CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-001

ADMINISTRATIVE DOCUMENTS

ITEMS 13 & 14
PATENT INFORMATION AND CERTIFICATION

1.	Active Ingredient	Almotriptan DL-hydrogen malate (almotriptan malate)
2.	Strengths	6.25 mg, 12.5 mg
3.	Tradename	AXERT™
4.	Dosage Form Route of Administration	compressed tablets oral
5.	Applicant Firm Name	Pharmacia & Upjohn
6.	NDA Number	21-001
7.	Approval Date	to be determined
8.	Exclusivity - Date first ANDA could be approved and length of exclusivity period.	Five (5) years after date of NDA approval, or March 28, 2014, or date of any patent extension--whichever occurs last.
9.	Patent Certification	Pharmacia & Upjohn hereby certifies that Almotriptan DL-hydrogen malate (almotriptan malate) is claimed *per se* in United States Patent 5,565,447 which expires March 27, 2014.

Roberta Krieger 11/16/99

Roberta Krieger Date
Associate Director
Regulatory Affairs

REQUEST FOR EXCLUSIVITY

Pharmacia & Upjohn Company requests five (5) years of exclusivity for AXERT™ (almotriptan malate) tablets pursuant to 21 U.S.C. 355(c)(D)(ii). The following is provided to assist FDA in the eligibility determination. This summary information follows the basic format contained in the letter of April 28, 1998 from Dr. Carl Peck to all NDA or ANDA Holders and Applicants.

1. Whether any active moiety in the drug product for which approval is sought has ever been approved in another drug product in the United States either as single entity or as part of a combination product.

   Reply:
   Pharmacia & Upjohn certifies that the active moiety (almotriptan malate) the drug product for which approval is being sought has not been approved in another drug product in the United States either as a single entity or as part of a combination product.

2. If not, whether any active moiety of the drug product has been previously marketed in the United States either as a single entity or as part of a combination product.

   Reply:
   Pharmacia & Upjohn certifies that the active moiety (almotriptan malate) in the drug product has not been previously marketed in the United States.

Roberta Krieger 11/16/99

Roberta Krieger
Associate Director
Regulatory Affairs

Date

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 #:

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:

/S/

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

Russell Katz, M.D.
Acting Director
DNDP, HFD-120

Final: October 17, 2000

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

DEBARMENT CERTIFICATION FOR Almotriptan, NDA #21-001

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ed L. Patt

10/18/99

Ed L. Patt
Associate Director
Global Regulatory Affairs, CMC

Date

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

Form Approved: OMB No. XXXX-XXXX
Expiration Date: xx/xx/xxxx

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Re: Almotriptan

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

Referring to Protocol M/3275/0009

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further clarify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Krishna K. Talluri, MD	

Referring to Protocols M/31416/10 – M/31416/14 (five protocols)

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

Refer to Item 8 for list of investigators

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Name Thomas W. Merritt	Title Vice President, R&D Finance
Firm/Organization Pharmacia & Upjohn	
Signature Thomas W. Merritt	Date September 15, 1999

Please DO NOT RETURN this application to this address

MEMORANDUM

DATE: December 14, 2000

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

TO: File, NDA 21-001

SUBJECT: Recommendation for action on NDA 21-001, for the use of Axert (almotriptan malate) as acute treatment for migraine headache

NDA 21-001, for the use of oral almotriptan malate, a selective $5HT_{1B/1D}$ agonist, as acute treatment of migraine headache, was submitted by Pharmacia & Upjohn on 12/17/99. The application contains the results of 4 randomized, placebo controlled trials (RCTs) of oral almotriptan designed to establish the effectiveness of the treatment, as well as the required safety, CMC, and pharmacology/toxicology data.

The application has been reviewed by Dr. Armando Oliva, medical officer (review of safety and efficacy dated 8/18/00), Dr. Richard Chen, statistician (review dated 8/31/00), Dr. Martha Heimann, chemist (reviews dated 5/15/00 and 12/5/00), Drs. Gobburu and Sekar, clinical pharmacology (review dated 9/19/00), Dr. Stolzenberg, pharmacologist (review dated 9/8/00), and Dr. Glenna Fitzgerald, Pharmacology Team Leader (memo dated 12/14/00).

Drs. Oliva and Chen recommend that the application be considered Approvable. Dr. Heimann concludes that the application is Not Approvable. I will briefly describe the clinical data, comment on other relevant issues, and offer the division's recommendation for action on the application.

EFFECTIVENESS

As noted above, the sponsor has submitted the results of 4 RCTs designed to establish the effectiveness of almotriptan as an acute treatment for migraine headache. These studies all evaluated the effects of almotriptan on relief of headache pain of a single migraine headache, except Study 14, which evaluated 3 headaches. All studies enrolled patients whose migraine pain for the attack to be treated was judged to be moderate or severe, and in all studies, the primary measure of effectiveness was percent of patients with relief (defined as mild or no pain) at 2 hours. Drs. Oliva and Chen focus on 3 of these as providing the primary evidence of effectiveness; Studies 12, 13, and 14. I will briefly describe each of these, and then turn to the one remaining RCT (Study 11). All effectiveness trials were performed in Europe.

