

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-006

CORRESPONDENCE

[]
September 17, 1999

Ms Lana Chen
Food and Drug Administration
Division of Neuropharmacological Drug Products (HFD-120)
5600 Fishers Lane
Rockville
Maryland 20857

**Re: Frovatriptan - NDA 21,006
General Correspondence – Sponsor Minutes of the Full CAC Meeting
of July 29, 1999**

Dear Ms. Chen:

As discussed at the teleconference held on August 31th 1999, we include with this letter a copy of the sponsor minutes from the Full CAC meeting held on July 29th 1999.

We would like to emphasise two areas of discrepancy between our minutes and those from the CAC. Firstly, we agree that frovatriptan gave a positive response under one particular set of conditions in the human lymphocyte chromosome aberration assay. However, it has not demonstrated genotoxic potential in any other test and has no genotoxic activity in vivo. Hence, it is the sponsor's conclusion that frovatriptan is not genotoxic when considering all of the genotoxicity studies in total.

In addition, from the CAC meeting minutes, it appears the CAC questioned whether frovatriptan has carcinogenic action in the rat. It is important to emphasise that no malignant tumours were observed in the rat carcinogenicity study and the only tumours that were increased were benign and that this was in one sex only. We ask that you send these requested changes to the CAC and that the FDA minutes of the meeting be corrected. Please forward a copy of the corrected record.

Finally, the CAC meeting minutes refer to a number of communications to the sponsor following the CAC's review June 11th 1996 of the rat carcinogenicity study protocol. In order to complete our records we would be grateful if we could be provided with copies of these which, as you may have noted from our letter of 20th May 1999, we do not appear to have in our files. Thank you very much for your assistance in this matter.

[] If you have any questions in regard to this communication or should you require further information, please call me at _____

Yours truly,

[]
Exec. Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
 ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

Form approved: OMB No. 0910-0338
 Expiration Date: April 30, 2000
 See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER
 NDA 21-006

APPLICANT INFORMATION

NAME OF APPLICANT Vanguard Medica Limited	DATE OF SUBMISSION September 17, 1999
TELEPHONE NO. (Include Area Code) 011-44-1483-787878	FACSIMILE (FAX) Number (Include Area Code) 011-44-1483-787811
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code), and U.S. License number if previously issued: Vanguard Medica Limited Chancellor Court, Surry Research Park Guildford, Surrey GU2 5SF, UK	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE []

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) frovatriptan succinate	PROPRIETARY NAME (trade name) IF ANY Miguard™ Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (+) 3-methylamine-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate monohydrate	CODE NAME (if any) VML 251	
DOSAGE FORM: Tablet	STRENGTHS: 2.5 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
 Treatment of Acute Migraine

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
 BIOLOGIC APPLICATION (21 CFR part 601)

IN AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
 Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT SUPAC SUPPLEMENT
 EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Drug Substance: DMF _____
 Drug Product: DMFs _____

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c)) <i>Section 3.1 only</i>
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
<input type="checkbox"/>	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k) (1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k) (3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. OTHER (Specify) General Correspondence - Sponsor Minutes of the Full CAC Meeting of July 29, 1999

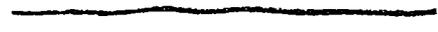
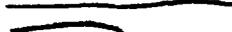
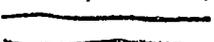
CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE 	DATE September 17, 1999
ADDRESS / Street, City, State, and ZIP Code 		Telephone Number 

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Washington, DC 20201

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Please DO NOT RETURN this form to this address.



NDA 21-006



APR 28 2000

Dear _____

Please refer to your new drug application (NDA) dated January 29, 1999, received January 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for frovatriptan succinate 2.5 mg tablets.

