to be "safe for use." A number of caveats accompany this conclusion, however.

At a generic level, this regulatory determination in no way reflects a conclusion that the use of naratriptan is risk free. To the contrary, it is expected that the use of a 5HT 1d/1b agonist will be associated, albeit in a very, very small fraction of users, with serious injury, even death. In addition, as with all active drug substances, there may be risks of treatment that are yet to be appreciated.

For the vast majority of users, however, 5HT 1d /1b agonist treatment will, at most, be associated with only minor discomforts, if any at all.

The societal risk-benefit decision to permit the marketing of members of this drug class for the acute treatment of a non-fatal condition, the serious untoward consequences of the use of drugs within this class for the unfortunate few among many who suffer harm notwithstanding, was made long ago. That decision, however, can only be justified if product labeling describes, completely and prominently, the risks involved, no matter how remote or rare they may be.

Toward this goal, the Division has developed, and continues in efforts to improve, what is tantamount to class labeling for 5HT-1d/1b agonist anti-migraine products (see comments on labeling, below).

Product Specific Safety Issues

Preclinical

The primary pharmacology toxicology reviews have been conducted by Drs. Robin Huff (5/30/97), and John Jessop (July 5, 1995) under the supervision of Dr. Fitzgerald, the Pharmacology/Toxicology Team leader. Dr. Fitzgerald (10/20/97) concludes that the information provided is sufficient to support NDA "approval." Dr. Fitzgerald's memo also

provides the text for several sections of product labeling: Clinical Pharmacology, Precautions (Canine Precorneal Tear Film, Melanin Binding, Carcinogenesis, Mutagenesis, and Impairment of Fertility, and Pregnancy Category C.

Clinical

Review Process

The primary safety review of Amerge was carried out by Dr. Michael Sevka of the Division's Safety Unit under the supervision of Dr. Greg Burkhart. Dr. Burkhart (memo of 10/6/97) concludes that the firm "has probably collected enough experience to adequately describe naratriptan's risks."

Based on subsequent discussions that I have had with Dr. Burkhart, it is my impression that the reservations about the application conveyed in his memorandum to the file derive not from a concern about the extent of exposure⁵ that has been gained with naratriptan, nor from clinical reports or affirmative findings indicating that naratriptan poses some unique and/or unreasonable risk, but from the failure of the firm to provide a reasonably complete, comprehensive, and detailed account of the clinical experience actually gained with the product in its development program.

I agree that aspects of the firm's submission raise concerns about the quality and comprehensiveness of its efforts. The reported failure to provide a precise accounting of the exact number of unique patients who actually participated in the Amerge pre-marketing development is an

⁵ On face, the total numbers of patients exposed (about 3500), the total number of headaches treated (13,500, all but a 1000 of which at the to be recommended dose of 2.5 mg) and the extent of repeated use (2, 2.5 mg doses were used in the management of almost 5000 headaches) seem entirely adequate under current agency policy to assess the safety of a drug product. Indeed, in regard to the extent of extended use (i.e., use in patients with an average of 2 attacks per month for a year), the experience gain with Amerge is more than sufficient by current standards (over 250 patients).

example of yet another deficiency that gives pause. Another sign of a less than complete safety evaluation is the lack of full case descriptions of all patients who discontinued prematurely⁶. The NDA provided only descriptions of the clinical circumstances associated with 'discontinuations' from clinical studies for what it deemed serious events. Counts of individuals who discontinued for "non-serious" reasons were provided, but were identified entirely in terms of a number of group 'explanatory' labels. Among the latter was a residual category, termed "other."

Not all clinical findings relevant to the decision on product safety were fully analyzed at the time of the NDA submission. In particular, an analysis of the EKG data collected during clinical testing was not provided; while not initially a matter of substantive concern, it became a somewhat more urgent issue when it was discovered the 3 patients experienced QT prolongation.

Thus, from a technical perspective, the presentation of the safety information in the NDA precluded a full review, a fact that led Dr. Burkhart and Sevka to conclude (late September/ early October) that further work was required before the review of the safety data could be deemed complete, and a definitive decision rendered on the application.