Study 13

This was a multi-center trial in which patients were randomized to receive either almotriptan 12.5 mg, 25 mg, sumatriptan 100 mg, or placebo, in a ratio of 2:2:2:1. The following table presents the results for the primary outcome measure, 2 hr response, with the p-values for the pair-wise comparisons to placebo:

	2 Hr response	P-value
Almotriptan 12.5 mg	104/183 (57%)	0.025
Almotriptan 25 mg	108/191 (57%)	
Sumatriptan 100 mg	123/193 (64%)	0.001
Placebo	42/99 (42%)	

(These results are taken from Dr. Oliva's review [page 17, Table 6 for the 12.5 mg contrast] and Dr. Chen's review [page 7, Table 3.2, for the 25 mg contrast]. There is a discrepancy between the reviews; the p-value for the 12.5 mg vs placebo contrast is <0.05 in Dr. Oliva's review, but not significant in Dr. Chen's review. Apparently, these conflicting statements arise from the sponsor's submission. Specifically, the p-value quoted above is taken from the sponsor's ISE, while the non-significant finding in Dr. Chen's review is taken from the sponsor's study report; both are reported to be the result of a Fisher's Exact test. Dr. Chen performed his own CMH test on the results, which yielded a significant overall result and significant results for each pairwise comparison, even if adjusted for multiple comparisons. At the moment, several issues remain unclear: 1) why the sponsor reports disparate results in different sections of the NDA, and 2) why Dr. Chen performed a CMH in the face of what he believed to be a non-significant result on the primary analysis. We will ask the sponsor to clarify its internal inconsistency; since Dr. Chen no longer works for the Agency, we are unlikely to determine why he chose to perform the CMH analysis.)

The following table presents the results for the important secondary outcomes of 2 Hr response rate (defined as absence of the symptom) for Nausea, Vomiting, Photophobia, and Phonophobia:

	Nausea (%)	Vomiting (%)	Photo (%)	Phono (%)
Almo 12.5	59/183 (32)	6/183 (3)*	48/183 (26)	36/183 (20)*
Almo 25	57/191 (30)	Not reported	53/191 (28)	44/191 (23)
Suma 100	60/191 (31)*	15/191 (8)	48/191 (25)*	34/191 (18)*
Pla	43/99 (43)	10/99 (10)	37/99 (37)	33/99 (33)

* denotes nominally significant difference between drug and placebo at p=0.05.

Study 14

This was a multi-center trial in which patients were randomized to almotriptan 6.25 mg, 12.5 mg, or placebo in a 2:2:1 ratio. In this study, patients treated 3 consecutive migraine headaches; the results presented below are for the first headache only:

	2 Hr response	P-value
Almotriptan 6.25 mg	200/360 (56%)	<0.001
Almotriptan 12.5 mg	240/370 (65%)	<0.001
Pla	58/176 (33%)	

The following table presents the results for the important secondary outcomes of 2 Hr response rate for Nausea, Vomiting, Photophobia, and Phonophobia:

	Nausea (%)	Vomiting (%)	Photo (%)	Phono (%)
Almo 6.25	122/356 (34)*	21/356 (6)	121/356 (34)*	103/356 (29)*
Almo 12.5	103/369 (28)*	20/369 (5)	101/369 (27)*	78/369 (21)*
Pla	81/175 (46)	15/175 (9)	83/175 (47)	73/175 (42)

* denotes nominally significant difference between placebo at p=0.05.

Study 12

This was a multi-center trial in which patients were randomized to receive either almotriptan 2 mg, 6.25 mg, 12.5 mg, 25 mg, or placebo in a 2:2:2:2:1 ratio. The following table presents the results for the primary outcome measure, 2 Hr response rate:

	2 Hr response	P-value
Almotriptan 2 mg	51/170 (30%)	0.77
Almotriptan 6.25 mg	94/167 (56%)	<0.001
Almotriptan 12.5 mg	96/164 (59%)	<0.001
Almotriptan 25 mg	107/161 (67%)	<0.001
Placebo	26/80 (33%)	

The following table presents the results for the important secondary outcomes of 2 Hr response rate for Nausea, Vomiting, Photophobia, and Phonophobia:

	Nausea (%)	Vomiting (%)	Photo (%)	Phono (%)
Almo 2	Data not provided in reviews			
Almo 6.25	45/163 (28)*	4/163 (2)*	43/163 (26)*	33/163 (20)*
Almo 12.5	54/159 (34)*	16/159 (10)	42/159 (26)*	35/159 (22)*
Almo 25	Data not provided in reviews			
Pla	37/78 (47)	14/78 (18)	38/78 (49)	31/78 (40)

- denotes nominally significant difference between placebo at p=0.05.

As noted in the table above, neither the clinical nor the statistical review contains the percent of patients symptom-free for the 2 and 25 mg dose groups. However, Dr. Chen in his review (pages 3 and 4) describes a dose-dependent statistically significant difference between drug and placebo on these symptoms.

These are the three RCTs on which the sponsor relies to support the effectiveness of almotriptan at the doses they propose to be recommended in labeling (6.25 and 12.5 mg). Another trial of essentially identical design was performed examining alternative doses.

Study 11

This was a multi-center trial in which patients were randomized to almotriptan 5 mg, 25 mg, 100 mg, 150 mg, or placebo. The following table presents the results for the primary outcome measure, 2 Hr response rate:

	2 Hr response	P-value
Almotriptan 5 mg	23/35 (66%)	0.08
Almotriptan 25 mg	28/35 (80%)	0.002
Almotriptan 100 mg	23/33 (70%)	0.043
Almotriptan 150 mg	30/35 (86%)	<0.001
Placebo	13/31 (42%)	

The results of the analyses of the secondary outcomes were not provided in the primary reviews.

SAFETY

A total of 3937 patients received at least one dose of almotriptan in Phase 2/3 controlled and uncontrolled trials. A total of 3672 patients received at least one dose of 6.25 mg or greater; of these, 3114 patients received at least one dose of at least 12.5 mg. A total of 1346 patients were treated with a single dose of 12.5 mg/headache for at least 6 months. As can be seen in Dr. Oliva's Table 46 (page 54), a total of 441 patients treated at least 2 headaches/month for at least 6 months, and 147 patients treated at least 2 headaches/month for at least 1 year. These numbers exceed the division's requirements for chronic treatment for drugs to treat migraine. These exposures were essentially all with at least a single dose of 12 mg/headache.

Deaths

There were no deaths in the NDA cohort.

Discontinuations

Because most of the controlled experience was in single dose studies, there were no true dropouts in these studies. There were 5 dropouts after the first headache in Study 14; as can be seen in Dr. Oliva's review (page 37), none were for serious adverse events attributable to almotriptan.