We acknowledge receipt of your submissions dated the following:

February 12, 1999	December 13, 1999	February 10, 2000
February 25, 1999	December 30, 1999	February 22, 2000
June 8, 1999	January 21, 2000	February 28, 2000
June 11, 1999	January 27, 2000	March 6, 2000
September 29, 1999	January 31, 2000	March 9, 2000
October 13, 1999	February 2, 2000	April 10, 2000
October 21, 1999	February 3, 2000	

We have completed the review of this application, as amended, and it is approvable. We have included draft labeling which is considerably different from the one you submitted with your application. We ask that you adopt this labeling as written, recognizing that there are sections (e.g., Carcinogenicity) that will change with the receipt of additional data requested below.

Before this application may be approved it will be necessary for you to address the following:

1. The carcinogenic potential of frovatriptan has not yet been adequately characterized. As you know, the results of the 6 month p53 mouse study will be critical to our decision about whether or not additional studies will be necessary prior to approval, and, indeed, to our decision about the ultimate approvability of the product.

Specifically, if the results of the mouse study yield a clear signal of carcinogenicity, the approval of the product will be in serious jeopardy. If the results are equivocal, it is likely that additional studies will be required prior to approval (at least including a repeat rat carcinogenicity study at higher doses). If the mouse study is clearly negative, no additional studies will be required.

2. You will need to provide safety data from 300 to 600 patients who have used the recommended dose to treat, on average, 2 or more migraines a month for 6 months.

Please provide detailed exposure history on the long term safety patients. This should be submitted as dataset(s) in SAS transport format in accordance with guidance documents. Each row should contain information about a single dose taken. Important variables include patient id, date of study entry, date/time of first dose, and date/time of current dose, attack number, and dose number for the attack.

3. As communicated to you in our August 13, 1999 facsimile, the tradename _____ is unacceptable due to potential confusion with currently existing products (e.g., Midrin, Maduramycin). Please propose a new tradename that is not likely to be confused with other marketed products.
4. Based on the stability data provided in your application, we have established a tentative expiration dating period of 24 months. The requirements for confirmation, and subsequent extension, of the tentative expiry period were detailed in our letters dated July 2, 1999 and November 30, 1999.

Your January 27, 2000 submission proposes that the expiration dating period be confirmed, and ultimately extended, based on new stability studies you have started to qualify a new supplier for the bulk active ingredient. These studies can not be considered in support of an extended expiry period until the proposed new supplier has been reviewed and approved by the Agency.

1. Please update the stability data for all primary stability batches for which you have additional data beyond the information provided in your September 29, 1999 submission.
2. The following dissolution specifications should be adopted:
Apparatus: USP Apparatus II (Paddle)
Medium: 900 ml phosphate buffer (pH=5.5)
Speed: 50 rpm
Q = _____ minutes
3. Your September 29, 1999 submission contained a commitment to revise immediate container (blister and bottle) labels. The full proposed text of the revised draft container labels should be submitted for review. Please note that we previously requested this information in our November 30, 1999 letter.

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

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

as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until approximately 2 years after approval of this application. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver of the pediatric study requirement is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and

Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy.

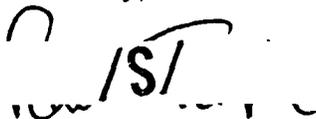
Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,



Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

ENCLOSURE

WITHHOLD 17 PAGE (S)

Draft

Labeling

Memorandum

Date: 7 Nov. 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 21-006
Trade name — Tablets (frovatriptan succinate)
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 21-006, dated 5 Nov. 1999 and 23 March 2000, Sidney Stolzenberg, Ph.D.
2. Pharm./Tox. Review of NDA 21-006 supplement, dated 24 Sept. 2001, Aisar Atrakchi, Ph.D.
3. Pharm./Tox. TL Memoranda of NDA 21-006, dated 7 Apr. 2000 and 5 Nov. 2001, written by Glenna Fitzgerald, Ph.D. and, Barry Rosloff, Ph.D.
4. CAC/ExecCAC Meeting Minutes regarding NDA 21-006, 11 June 1996, 27 Apr. 1999, 29 July 1999, 18 Jan. 2000, 14 Mar. 2000, and 2 Oct. 2001
5. Statistical Review of Carcinogenicity studies for NDA 21-006, 28 July 1999, Roswitha Kelly, M.S.
6. NDA 21-006 Approval Package with Draft Product Labeling (6 Nov. 2001: 10:43 AM).