Upon learning of the Safety Unit's concerns, Dr. Levin, attempted to repair, or to have the firm repair, the defects they had identified. Dr. Levin's 11/14/97 summary memorandum reflects his conclusion, based in part on his own assessment of the NDA in light of the deficiencies identified by the Safety team, that there is sufficient information available to support an approvable action.

On November 20, 1997, I held a brief meeting with the review team to determine whether the concerns raised by the safety team, based on interim submissions, and the efforts of Dr. Levin, had been resolved to the satisfaction of all members of the Review Team. It was agreed by those attending (Drs. Levin, Burkhart and Sevka) that the information provided

⁶ A complete accounting would not have been burdensome; there are said to be only 91 discontinuations

and reviewed was sufficient to support an approvable action; final approval, all agreed, would be contingent upon our determination, based upon the review of information yet to be submitted by the sponsor, that it provided no new findings of concern.

Specific Naratriptan findings

As to specific findings, there are none that are so unusual, unexpected or serious that they would preclude the marketing of naratriptan. There are some findings, however, that deserve comment.

Clinical reports of cardiac ischemia following naratriptan's use

Two patients are reported to have experienced clinically serious symptoms that were presumably due to cardiac ischemia. The dose administered in one case, however, was 3 fold (7.5 mg) the maximum being recommended.

Pulmonary arterial pressure elevation as a possible mechanism to explain 5 HT 1d/1b agonist associated chest pain?

Beyond coronary vasoconstriction, naratriptan may conceivably cause chest pain by other mechanisms. Esophageal dysfunction has been proposed as one possible, albeit arguable, explanation, for 5HT 1d/1b agonist induced chest pain/discomfort. A report to this NDA suggests another possibility: acute pulmonary arterial pressure elevation.

In a clinical pharmacology study in which right heart catheterization was performed, the parenteral administration of naratriptan, but not placebo, was associated with an increase in pulmonary arterial pressure. A proportion of the patients who received parenteral naratriptan in the study reported chest pain; placebo infusion was not associated with any.

Of course, since coronary flow/resistance was not measured, the observations cannot establish that the change in pulmonary pressure is responsible for the bouts of chest pain (unfortunately, the report did indicate whether or not the extent of pulmonary artery pressure increment

"predicted" the occurrence of pain).

In any case, although this matter is not immediately relevant to approval of naratriptan, it is of general interest vis a vis the drug class. Dr. Burkhart has informed me (personal communication) that a report of a similar study conducted with sumatriptan (also the sponsor's drug) indicates that it also causes pulmonary arterial pressure elevation upon parenteral administration.

QT prolongation

It is now widely held that any drug that can prolong the QT interval poses some risk of causing potentially fatal cardiac arrhythmia. Accordingly, the discovery that QT intervals were prolonged in 3 patients who had "discontinued" naratriptan use, led the review team to request a complete analysis of all EKGs collected during clinical trials (the failure to provide these results in the original filing has already been mentioned.). Upon review of the firm's 9/2/97 submission (see Dr. Sevka's 11/7/97 review), it was determined that the evidence available does not support a conclusion that naratriptan has a capacity to prolong the QT interval.

Labeling

The product labeling attached to the approvable action letter is virtually identical in format to that developed/proposed for use with the labeling for the last 5HT 1d/1b agonist antimigraine drug product (i.e. Zomig) evaluated by the Division. Importantly, the text of the labeling for Amerge reflects editorial format and content changes made very recently by the Director of ODE 1 to Zomig product labeling.

In regard to the latter, I take note that the Office Director has struck from the text of the Clinical Trials section of Zomig product labeling, the final sentence of a generic statement⁷ advising prescribers that the

⁷ "Comparisons of drug performance based upon results obtained in different clinical trials are always of arguable validity and reliability. Because studies are conducted at different times, with different samples of patients, by different investigators,

numerical estimates of treatment effect developed in randomized clinical trials "have limited values as estimates of the likely effect of a drug in the population as a whole." Accordingly, the sentence has also been removed from the draft of Amerge product labeling. I do so with reluctance, however.