As Dr. Oliva notes, a total of 4.7% (63/1346) of patients in the long-term safety studies discontinued treatment secondary to adverse events. As he describes, none were due to serious events.

A total of 4 subjects discontinued treatment in the Phase 1 studies, none for serious events.

Serious Adverse Events

In the controlled trials of oral almotriptan, there were 3 serious adverse events reported in patients taking almotriptan (there was 1 SAE in a placebo patient). Two of the three appeared to clearly not be drug related (1 episode of colitis 3 weeks after drug, 1 episode of biliary colic 6 weeks after treatment).

One patient, a 47 year old woman, reported nausea, vomiting, and epigastric discomfort the day after her 4th dose of 6.25 mg in Study 14. Her EKG showed "posterolateral repolarization changes"; cardiac enzymes, stress test, and coronary angiography were negative.

In the long-term studies, a total of 38/1346 (2.8%) of patients reported a serious adverse event. Table 30 in Dr. Oliva's review (page 36) lists these events. No event occurred at an incidence of 1%; the most frequent event was trauma, with an incidence of 0.3% (4 cases). The next most frequent events were migraine and hemorrhoid, each with 3 cases (0.2%). Few, if any, events reported as serious can reasonably be considered drug-related.

Other Adverse Events

The following table (taken from Dr. Oliva's Table 32, page 39) presents the percent of adverse events occurring at a rate of at least 1% in the single dose controlled trials, and with a greater frequency than in the placebo group:

Event	Pla (N=386)	Almo 6.25 (N=527)	Almo 12.5 (N=1313)
Dry Mouth	0.5%	1.1%	0.7%
Nausea	1.3%	0.8%	2.0%
Paresthesia	0.5%	1.1%	0.7%

Overall in the controlled studies, 12%, 14%, and 15% of patients in the placebo, 6.25 mg, and 12.5 mg groups, respectively, reported at least one adverse event after a single dose. The incidence of patients who reported at least one adverse event after two doses was 9.5%, 20%, and 19% for the placebo, 6.25 mg, and 12.5 mg groups, respectively.

In the long-term, open, uncontrolled studies, the incidence of reported adverse events was, as expected, greater than in the controlled studies. A total of 62% (831/1346) of patients in this setting reported at least one adverse event (recall that patients in these studies received at least one single dose of 12.5 mg of almotriptan for each headache). Dr. Oliva's table 36, page 41, presents the adverse events reported in at least 2% of patients. In this experience, the most frequently reported adverse events were unlikely related to treatment (e.g., URI, flu, trauma, sinusitis). The incidence of chest pain was 2% (28/1346); in the controlled trials, the incidence of chest pain at the 12.5 mg dose was 0.2%, compared to 0.3% in the placebo group.

Other adverse events of interest were: nausea (4%), vomiting (4%), and dizziness (4%).

In general, the frequency of adverse events increased with increasing doses above 12.5 mg (see, for example, Dr. Oliva's Figure 2, and Tables 31 and 32, pages 38 and 39).

Laboratory Tests

There were isolated abnormal lab results in the controlled and uncontrolled studies, but no systematic abnormalities were noted. One patient had elevated LFTs and bilirubin in the long-term, open study 4 months after starting treatment. This patient was discontinued from the study for presumed heroin use, but we will ask the sponsor for more details.

Vital Signs

As Dr. Oliva notes (pages 43-4), 3 phase 1 studies examined the effects of almotriptan on blood pressure and heart rate.

The following table presents the mean changes in systolic and diastolic blood pressure in the 2 studies that examined the effects of a single 12.5 mg dose of almotriptan:

	Systolic	Diastolic
Study 1*		
12.5	0.21mm	1.35mm
25	2.8mm	3.77mm
50	4.2mm	6.1mm
Study 2		
Placebo	1.4mm	1.6mm
12.5	6.3mm	1.9mm
25	11mm	4.8mm

* denotes change from placebo

In general, these changes began within 30 minutes after dosing, and were resolved by 8 hours. Increases were greater at doses greater than 25 mg.

There were no significant blood pressure changes noted in the other clinical trials.

In one of these studies, a dose related increase in heart rate was noted. In this study, doses of 25-200 mg were compared to placebo; at 25 mg, the mean increase was 11 bpm, compared to 3 bpm for placebo. The maximum increase was 17 bpm for the 150 and 200 mg groups.

EKG

Almotriptan was associated with a variable increase in heart rate and QTc interval (as measured using the Bazett correction) in dogs. Although we now believe that the Bazett correction may bias the estimate of QTc prolongation in the face of an increased heart rate (i.e., it will give a falsely increased QTc interval), this was seen as a signal of concern at the time these studies were done.

Dr. Oliva has performed extensive analyses of the EKG data in the NDA (pages 54-76), in which he has examined QTc interval data from several studies individually as well as pooled. His analyses included 3 Phase 1 or 2 studies that examined EKG frequently after dosing, as well as 18 Phase 1 or 2 studies in which EKGs were collected "immediately" after dosing (see his Table 48, pages 56-7 for a complete account of the timing of EKGs in these studies).

Because almotriptan was generally seen to be associated with an increase in heart rate, Dr. Oliva examined the placebo/baseline database to determine an appropriate exponent with which to correct the QTc data. Using these exponents (derived for each of the three studies he examined separately, as well as a pooled correction factor for the pooled dataset), he has concluded that there is no systematic increase in QTc interval seen in patients treated with almotriptan up to doses of 200 mg (see his Table 63, page 76, for the results of Dr. Oliva's pooled analysis), save for a possible increase at 4 hours in the 150 mg dose group in one study, not seen at 2 hours at this dose in at least 2 studies (see his Table 55 page 67).

In the pooled dataset, 2 subjects had EKGs that had a QTc interval >500 msec.

One subject was a 70 year old woman who received a single12.5 mg dose and had a QTc measurement of 516 msec at 2 hours post-dose and 515 msec at 8 hours post-dose (baseline QTc of 427 msec). QTc intervals at 3, 4 , and 6 hours post dose and at 12 and 24 hours post-dose were <500 msec (see Dr. Oliva's Table 64, page 77).