II. Background

The sponsor (Elan Pharmaceuticals) is seeking approval of frovatriptan succinate tablets (Trade Name —), for the acute treatment of migraine headaches — . Frovatriptan succinate is considered to be a selective agonist of the 5-HT_{1B/1D} receptor population. Almotriptan is thought to act selectively on intracranial extracerebral arteries, causing constriction/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 and almotriptan hydrogen malate (IMITREX™ and AXERT™) which have been previously approved for this indication.

III. Comments and Conclusions

1. A review of the action package for NDA 21-006, frovatriptan succinate, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including 3-6 month and 12 month repeat-dose toxicology studies in rodents and dogs, an 84 week carcinogenicity study in mice, a two year oral carcinogenicity study in rats, a 26

week oral carcinogenicity study in p53 (+/-) transgenic mice, and multiple genotoxicity and reproductive toxicology studies) for approval for repeated acute use in the treatment of patients with ~~_____~~ migraine headaches. The proposed product labeling adequately reflects the toxicological findings for frovatriptan succinate as regards carcinogenesis, mutagenesis, fertility, pregnancy and overdose, except as noted below.

2. Specific comments related to the product label follow:

A) Under the heading of "PRECAUTIONS – Binding to Melanin-Containing Tissues" (pages 13-14 of draft labeling) it is recommended that:

- the non-clinical species studied, the maximum duration of the studies, the administered doses, dose ranges or maximum doses studied, and the relative interspecies dose comparisons (preferably based on AUC) be included in the discussion.

B) Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" (pages 15-16 of draft labeling) it is recommended that:

- reference to a ~~_____~~ greater exposure to drug having been achieved in the mouse and rat carcinogenicity studies (2nd sentence of the 1st paragraph) be eliminated from the product label as this represents a subjective evaluation of the relative interspecies drug exposure in the referenced studies,
- 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 reverse mutation assay [Ames test]),
- the period of drug treatment prior to mating for male and female animals used in the fertility studies should be included in the study descriptions (i.e., 4 weeks in males and 2 weeks in females prior to mating, or, approximately 1 spermatogenic cycle in males and 1 estrous cycle in females prior to mating, throughout the period of cohabitation, until implantation of the fertilized ovum).

C) Under the heading of "Pregnancy" (page 16 of the draft labeling) it is recommended that:

- the description of the *in utero* embryofetal development studies discussed in this section of the label be revised to include information pertaining to the period of dosing (i.e., "during the period of organogenesis"),
- a full presentation of the results of the pre- and post-natal reproductive toxicology study conducted in the rodent should be discussed in this section of the product label (to include, duration or period of dosing, doses or dose range tested, observations, etc.).

[

E) Under the heading of "Overdosage" (page 22 of draft labeling) it is suggested that:

[]

IV. Summary

A review of the action package for NDA 21-006, frovatriptan succinate tablets, 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.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DATE: April 24, 2000

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

TO: File, NDA 21-006

SUBJECT: Division's Recommendation for Action on NDA 21-006, for the use of (frovatriptan succinate) for the acute treatment of migraine

NDA 21-006, for the use of frovatriptan succinate, a selective 5HT_{1B/1D} agonist proposed for the acute treatment of migraine, was submitted by on 1/29/99. During the review of the application, it became clear that a human lymphocyte assay, performed with whole blood, yielded positive results. The sponsor submitted documentation to support their view that this result was an artifact of lysis of red cells. As a result of subsequent submissions and their timing, including the performance of an alternate human lymphocyte assay done in the absence of red cells, the original 10 month review clock was extended an additional 3 months; as a result, the current PDUFA due date is 4/29/00.

The sponsor has presented 5 adequate and well controlled trials that by design were capable of establishing the effectiveness of frovatriptan as an acute treatment for migraine. In addition, they have presented safety data for over 3000 patients who received at least one dose of drug.