I continue to believe the statement, which I had intended become a standard statement in the labeling of drug products that are identified as belonging to particular therapeutic class with numerous members, is accurate, relevant, and informative. Although I do not dispute the Office Director's observation (advanced both in private conversations and in his November 17, 1997 memorandum to me about Zomig) that the statement can be viewed as applying broadly to the results of controlled clinical trials in general, I do not see why that attribute would preclude its adoption in the labeling of Amerge, Zomig, Imitrex, Migranal or any other drug product for which I and my staff can document it is appropriate. The fact that some ad hoc group in the agency is currently developing a policy about the Clinical Trials section of product labeling hardly seems an adequate reason to suppress an innovative improvement to product labeling.

Many of the sections of drug product labeling that today have been widely adopted for use across many different drug products in a spectrum of the therapeutic areas were developed by individual review teams in an effort to resolve specific problems affecting a single NDA. The generic warnings against comparisons of drug associated risk based on reported incidence now widely prevalent in drug product labeling, in particular, have their origin in labeling initiatives I developed for DNDP drug products. The capacity to innovate in such a manner is not harmful or undermining of any interest. In fact, the only harm the inclusion such a statement in labeling will cause is to those who would capitalize on meaningless numerical

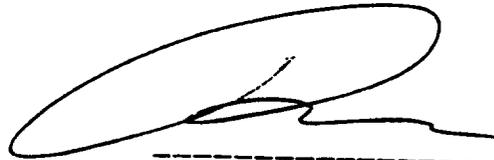
employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study. Accordingly, estimates of treatment effects obtained from a single study or small series of studies have limited value as estimates of the likely effect of a drug in the population as a whole. "

estimates of treatment effect size to misleadingly inflate the value of their drug products.

**APPEARS THIS WAY
ON ORIGINAL**

Conclusions and Recommendations.

The evidence presented is sufficient to justify a conclusion that Amerge is effective in use, and, very likely, if the firm's responses to a number of pending questions are as we expect them to be, safe for use. Accordingly, I would recommend that the NDA be declared approvable, final approval of the application being conditioned upon the firm's satisfactory response to the questions and requirements enumerated in the approvable action letter, including the draft labeling attached to it, being forwarded to the Office for issuance.



Paul Leber, M.D.
November 20, 1997

**APPEARS THIS WAY
ON ORIGINAL**

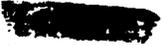
**APPEARS THIS WAY
ON ORIGINAL**

Leber: Amerge approvable Action

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cc: NDA 20-763 -

HFD-101


HFD-120

Katz

Levin

Burkhart

Sevka

Fitzgerald

Huff

Guzewska

Bates

Chen

HFD-710

Sahlroot

Choudhury

HFD-860

Sahajwalla

Mahmood

NDA: 20-763
Trade Name: AMERGE
Generic Name: Naratriptan
Applicant Name: Glaxo Wellcome
Division: HFD-120
Project Manager: Lana Y. Chen, R.Ph.
Approval Date: February 10, 1998

PART I

IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a. Is it an original NDA? Yes

b. Is it an effectiveness supplement? No
If yes, what type? (SE1, SE2, etc.)

c. Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") Yes

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: N/A

d. Did the applicant request exclusivity? Yes
If the answer "yes," how many years of exclusivity did the applicant request? 5 yrs

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? No

If yes, what is NDA number

If yes, what is Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade?

No

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

**APPEARS THIS WAY
ON ORIGINAL**

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PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate).

1. **Single active ingredient product.**

No

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. **Combination product.**

N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR-EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

- b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

- 1) If yes, explain:
- 2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

If yes, explain:

If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

APPEARANCE

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

Investigation #2

Investigation #3

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA: Study:

NDA: Study:

NDA: Study:

b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

Investigation #2

Investigation #3

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA: Study:

NDA: Study:

NDA: Study:

- c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #: Study #:

Investigation #: Study #:

Investigation #: Study #:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND#: Explain:

Investigation #2

IND#: Explain:

Investigation #2

IND#: Explain:

- b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

Explain:

Investigation #2

Explain:

Investigation #3

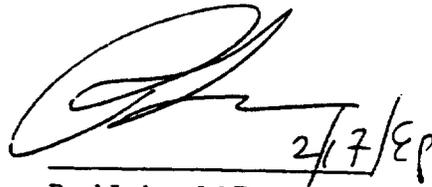
Explain:

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

If yes, explain:



Lana Y. Chen, R.Ph.
Project Manager
DNDP, HFD-120



Paul Leber, M.D.
Director
DNDP, HFD-120

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Final: June 30, 1997

cc:

Original NDA
Division File
HFD-120/Chen
HFD-85/Holovac

ITEM 13

**Patent Information Pursuant to 21 U.S.C. §355
for
Naratriptan Tablets**

NDA 20-763

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Active Ingredient(s): Naratriptan hydrochloride
Dosage Form: Tablets
Strength(s): 1mg and 2.5mg

U.S. Patent 4,997,841

Expiration Date: August 12, 2008
• pursuant to the Uruguay Round Agreements Act,
Public Law 103-465 (1994)

Type of Patent: Drug Product
• Formulation / Composition
Method of Use
• Method of treating migraine

Name of Patent Owner: Glaxo Group Limited

U.S. Agent: David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, North Carolina 27709
(919) 483-2723

The undersigned declares that U.S. Patent 4,997,841 covers the formulation, composition and method of using Naratriptan Tablets and should be included in Item 13 of NDA 20-763.

17 Sept 96

Date

Robert H. Brink

Robert H. Brink, Ph.D.
Registered Patent Attorney
Registration No. 36,094

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NDA 20-763

Naratriptan Tablets

Request for Marketing Exclusivity

pursuant to 21 C.F.R. §314.50(j)(3)

Under sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act, Applicant, Glaxo Wellcome Inc., requests five years of exclusivity from the date of approval of this new drug application for Naratriptan Tablets 2.5mg for the acute treatment of migraine with and without aura as a new chemical entity pursuant to §§ 314.108(a) and 314.108(b)(2).

The active ingredient of the drug product for which approval is being sought under this application is naratriptan hydrochloride also known as 2-[3-(1-Methyl-piperidin-4-yl)-1H-indol-5-yl]-ethanesulphonic acid methylamide hydrochloride.

Applicant states that to the best of its knowledge and belief that the drug product which is the subject of the instant application contains no "active moiety" as defined under 21 C.F.R. §314.108 that has been approved by the FDA under §505(b) of the Federal Food, Drug and Cosmetic Act; and that therefore, the drug product of the instant application falls within the definition of "new chemical entity" under 21 C.F.R. §314.108.

Whereas the drug product for which approval is being sought under the instant application lies within the definition of a "new chemical entity" pursuant to the Agency's regulations promulgated October 3, 1994 in the Federal Register, Applicant respectfully submits that nothing in the present request be interpreted as it conceding to the validity of the Agency's definition of "new chemical entity".

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NDA 20-763

NARATRIPTAN TABLETS

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.



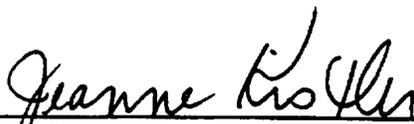
5 Nov 96

Richard Kiernan
Vice President & Director
Worldwide Preclinical & Clinical Compliance

Date

.....

The attached list of Glaxo Wellcome Principal Investigators for the Naratriptan Tablets submission has been compared with the 19Jun96 Food and Drug Administration Debarment List and the 21Nov95 disqualified, restricted, and given assurances lists.



5-Nov-96

Jeanne Kistler
Compliance Services Coordinator
Worldwide Compliance Services

Date

MEMORANDUM

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

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

Date: 11/14/97
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-763 Naratriptan
To: file

Background:

This NDA is for Naratriptan, a 5 HT₁ agonist for the acute treatment of migraines. The NDA was received by the Agency from Glaxo on 12/4/96. The NDA review team included Dr. Doris Bates (chemistry), Dr. Robin Huff/Dr. Glenna Fitzgerald (nonclinical pharmtox), Dr. Iftexhar Mahmood (biopharm), Dr. Micahel Sevka/Dr. Greg Burkhart (clinical safety), and Dr. Jopa Choudhury (statistical consultant).