A second patient was a 24 year old man who received a single oral dose of 150 mg and whose QTc at 24 hours was 529 msec (all other measurements were well below 450 msec).

Pharmacology/Toxicology

The sponsor submitted the results of a human lymphocyte assay for chromosomal aberrations that was considered equivocal. As a result, they repeated the assay; the repeat assay was also equivocal, or weakly positive, in the view of divisional reviewers as well as genotoxicity expert reviewers outside

the division. The sponsor also performed a mouse micronucleus assay which evaluates similar, though not identical, potential effects, and this assay was negative.

The resultant panoply of results raised concerns about the acceptability of the carcinogenicity studies that the sponsor had performed. Specifically, if these in vitro results established that almotriptan was genotoxic, the carcinogenicity studies would have had to have been performed using a maximally tolerated dose (MTD); if not, studies that used doses that resulted in exposures in animals of up to 25 times the exposures seen in humans would be acceptable. The sponsor's studies met this latter standard.

To resolve this issue, the data were presented to the full CAC in a meeting held on 12/13/00, which was attended by division staff, members of the genotoxicity committee, and the sponsor. The CAC concluded that the carcinogenicity studies were adequate.

CMC

Dr. Heimann recommends that the application be judged Not Approvable because of significant residual CMC deficiencies that span multiple areas of concern (see her 12/5/00 review, page 23-4 for a comprehensive list of deficiencies). I have spoken with her about this; while these deficiencies are significant, she is satisfied that they can be communicated to the sponsor in an Approvable letter if necessary.

Clinical Pharmacology

As noted by Drs. Gobburu and Sekar, (page 5), almotriptan is metabolized by MAO-A (about 25% of the dose) and to a lesser extent CYP 3A4 and 2D6 (about 10%). However, in a study in which subjects receiving ketoconazole 400 mg qd for 3 days were given a single 12.5 mg dose of almotriptan, the Cmax and AUC of almotriptan increased by about 60% compared to the exposure seen when almotriptan was given without concomitant ketoconazole. This finding was unexpected, and we will ask the sponsor to further address this issue. Also, because patients with hepatic impairment were not studied, we will ask the sponsor to perform such a study.

COMMENTS and RECOMMENDATIONS

Almotriptan is a member of the triptan class of $5HT_{1B/1D}$ agonists. This application contains the results of several RCTs of the type typically performed to evaluate the effectiveness of this class of compounds as acute treatment of migraine headache and associated symptoms. In addition, the application contains safety data on several thousand patients exposed to at least a single dose of almotriptan.

The controlled trials establish the effectiveness of almotriptan in single doses of at least 6.25 mg, and the safety data establish an acceptable toxicity profile for the 6.25 and 12.5 mg doses. Study 13 may not have demonstrated a statistically significant difference between treatments on the protocol specified analysis, although we will ask the sponsor to further address the discrepancies in their submission on this point. If this is indeed, not positive (Dr. Chen's review suggests that the p-values would be greater than 0.05, but not by very much), it might be related to a somewhat higher placebo response rate (about 42%) than was seen in the other 2 trials (placebo rates of 33% in both) in which doses of 6.25 and 12.5 mg almotriptan were evaluated. In Study 13, the response rate for the 12.5 mg dose group was similar to that seen in Studies 12 (59%) and 14 (65%).

There is no consistent evidence that a dose of 12.5 mg is superior to a dose of 6.25 mg, although the response rates were somewhat numerically greater on the higher dose in both Studies 12 and 14, with similar response rates on the secondary symptoms of interest. Of interest is the observation, based on Study 11, that a dose of 5 mg appears likely to be effective (response rate of 66% compared to 42% for placebo), but failed to reach statistical significance, probably due to small sample size (N=35 on drug). In this study, however, doses of 25 mg, 100 mg, and 150 mg were all significantly different from placebo, with response rates from 70-86%), suggesting that they might confer additional benefit beyond that associated with the 2 doses the sponsor proposes be recommended in labeling (there may not be much additional benefit above 25 mg-see the Clinical Pharmacology review, page 2-3, as well). While we clearly do not have adequate safety experience at these doses to support the inclusion of doses greater than 12.5 mg in labeling, and what little data we do have suggest that adverse events (including effects on heart rate and blood pressure) are dose related, the full exploration of the risks and benefits at these doses might be warranted at some point. In particular, it seems to me that exploring the utility of the 5 mg dose, as well as perhaps lower doses, might be especially important, although it does appear that a dose of 2 mg is probably not effective.

It is worth noting that all the effectiveness data and most of the long-term safety data were generated in studies performed outside the United States, in Western and Eastern European countries (the RCTs which establish the effectiveness of the drug were not conducted under an IND). While we have not previously approved ~~an NDA~~ for a triptan in which all of the effectiveness data were generated outside the US, at least some of the controlled trials on which we based our finding of substantial evidence were performed outside the US in some of the previously approved applications. I have no reason to believe that the controlled trials submitted in this application are not reliable or relevant for the US population.

In this regard, Dr. Oliva notes that the incidence of adverse events in the experience reported in the NDA is relatively low. Given that most of the data were generated outside of the US, this might be a function of differences in reporting between the US and European countries, raising the possibility that the rates we've seen here may not be applicable or representative of the rates we might have seen in US studies, or worse, that events might have occurred that were not reported at all in the European experience (of course, the absolute rates of adverse events seen in clinical trials in general, domestic or foreign, cannot routinely be expected to predict the rates of adverse events seen in the population at large, once a drug is approved). To address this concern, Dr. Oliva examined and compared the ADR rates in a US trial (Study 0008, which compared almotriptan 12.5 mg with sumatriptan without placebo) with the foreign ADR rates and found no substantive differences. On the other hand, a comparison of the ADR rates in the two open, uncontrolled trials, one US (Study 0011) and one European (Study CL25), demonstrates the systematically increased reporting of adverse events in the US (see Dr. Oliva's Table 36, pages 41-42).