The application has been primarily reviewed by Dr. Oliva, medical officer (safety and efficacy review dated 10/14/99), Dr. Koti, statistician (efficacy review dated 11/16/99), Dr. Levin, Neurology Team Leader (memo dated 4/11/00), Dr. Stolzenberg, pharmacologist (review dated 3/23/00), Dr. Fitzgerald, Pharmacology Team Leader (review dated 4/7/00), Dr. Sunzel and Mahmood, biopharmaceutics (reviews dated 11/10/99 and 3/22/00), and Dr. Martha Heimann (reviews dated 6/30/99, 11/30/99, and 3/22/00).

In this memo, I will briefly review the relevant issues in this application, and offer the division's recommendation for action.

EFFECTIVENESS

The results of the controlled trials clearly demonstrate the effectiveness of a single 2.5 mg dose of frovatriptan as an acute treatment of migraine. These trials assessed primarily the proportion of responders at 2 hours in patients with moderate or severe migraine pain at baseline, as is typical for these treatments. The proportion of responders ranged in the 5 studies from about 37-46%, a somewhat lower 2 hour response rate than other marketed triptans, but

statistically significant in each case (Dr. Oliva performed a worst case analysis, in which he imposed a rule that ascribed failure to all frovatriptan patients and success to all placebo patients for whom 2 hour data were unavailable-due to missing scores or sleep-and all studies remained positive on this primary outcome except Studies 09 and 14; see his review, pages 49-50). In 3 of the trials (Studies 02, 06, and 07), nominal statistically significant differences in favor of frovatriptan compared to placebo were seen for the associated symptoms of photophobia and phonophobia at 2 hours, but only in study 02 were nominally significant differences seen for both the associated symptoms of nausea and vomiting (see Dr. Oliva's review, page 28, Table 17; in general, the incidence of vomiting in these studies was low, ranging from about 1-9%).

Studies 02 and 14 examined various single doses of frovatriptan, from 0.5 mg to 40 mg. In these studies, doses below 2.5 mg are not shown to be effective, and doses greater than 2.5 mg are not shown to provide consistently greater effectiveness than 2.5 mg.

Interestingly, Study 09 compared frovatriptan 2.5 mg to sumatriptan 100mg. In this study, sumatriptan was shown to be statistically significantly superior to frovatriptan on the primary outcome of proportion of responders at 2 hours ($p < 0.001$; see Dr. Oliva's review, page 23, Table 12).

SAFETY

The sponsor has provided safety data in 2772 patients who have received at least one dose of 2.5 mg, and a total of 3843 unique patients who received at least one dose of frovatriptan. There was one death, unrelated to treatment (sepsis), and 0.5% of the 1554 patients who received at least one dose of 2.5 mg of frovatriptan in the controlled trials had at least 1 serious adverse event. The adverse events seen in association with frovatriptan are those seen with other triptans, and there are no adverse events or effects on vital signs or lab tests that would preclude approval.

Typically, the division has required sponsors of new migraine treatments to supply safety data for at least 300-600 patients who have treated an average of at least 2 headaches/month for 6 months, and at least 100 patients treating at least 2 headaches/month for 1 year. Currently, the sponsor has submitted data on only 258 patients who treated an average of at least 2 headaches/month for 6 months, although 178 patients have done so for at least 1 year.

OTHER ISSUES

The primary outstanding issue relates to pre-clinical findings.

As noted earlier, results of a human lymphocyte assay performed with whole blood revealed evidence of clastogenicity. Although the sponsor suggested that

this result was secondary to red cell lysis, a repeat study in the absence of red cells was also positive. For this reason, the drug was considered to be genotoxic, and therefore, in keeping with Agency policy, the in vivo carcinogenicity studies in rat and mouse were to be performed at a maximally tolerated dose (MTD), not at a maximum dose giving 25 times the human exposure (acceptable for a non-genotoxic compound).