I have reviewed the efficacy portion of the application as well as the evaluations submitted by the review team and conclude that the application is approvable. The following is a summary of information from the NDA reviews on which I based my decision.

Chemistry:

Conclusion: Following review of the chemistry section of the NDA, Dr. Bates noted minor deficiencies which the sponsor adequately addressed in amendments to the NDA. Following review of these amendments, Dr. Bates concluded that the application could be approved for CMC. The only issue not completed is a validation of the regulatory methods which is pending.

Non clinical pharmtox:

Conclusion: Following review of the nonclinical toxicology section of the NDA, Dr. Huff, Dr. Jessop and Dr. Fitzgerald concluded that they can recommend that the application be approved. There are no outstanding issues.

In anesthetized dogs given IV naratriptan 1-1000ug/kg, dose-dependent carotid artery vasoconstriction lasting longer than 2 hours (following the highest dose) was observed with little change in systemic arterial blood pressure.

Following IV administration to dogs at doses which cause carotid vasoconstriction, naratriptan causes small increases in vertebral and femoral vascular resistance. It also caused small increases in coronary vascular resistance (i.e. 33% compared to 184% for carotid artery) accompanied by a dose-dependent bradycardia; but injection directly into the coronary artery (0.03-300ug/kg) caused little or no acute effect on coronary blood flow, suggesting no direct coronary vasoconstrictor action.

In anesthetized dogs ECG changes were observed at 300µg/kg (slight increase in T wave amplitude) and at 30µg/kg (loss of P wave and ST segment shortening). These effects are reportedly slightly less than those observed following sumatriptan administration to dogs where doses of 10ug/kg caused some ECG change.

In anesthetized cat given IV naratriptan 10-100ug/kg, transient increases of 28-53mmHg in blood pressure were observed lasting 5-10 minutes with no effect on heart rate or ECG. The blood pressure increase was similar at 1000ug/kg IV. In one of two conscious Cynomolgus monkeys, small decreases in arterial blood pressure after IV naratriptan 100-1000ug/kg and dosage-related decreases in heart rate were seen at 10-1000ug/kg, with increase in QT interval at 100-1000ug/kg. No significant effects on blood pressure or heart rate was observed in the other animal. In conscious dog, oral and IV naratriptan induced tachycardia at systemic exposures about 4-5 times that seen in man after a 5 mg oral dose.

Biopharm:

Conclusion: Dr. Mahmood and Dr. Hossain reviewed the clinical pharmacology and pharmacokinetic section of the NDA and concluded that the application was could be approved. They offered suggestions for labeling. They also suggested that the sponsor adopt their specific dissolution specifications. Dr. Mahmood noted that the sponsor had not conducted PK studies in patients with severe renal or hepatic impairment and suggested that a reduction in dosing be recommended for these patients. From Dr. Mahmood's review, I have summarized the PK information in the following table.

Naratriptan PK	
Parameter	Results
Bioavailability	75% in females and 64% in males
Absorption	Tmax 2 to 3 hours, Cmax following a 2.5 mg dose is 12 ng/mL
Protein binding	15 to 26%
Metabolism	70% excreted unchanged, major metabolites N-oxide and a piperidineone, both inactive, no single isozyme responsible for metabolism
Interactions, in vitro	At concentrations up to 100 µg/mL no inhibitory effect various CYP isoenzymes in vitro, no interaction with MAO enzyme systems in vitro
Interaction studies	Population PK analysis in 127 patients showed no effect in 23 patients on SSRIs, 8 patients on beta blockers and 15 patients on tricyclic antidepressants 29% increase clearance with tobacco use, oral contraceptives in 25 patients reduced clearance by 32%
Elimination half life	6.5 hours, 30 to 44% excreted in the urine
Dose proportionality	Linear pharmacokinetics from 1 to 10 mg
Food effects	None
Multiple dose kinetics	Dosing daily for 5 days did not result in accumulation. PK similar with doses separated by 4 hours
Hepatic impairment	41% increase in half life, 48% increase in AUC, 50% decreases in renal clearance. No change in Cmax and Tmax
Renal impairment	50% increase in half life, 50% decrease in clearance
Age	26% decrease in clearance in elderly females and 13% decrease in elderly males. No change in the Cmax or tmax
Sex	Females have a 12% higher bioavailability with a decrease in clearance.
Race	No studies