There is, however, no affirmative evidence that serious events occurred in the European experience that were not reported. For example, a comparison of the serious ADRs seen in the US and European studies referenced immediately above shows no systematic discrepancy in the number of such reports between the 2 locales, although there were some ADRs seen in the US experience not seen in Europe, and vice versa, and the number of patients in the US experience is somewhat less than in the European experience (see Dr. Oliva's Table 30, pages 35-6) and I have already noted Dr. Oliva's conclusion that the ADR profile was similar in the one US controlled trial to that of the European controlled trials). Nonetheless, I am still somewhat concerned about the discrepancy in the incidence of adverse events between Europe and the US, and we will ask the sponsor for a detailed account of the differences employed to solicit and collect ADR data in the US and Europe.

Finally, the sponsor has not provided an analysis of patients who met appropriate "outlier" criteria for elevated blood pressure, and we will ask them to do so.

Therefore, for the reasons stated, we recommend that the sponsor be sent the attached Approvable letter, with the accompanying draft label.

/S/

Russell Katz, M.D.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 14, 2000

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Supervisor
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 21-001
Axert™, almotriptan DL hydrogen maleate
Pharmacea and Upjohn
6.25 and 12.5 mg tablets

SUBJECT: Pharmacology and Toxicology Supervisory Overview

Axert (almotriptan) is the seventh of the triptan series; the other marketed ones are Imitrex (sumatriptan), Zomig (zolmitriptan), Amerge (naratriptan), Maxalt (rizatriptan) and an approvable letter has been issued for [redacted] Like the others, almotriptan is indicated for the acute treatment of migraine with or without aura in adults.

The pharmacology and toxicology data submitted to this NDA have been reviewed by Dr. Sidney Stolzenberg. For details the reader is referred to his September 8, 2000 primary review of the NDA, to two reviews which were prepared for consideration by the Executive Carcinogenicity Assessment Committee (E-CAC) meetings of July 18 and November 21, 2000, and to the review prepared for the meeting of the full Carcinogenicity Assessment Committee (CAC) of December 13, 2000. The minutes of the two E-CAC meetings are appended to this memo.

The only issue with respect to an approvable action for this drug has been a concern about the adequacy of the carcinogenicity studies. The dose selections for those studies were based on an AUC option. The pharmacokinetic endpoint for high dose selection may be used for non-genotoxic drugs according to the ICH Guideline for Industry, "Dose Selection for Carcinogenicity Studies of Pharmaceuticals". However, two of the submitted genetic toxicology assays which were submitted to the almotriptan NDA, the human lymphocyte assay and the mouse lymphoma assay, had equivocal or weakly positive findings. Because of this, the sponsor was requested to repeat both studies under identical conditions (except for controlling the pH in the mouse lymphoma assay) and using the same laboratories.

The July 18, 2000 E-CAC concluded that there was insufficient information available to

support dose selection based on the PK endpoint. They did consider that the female mouse had reached an MTD based on mortality, however.

It had been suspected that the equivocal results in the first mouse lymphoma assay had been the result of a lack of control of the pH in the medium. This was confirmed when the study was conducted under conditions in which the pH was controlled and the results were clearly negative. However, the repeat human lymphocyte assay still produced equivocal or weakly positive results, as determined by members of the CDER Genotoxicity Committee and experts from other centers within the Agency (see September 18, 2000 review by Dr. Aisar Atrakchi).

At a second meeting of the E-CAC on November 21, 2000, there was a discussion about what weight equivocal findings in the human lymphocyte assay should be given (see minutes). Three of four members believed that the carcinogenicity studies should be accepted as adequate and the Division was informed that a full CAC could be requested to resolve the issue. A meeting was held in the Division to discuss further options. It was attended by Drs. Robert Temple (Director ODE-1), Russell Katz (Division Director), Glenna Fitzgerald (Pharmacology Supervisor), Sidney Stolzenberg (Pharmacology Reviewer, and members of the CDER Genetic Toxicology Committee (Drs. Aisar Atrakchi, Anita Bigger, R. Daniel Benz and James MacGreggor). The members of the Genetic Toxicology Committee were in agreement that the human lymphocyte assay was clearly not negative, and described it as weakly positive. Both structural and numerical aberrations occurred at low levels. These were within historical control data ranges, but in some cases outside of the concurrent control data. Dr. Temple recommended that, given these findings, we should call a meeting of the full CAC to determine whether or not the carcinogenicity studies, based on a PK endpoint, could be considered adequate to support approval.

At a full CAC meeting on December 13, 2000 both the sponsor and the Division presented results of the human lymphocyte assay, as well as results of the rat and mouse bioassays. One of the genetic toxicology experts noted that some of the data which were presented by the sponsor made the issue clearer to him, and concluded that the results were in a "gray area". During the closed portion of the meeting, the results of the human lymphocyte assay for frovatriptan were presented and discussed. This is a drug from the same class which represents an analogous situation, and there has been concern about equitable treatment of the sponsors if the situations are really the same. In the case of frovatriptan, the carcinogenicity studies were also conducted using multiples of the human exposure to select high doses and the human lymphocyte assay was positive. The sponsor is conducting a p53 mouse assay, which must be completed prior to approval. The results of that assay will determine whether or not additional carcinogenicity studies need to be conducted. The committee members concurred that the frovatriptan lymphocyte assay was clearly positive, as opposed to the almotriptan assay. Although the minutes of the meeting are not yet available, the discussion among members indicated that they believed that the carcinogenicity studies conducted for almotriptan were adequate, based on appropriate multiples of human exposure and lack of tumor findings, and that the results of the human lymphocyte assay are not sufficiently robust to cause concern or to require

that the bioassays be conducted at a maximum tolerated dose.

Summary and Recommendations:

Dr. Stolzenberg has recommended that the NDA be approved if the results of the repeated genotoxicity studies are clearly negative. Although the human lymphocyte assay was not clearly negative, the full CAC did not indicate that there is reason for concern since the response was a weak one. Comments to the sponsor may be indicated when the report of that meeting is available. The NDA is approvable for Pharmacology and Toxicology with the following recommended labeling.