However, neither the rat nor mouse carcinogenicity study was performed at what appeared to be an MTD. The sponsor is in the process of performing a p53 mouse study, and performed a 3 month dose ranging study in the rat to determine whether the maximum dose used in the rat carcinogenicity study (85 mg/kg) was reasonably close to an MTD (the CAC suggested that if the MTD were within 2-3 times 85 mg/kg this would make the rat CA study acceptable).

According to the CAC (meeting minutes of 3/14/00) the MTD as determined from the 3 month rat study was about 255 mg/kg/day for males and greater than 440 mg/kg/day in females. However, considering the high levels of exposure achieved in the rat CA study (about 45 times that seen in humans), the intermittent dosing of the drug in humans, and the fact of an on-going p53 mouse study, the CAC executive committee concluded that the rat study need not be repeated, assuming the p53 *mouse study is clearly negative*.

In her review, Dr. Fitzgerald argues that the MTD in the 3 month rat dose finding study is not 255 mg/kg/day in the males, but actually at least 440 mg/kg in males and about 750 mg/kg/day in females, both considerably greater than what the CAC Executive Committee concluded were the MTDs.

[.....]

Dr. Fitzgerald does note that current Agency policy gives the CAC the authority to determine if the doses in the animal CA studies are acceptable, but also notes that the language in the relevant MAPP refers to "proposed" CA protocols; in this case, the CAC Executive Committee has determined that the doses in the rat CA study were acceptable after the study was completed.

NOMENCLATURE

The Labeling and Nomenclature Committee, in a memo of 8/11/99, concluded that the proposed name _____ has a high potential for confusion with Midrin and Maduramycin, as well as the potential for confusion with Cardura and Midamor. The sponsor has been informed of this finding, and has not responded to it.

INSPECTIONS

As Dr. Levin notes, we have not received reports of the inspections of the clinical studies, although we are informed that a verbal report will be received imminently.

COMMENTS AND RECOMMENDATIONS

The sponsor has demonstrated the effectiveness of a single 2.5 mg dose of frovatriptan as a treatment for acute migraine. In particular, they have demonstrated a robust effect on pain relief at 2 hours in an appropriate population, and have demonstrated a beneficial effect on the associated symptoms of migraine, although in only one trial have they shown a nominal effect on vomiting (although the rate of vomiting in the samples studied here was quite low). It is interesting to note that the estimate of the treatment effect for frovatriptan is somewhat less than other marketed triptans, although, of course, cross study comparisons are treacherous (it is also interesting to note that in the one study in which they were directly compared, sumatriptan was superior to frovatriptan). Dose response data do not support the effectiveness of doses lower than 2.5 mg nor the conclusion that doses greater than 2.5 mg are more effective than 2.5 mg. Studies also suggest that a second dose in the face of a failed first dose does not confer benefit. Nonetheless, the sponsor has submitted substantial evidence of effectiveness.

Interestingly, the C_{max} and AUC in women are about twice that in men. Close to 90% of the patients in the controlled trials were women, and while women had a slightly greater 2 hour response rate than men, this difference was not significant (see Dr. Oliva's review, page 33, Table 24).

There is no safety issue that would preclude approval, and we would expect this drug might be associated with all of the known adverse events reported with other triptans. The sponsor alleges that this drug is highly selective for cerebral vessels and even did a relatively small study in patients at risk for coronary artery disease, and saw no untoward cardiovascular events. This data, although suggestive, is not definitive on this point.

However, as noted by Dr. Levin, the sponsor has not submitted even the minimum number of patients treated appropriately for 6 months, and should be expected to do so (I understand that the sponsor has, or is accruing, this data).

Regarding the carcinogenicity issue, I agree with Dr. Fitzgerald that the MTD in the rat, as determined by the 3 month dose ranging study, is at least 440 mg/kg/day in males, and probably greater than 750 mg/kg/day in females, making the MTD at least 5-9 times the 85 mg/kg/day maximum dose used in the CA study.

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As noted earlier, the Nomenclature Committee has determined that there is a high potential for confusion with several other marketed drugs, and the sponsor has been informed of this. I believe that this is an important issue, and must be adequately addressed by the sponsor (ideally with a new name) prior to approval.