Safety:

Conclusions: The clinical safety portion of the NDA was reviewed by Dr. Sevka and Dr. Burkhart. Dr. Burkhart, the safety team leader, concluded that while the sponsor collected sufficient data to adequately describe the safety risk, they need to provide a more complete description of the clinical nature of the events resulting in discontinuation prior to writing labeling.

Exposure: From the efficacy data, the marketed doses will be in the range of 1 to 2.5 mg. The sponsor has an adequate number of patients exposed to recommended doses of the drug in terms the number of patients treating a single headache with one or two doses of 2.5 mg. They also have an adequate number of patients with long term exposure to doses of 2.5 mg.

There were between 3000 and 3500 patients exposed to at least a single oral dose of naratriptan with over 2000 exposed to doses of 2.5 mg or more. The exact number of unique patients cannot be determined because in study 2004, a 450 patient study, the sponsor did not collect information on the previous use of naratriptan.

814 patients were exposed to the subcutaneous dosage formulation.

In some trials, patients who did not have complete relief of their headache or had a recurrence of pain were allowed to repeat a dose 4 hours after the initial dose. Approximately 581 patients treated a single headache with 2 doses of 2.5 mg (total of 5 mg). An additional 314 patients used two doses of 1 mg (total of 2 mg) to treat a single headache.

In regard to long term exposure, 276 patients treated 2 or more headaches, on average, over 6 months with 2.5 mg plus an optional 2.5 mg dose. Of these patients, 253 treated 2 or more headaches, on average, over 12 months.

Demographics: The demographics was similar to that seen in other migraine drug trials. There was an over representation of white females in reference to what is probably seen in the general population. In the placebo controlled clinical trials, 84% of the patients were female, 95% of the patients were Caucasian and 80% of the headaches treated were without an aura. Patients with cardiac disease and hypertension were excluded from the studies. In the placebo controlled trials, the mean age was about 40. 300 patients were between 12 and 18 years old, no patients were over 65. In the phase 1 studies, 10 subjects over the age of 65 were exposed to the drug.

Dropouts and withdrawals: There were 91 withdrawals for adverse events and 53 patients were reported to have had a serious adverse event. Assessment of dropouts gives insight into the tolerability of the drug and the type and severity of side effects. In this and other migraine trials, the conclusions drawn about tolerability is limited because in many of the studies, patients treat only one headache. Discontinuation rates from these single treatment studies can be misleading since patients were not obligated to take additional doses even if they had adverse events. The multiple dose and long term studies provided more insight into tolerability, however, since the treatment of headaches is decided by the patient, they could avoid treating more headaches because of adverse events and it would not be necessarily counted as a discontinuation for an adverse event. Patients discontinued for "lack of efficacy", "refused to go on with study" or "few attacks" may have stopped the study because they were not tolerating the drug. Only more questioning would reveal the specific reason for discontinuing.

As noted by Dr. Sevka and Dr. Burkhart, the reasons for discontinuations were not clearly summarized in the NDA. While the reason for all discontinuations are listed in the appendices for the individual study reports, the information is not summarized across studies. The following table summarizes the discontinuations from the oral studies including information from the safety update. In the clinical pharmacology studies for all dosage formulations, 3%, 11 of the 393 patients, withdrew due to adverse events. Events included headache, dizziness, nausea, vomiting, warm sensation and drowsiness. In the long term study, 451 patients were enrolled. 115 patients withdrew; 69 because of loss of efficacy, 12 failed to return, 5 did not treat in the specified period of time, 11 had AEs (10 different reasons, one for increase BP, one depressive moods, one chest pain), 18 for other reasons (6 for pregnancy, 3 no attacks, 3 too many attacks and 6 for other reasons (increase epilepsy duration about 6 days following treatment, protocol violation, noncompliance).