/S/
Glenna G. Fitzgerald, Ph.D

NDA 21-006
cc. HFD-120/Katz/Oliva/Stolzenberg/Fitzgerald/Nighswander/Chen

2 page(s) of revised draft labeling has been redacted from this portion of the review.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 20, 2000

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: NDA 21-001 (almotriptan, Axert)

TO: File, NDA 21-001 (almotriptan tablets, Pharmacia and Upjohn)

Russell Katz, M.D.
Director, Division of Neuropharmacologic Drug Products, HFD-120

I concur with the Division's approvable action recommendation. The 4 placebo-controlled European trials appear to cover the full range of possibly effective doses; 25-150 mg does not seem sufficiently superior to 12.5 mg to suggest use of higher doses, although further study might show some added effect. I believe there is fairly consistent evidence of dose responsiveness over the [redacted] range and considering all data (remedication, response), I believe the 12.5 mg dose is pretty clearly more effective than 6.25 mg. Given the borderline effect at 5 mg, no effect of 2 mg and the proposed dose of 6.25 mg, I don't see too much use in further exploration of the 5 mg dose, although perhaps doses in the [redacted] range would be worth looking at. It is also worth noting that about 450 patients received doses of 25 mg or more, fairly close to supporting that dose if there were reason to use it (although asthenia, chest pain, palpitations and perhaps somnolence seem increased at that dose, as is blood pressure). The response rates at 2 hours in these European studies seem generally similar to those in U.S. trials of other triptans, which is reassuring. I note, in light of recent reports in the Post, that the Euro-origin of these studies was the result of a European initial developer, not any decision by Pharmacia-Upjohn, which did all its studies in the U.S. once it became involved. The letter will ask for the sponsor's explanation of the lower ADE rates in the European long-term study CL25 compared to the U.S. long-term study 0011 and the answer will be interesting, but open study reporting rates are hard to interpret and the most striking differences are in URI's and related symptoms. Serious events were more reported in CL25 than in OG11. I note, moreover, as Dr. Oliva points out, that rates were similar in the European single dose and the U.S. single dose active comparator trial even though they were all somewhat lower than reported with other triptans.

I am satisfied with the CAC's conclusion that almotriptan is not genotoxic and that the dosing in the carcinogenicity studies was adequate.

The large QT data base is of interest for several reasons. First, about 1% of patients on placebo or drug had a QTc (Bazett's) > 500 msec at some point and about 10-12% had an increase in QTc greater than 30 msec, a good indicator of how variable these numbers are. The discussion of corrections (page 59 and following of Dr. Oliva's review) is most interesting. Do you know if Dr. Burkhart has committed his memo to publication; perhaps a combined effort would be worthwhile based on the interesting idea, as I follow it, of using the baseline or placebo group to choose a correction for the population. This approach is fairly similar in outcome, I think, to using no correction, but plotting QT vs. RR regression lines before and after treatment.

I would like to discuss further the suggested limitation on treating ≥ 2 episodes per month. I do not think that ICH guidelines are meant to apply to every subset of treatment (e.g., the largest dose or the greatest

treatment frequency). In study 0011, an average of 3.7 migraines per month were treated, giving a fairly substantial number of patients (study had 585 patients) with at least 4 attacks per month.

I also think too strict an interpretation of what it takes to assert there is a dose response needs consideration. It is, of course, difficult to distinguish adjacent doses but if all study results were plotted, and all data, including retreatment need considered, would be apparent that there is a consistent dose-response relationship. The "no-conclusive evidence" statement seems excessive.

/S/

Robert Temple, M.D.

cc:
Orig. NDA 21-001
HFD-120
HFD-120/Project Manager
HFD-101/R Temple
drafted:sb/12/19/00
final:12/20/00

MEMORANDUM OF TELECON

DATE: February 14, 2001

APPLICATION NUMBER: NDA 21-001

BETWEEN:

Name: Roberta Krieger, Christine Walker, Cecile Teagarden, John Stodola, Mark VanArendonk
Phone: 616-833-8162
Representing: Pharmacia & Upjohn

AND

Name: Lana Chen, Martha Heimann, Maryla Guzewska, Armando Oliva
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Response to Approvable

The Division initiated this phone call to the Sponsor regarding their January 23, 2001 Response to Approvable Letter. The Sponsor was told that because the following Chemistry, Manufacturing and Controls information was not submitted, the response will not be considered complete until such information is supplied.

Classification of the response will be determined at the time of submission. While the Division anticipates the response to be classified as a Class 1 Resubmission (2 month clock), any new information that would cause a reinspection may lead to classification as a Class 2 Resubmission (6 month clock)

Analytical Procedure (Response to Item 5 and method validation package).

- The firm needs to provide sufficient detail for each analytical procedure (e.g., equipment, sample size, specific reagents used, calculations) to allow a competent analyst to reproduce the method. In the case of automated equipment/software packages sufficient information should be provided to allow FDA analyst to select equivalent equipment/software or perform the same calculations manually.
- All regulatory procedures for drug substance and product must be included in the method validation ~~section~~ to be sent to field labs.
- Submission of copies from Ph. Eur. is acceptable if sufficient detail regarding specific conditions used by applicant is provided.
- Applicant needs to submit detailed procedure for the following tests for review or include Ph. Eur. procedures referenced but not submitted to NDA in MV section.

  Dug Substance: Color of Solution, Water content and Sulfated Ash.

  Drug Product: Moisture, Degradation products by CE (was not included in MV section)
- It is not necessary to submit all the SOPS listed in 13-FEB-2001 fax but applicant should

review to ensure that any information needed to reproduce method (specific equipment or calculations) has been provided in the test instructions.

Expiry Calculations (Response to Item 5)
The specific information requested, calculated shelf life prediction for Potency of each primary stability batch, was summarized. The firm confirmed that this had been adequately conveyed in the previous (06-FEB-2001) telecon with Ms. Rogers.