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Reasons for discontinuation from the oral studies					
Type of Study	Treatment	Total N	% Adverse event (N)	% Lack of efficacy (N)	% Other (N)
Clinical pharmacology					
	Placebo	175	2% (3)	0	2% (3)
	Naratriptan	310	1% (4)	0	2% (5)
Placebo and active controlled studies					
Single attack	Placebo	324	0	<1% (1)	<1% (2)
	Naratriptan	1341	<1% (1)	<1% (2)	<1% (2)
Multiple attack	Placebo	716	1% (9)	3% (18)	6% (45)
	Naratriptan	1783	<1% (17)	3% (55)	15% (275)
Long term, open label studies					
Multiple attacks	Naratriptan	451	2% (11)	15% (69)	4% (18)

To describe the tolerability of the drug, the sponsor should separate studies where a single headache was evaluated and those in which multiple doses were used. The sponsor should detail the reasons for all discontinuations by separating out those reasons currently included in the "other category". The reasons for discontinuation should include those who discontinued for lack of efficacy, those who elected not to treat additional headaches and those who were discontinued because the study was stopped by the sponsor.

The other reason for describing patients who discontinue is to identify AEs that are more severe. The AEs that led to discontinuation were not dissimilar from those seen with other 5HT₁ agonists including chest pain, nausea, warm/cold sensation, paresthesias, hypertension.

Similar effects were seen with the subcutaneous formulation. A single patient was reported to have dystonic movements and syncope. Another patient discontinued for faintness.

Adverse events in the controlled clinical trials: The adverse event profile for naratriptan was similar to that seen with sumatriptan. Patients noted the "characteristic symptoms" of pressure sensation, paresthesias and warm/cold sensation. An elevation of systemic and pulmonary BP was noted. Cardiac symptoms including chest pain was noted but only on one occasion was associated with ischemic changes on ECG.

Serious AEs: A total of 42 patients experienced serious AEs with an additional 12 patients reported in the safety update. These AEs were similar to those reported with other 5HT1 agonists. One patient had lupus nephritis that developed 3 days after dosing. Some of the serious AEs were suggestive of cardiac events including one episode of chest pain associated with T wave changes 2 hours following dosing with a 7.5 mg dose.

Cardiac events: Chest pain was a relatively infrequent adverse event. Two patients had cardiac events that were suggestive of cardiac ischemia. One patient developed chest pressure minutes after taking naratriptan. The symptoms lasted 12 hours but was not associated with cardiac damage. Another patient had an asymptomatic change in the ECG 2 hours following dosing with 7.5 mg. The ECG was read as being suggestive of coronary vasospasm. There was no evidence for cardiac damage. To investigate the cardiac safety of the drug, the sponsor conducted additional studies.

One study involved an assessment of subjects who were undergoing cardiac catheterization. Ten subjects had normal coronary arteries and one had disease on the cardiac cath. All subjects had pulmonary and aortic artery pressures assessed as well as coronary digital subtraction angiography. Subjects were first given placebo and then 1.5 mg subcutaneous. Differences were compared at 10 minutes. There was a 7% increase in BP, a mean 18% increase in pulmonary pressure, a 1% increase in heart rate and an 8% increase in systemic vascular resistance with a 6% decrease in pulmonary vascular resistance. There was a decrease in the coronary artery lumen diameters up to 10%. Four subjects had chest discomfort though this was not correlated with the findings.

40 patients with no history of cardiac disease were randomly given placebo or 1.5 mg SC in a crossover study with myocardial blood flow measured with PET scanning. Coronary vascular reserve was lower and resistance higher following treatment with the drug compared to placebo. One patient had an elevation in BP 5 minutes after dosing from 160/90 to 180/110. 8 subjects had ECG changes; 5 occurring after treatment with placebo. Similar results were seen in a study evaluating ergotamines.

Two patients who complained of chest pain following treatment were rechallenged. No ECG changes or AEs were noted.

QT prolongation: The sponsor sent in, at the division's request,