Testing Facilities
The firm was asked to provide exact location of Almirall "Analytical R&D" and "Industrial Plant QC" facilities so that we could confirm with compliance and field that both facilities were inspected. Potential impact on classification of resubmission was discussed with the firm.

Samples
The request that firm reserve 6.25 mg tablets samples for method validation was clarified. FDA will need samples of both strengths but will only do separate validation on 6.25 mg for tests where matrix interference or probable or procedure is different. Sample of bulk drug substance batch corresponding to 6.25 mg tablets is not needed since sponsor has previously identified a suitable bulk batch.

/S/ 3/7/01

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

TELECON - Incomplete Response

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 21-001

Drug:	Almotriptan
Sponsor:	Pharmacia & Upjohn
Date:	April 4, 2001
NDA:	21-001

Conversation Between:	Agency:	Sponsor:
	Lana Chen, R.Ph.	Ms. Marcia Rogers
Telephone #:	616-833-6579	

Purpose: The sponsor was advised that our acknowledgment letter dated March 20, 2001contained an error. The letter states the primary user fee goal date to be May 6, 2001. The user fee goal date is, in fact, May 7, 2001. The May 7, 2001 goal date is 2 months from the receipt of their March 6, 2001 resubmission, received March 7, 2001. The Sponsor acknowledged this and agreed to document our conversation accordingly.

Lana Chen, R.Ph.

MEMORANDUM

DATE: April 27, 2001

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

TO: File, NDA 21-001

SUBJECT: Recommendation for Action on NDA 21-001, for the use of Axert (almotriptan malate) for the acute treatment of migraine headache

NDA 21-001, for the use of Axert (almotriptan malate) for the acute treatment of migraine headache, was the subject of an Approvable letter, dated 12/20/00. In that letter, we asked the sponsor, Pharmacia and Upjohn Co., to address a number of issues:

1) Clinical

We asked the sponsor to explain an apparent inconsistency in the reported statistical results of Study M/31416/13/R. In addition, we asked the sponsor to re-analyze this study with and without the data generated by Dr. Zintsch, whose center was noted to have had significant irregularities on inspection by DSI. We also asked the sponsor to provide more details about a single patient with LFT and bilirubin elevations, and to address the observation that the reported rate of ADRs in the European open label studies was considerably less than that for the domestic open label, long term study. Finally, we asked the sponsor to re-analyze Phase 1 and 2 studies for blood pressure outliers. In addition, we asked the sponsor to submit a plan for development of this drug in pediatric patients.

2) Clinical Pharmacology

We asked the sponsor to perform a study in patients with hepatic impairment, and in the interim to revise labeling to include a recommendation for a reduced dose in these patients.

3) CMC

There were extensive CMC questions.

The sponsor made a number of submissions in response to the Approvable letter, with a submission of 3/6/01 constituting a complete response. These submissions have been reviewed by Dr. Martha Heimann, chemist (reviews dated 3/12/01 and 3/29/01), Dr. Vanitha Sekar, Office of Clinical Pharmacology and Biopharmaceutics (review dated 4/20/01), Dr. Kallapa Koti, statistician

(review dated 4/2/01), and Dr. Armando Oliva, Neurology Team Leader and primary reviewer (reviews dated 4/5/01 and 4/16/01). In addition, Dr. Lisa Stockbridge, of DDMAC, has reviewed the sponsor's proposed Patient Package Insert (PPI).

In this memo, I will briefly review the sponsor's responses to our requests, and offer the Division's recommendation for action on the NDA.

Clinical

The sponsor has argued that what we perceived to be an inconsistency in the presentation of the results (in the Study Report for Study CL13, the 95% confidence intervals for the 2 hour headache response rate for drug and placebo overlapped, but in the ISE they reported a p-value <0.05), was, in fact, not (see Dr. Oliva's review, pages 2-3). Ultimately, the matter is essentially moot, because, as I understand it, our statistical consultants (both Dr. Chen, the original reviewer, and Dr. Koti , the current reviewer) have performed a statistical test that they believe is standard and appropriate (CMH), and the results are clearly significant.

Analyses with and without Dr. Zintsch's data were still significant (see Dr. Oliva's review (pages 3-5).

The sponsor provided more information about the single patient in the European long term study with elevated LFTs and bilirubin. This patient's history is complicated by his drug and alcohol use (no evidence of laboratory evaluation to R/O hepatitis was presented). The patient's levels did return to normal, presumably off drug. Dr. Oliva concluded that it was possible that these abnormalities were drug related, but that the patient's drug and alcohol use clearly complicate the picture.

As noted, there appeared to be a discrepancy between the reported rates of ADRs in the European compared to the US long term, open label studies. The sponsor presented a detailed description of the methodologies used to elicit adverse event reporting from patients, and there does not appear to be any major, obvious difference that would adequately explain the phenomenon (see, for example, Dr. Oliva's pages 11-12).

Dr. Oliva then analyzed the adverse event incidence rates for the European controlled trials (pooled) and the one US controlled trial, in which almotriptan was compared to sumatriptan, 50 mg. In these studies, the ADR rate was 15.5% for the European trials, and 15.2% for the US trial. In the US trial, the rate of ADRs in the sumatriptan treated patients appeared to be consistent with what has previously been reported for this dose.

While the source of the discrepancy in reported ADR rates in the long-term, open-label trials is unknown, the analyses of the controlled trial data suggest that there was not systematic under-reporting in the European controlled trials (this is further supported by the similarities of the sumatriptan ADR rates in the controlled trial in this NDA and those previously reported). For this reason, the ADR table in labeling will remain as it was in the Approvable letter, with only 3 events listed. We have chosen to not include language in labeling that discusses the apparent freedom from ADRs (in comparison to other approved triptans) that this table implies.

There were few, if any, systematic effects on blood pressure, although there did appear to be a trend in the proportion of subjects meeting outlier criteria for elevated systolic and diastolic pressure at doses of 100 mg and above in Study CL02, a small Phase 1 study in healthy volunteers (see Dr. Oliva's Table 16, page 17, and Table 18, pages 18-19).

Clinical Pharmacology

The sponsor is considering performing the suggested study in patients with hepatic dysfunction. In the interim, the dosing recommendations for these patients will stay as in the draft labeling accompanying the AE letter; it is recommended that the initial dose in these patients be 6.25 mg, and that the total daily dose should not exceed 12.5 mg (half that for other patients).

CMC

The sponsor has adequately addressed the CMC deficiencies.

Finally, Dr. Oliva and Dr. Sekar have reviewed the sponsor's pediatric development plans. They each have comments that will be communicated to the sponsor.

Labeling

The labeling accompanying this package is very similar to the draft labeling sent to the sponsor with the AE letter. There has been some re-structuring of the PK sub-section, and other minor changes throughout. In addition, DDMAC has offered some suggestions for the PPI, which we have incorporated.

In a telephone conversation on 4/27/01, the sponsor agreed to the labeling and PPI that we are forwarding with this package.

RECOMMENDATION

For the reasons stated above, we recommend that the attached Approval letter with appended labeling be issued.

/S/

Russell Katz, M.D.

Memorandum

Date: 3 May 2001

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation I

To: Robert Temple, M.D.
Director, Office of Drug Evaluation I

Cc: Russell Katz, M.D., Dir., DNDP (HFD-120)
Barry Rosloff, Ph.D., TL Pharm./Tox., DNDP (HFD-120)

Subject: NDA 21-001
AXERT® Tablets (almotriptan hydrogen malate)
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-001, dated 8 Sept. 2000, Sidney Stolzenberg, Ph.D.
2. Pharm./Tox. Review of IND [redacted] lated 12 Oct. 1997, Thomas D. Steele, Ph.D.
3. [redacted]
4. Statistical Review of Carcinogenicity studies for NDA 21-001, 6 Nov. 2000, Sharon Yang, Ph.D.
5. NDA 21-001 Approval Package with Draft Product Labeling (3 May 2001).

II. Background

The sponsor (Pharmacia & Upjohn Co.) is seeking approval of AXERT® Tablets, for the acute treatment of migraine headaches in patients with recurring attacks. AXERT® (almotriptan hydrogen malate) is considered to be a selective partial agonist of the 5-$HT_{1B/1D}$ receptor population. Almotriptan is thought to act selectively on intracranial extracerebral arteries, inhibiting the dilation of these vessels during migraine attacks. The mechanism of action of almotriptan is thought to be related to that of sumatriptan succinate (IMITREX®) which has been previously approved for this indication.

III. Comments and Conclusions

1. A review of the action package for NDA 21-001, AXERT® Tablets, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including 6 month and 12 month repeat-dose toxicology studies in rodents and dogs, two year oral carcinogenicity testing in rodents, and multiple genotoxicity and reproductive toxicology studies) for approval for repeated acute use in the treatment of patients with recurrent migraine headaches. The proposed product labeling adequately reflects the toxicological findings for almotriptan hydrogen malate as regards carcinogenesis, mutagenesis, fertility, pregnancy and overdosage, except as noted below.

2. Specific comments related to the product label follow:

A) Under the heading of "PRECAUTIONS" (page 7 of draft labeling) it is recommended that:

- in the paragraph pertaining to the potential binding of almotriptan to melanin containing tissues, the administered doses or dose range studied and the relative interspecies dose comparisons for the referenced 52-week dog toxicology study be included in the discussion.
- in the paragraph pertaining to corneal opacities seen in the 52-week toxicology study conducted in dogs, the basis (AUC, Cmax, BSA, etc.) for the cited interspecies dose comparison be included in the study description.

B) Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" (page 8 of draft labeling) it is recommended that:

- reference to an "equivocal weakly positive response" in the cytogenetics assay conducted in human lymphocytes be eliminated from the product label since:
  - these results were not reproduced in repeat studies,
  - the results were not reproduced (within study) in lymphocytes taken from male and female donors (members of the Genetic Toxicology Committee were not aware of a single case in which a compound with similar male/female differences in cellular responses was then found to be positive in a two-year bioassay test system),
  - the results were not consistent for individual sample replicates within the "weakly positive" study, and
  - the "weakly positive" results were generally within the historical control range for the assay (when there was adequate performance of the positive and negative controls for the study),
- each genotoxicity study described in the product label be clearly identified as having been conducted "in vitro" or "in vivo" as is appropriate for each study methodology or, that the studies be enumerated in list fashion preceded by the "in vitro" or "in vivo" designation (i.e., in vitro bacterial cell mutation assay [Ames test]).

C) Under the heading of "Pregnancy" (page 8 of draft labeling) it is recommended that:

- the second sentence of the section be revised to include the basis (AUC, BSA, etc.) for the 80 fold interspecies dose comparison cited,
- the second sentence of the section be revised to specify the type(s) of "skeletal variations" observed, (Generally a delay in skeletal ossification is considered an effect on embryo-fetal "growth" [a potentially recoverable effect] and is not necessarily associated with an increase in "skeletal variations" [i.e., an altered incidence of vestigial ribs, alteration of the vertebral arches, etc., which constitute dysmorphologies and are un-likely to undergo spontaneous recovery].)
- the description of the pre- and post-natal reproductive toxicology study discussed at the end of this section be revised to include information pertaining to the period of dosing (i.e., dosing being started "prior to" or "post-implantation".

D. Under the heading of "Overdosage" (page 10 of draft labeling) it is suggested that:

- a discussion of the signs and symptoms associated with acutely lethal doses of almotriptan as administered to animals be included in the product label, since relevant clinical overdosage data are unknown.

IV. Summary

A review of the action package for NDA 21-001, AXERT® Tablets (almotriptan malate), suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication (acute symptomatic treatment of migraine headaches). The proposed product label, with possible revision as suggested in the preceding section of this memorandum, adequately reflects the non-clinical safety data for this product.