In addition, there are several CMC and biopharmaceutics issues that need to be addressed.

For the reasons stated, then, I recommend that the attached Approvable letter be issued.

[^]
/S/
Russell Katz, M.D.

Cc:
NDA 21-006
HFD-120/Katz/Oliva/Levin/Stolzenberg/Fitzgerald/Heimann/Guzewska

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Draft

Labeling

Chen, Lana Y

From: Baweja, Raman K
Sent: Wednesday, October 31, 2001 3:35 PM
To: Chen, Lana Y
Cc: Mahmood, Iftekhar; Baweja, Raman K; Oliva, Armando
Subject: NDA 21,006; Frovatriptan

Lana

The dissolution method and specification for frovatritan 2.5 mg tablet as suggested by the Agency have been accepted by the sponsor. This is acceptable to OCPB.

Mahmood and Ray

**APPEARS THIS WAY
ON ORIGINAL**

Chen, Lana Y

From: Gilman, Sydney [Sydney.Gilman@elancorp.com]
Sent: Wednesday, October 31, 2001 3:19 PM
To: 'CHENLA@cder.fda.gov'
Subject: RE: N 021006



wssinfo.txt

Lana -

Please refer to my voice mail message left earlier.

A response to the dissolution specifications addressed in the Approvable Letter, received April 28, 2000, was submitted to the Agency on October 03, 2000 (page 2 of the response). Our response was as follows:

"The dissolution specification has been adopted and the product specifications have been modified accordingly including the use of Stage 2 and Stage 3 testing as per the USP.

The following dissolution specifications were adopted:

Apparatus: USP Apparatus 11 (paddle)
Medium 900 mL phosphate buffer (pH = 5.5)
Speed 50 rpm
Q = _____ minutes

The answers to each of the questions in the Approvable Letter were delineated in a table submitted on May 25, 2001.

Also, as stated on the voice mail, we are preparing our responses to the clinical trial portion of the label. We have a worldwide project team and plan to finalize our comments on Saturday, November 04, 2001. I will send them to you via email on or before Monday, November 06, 2001. Based on our comments regarding 4-hour data and recurrence, we would like to plan a teleconference with Dr. Oliva and Dr. Katz at their earliest convenience to further discuss, if necessary.

I welcome your comments.

Best Regards,

syd

-----Original Message-----
From: Chen, Lana Y [mailto:CHENLA@cder.fda.gov]
Sent: Wednesday, October 31, 2001 11:34 AM
To: 'Gilman, Sydney'
Cc: Chen, Lana Y
Subject: N 021006

Syd,

Would your response include agreement to the dissolution specs stated in our AE letter (see attached, pg 2 of AE letter)?

Also, do you have an update as to when you expect to respond to our

BEST POSSIBLE COPY

proposed
labeling?

anks,
.a

-----Original Message-----

From: Gilman, Sydney [mailto:Sydney.Gilman@elancorp.com]
Sent: Monday, October 29, 2001 2:57 PM
To: 'CHENLA@cder.fda.gov'
Subject: RE: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes

Lana

Received labeling comments; current plans are to have complete response
by
Thursday.

talk to you soon,

syd

-----Original Message-----

From: Chen, Lana Y [mailto:CHENLA@cder.fda.gov]
Sent: Monday, October 29, 2001 7:41 AM
To: Gilman, Sydney
Cc: Chen, Lana Y
Subject: RE: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes

vd,

This response was received. We are currently awaiting your response to
our
draft labeling, sent to you via email on Thursday, 10/25. Please
confirm
receipt of the 10/25 email, and an estimate of when you intend to
respond.
Please send your labeling response via email to me and cc: Dr. Armando
Oliva
(olivaa@cder.fda.gov).

thanks,
Lana

-----Original Message-----

From: Gilman, Sydney [mailto:Sydney.Gilman@elancorp.com]
Sent: Thursday, October 25, 2001 8:19 PM
To: 'CHENLA@cder.fda.gov'
Subject: RE: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes
Importance: High

Lana -

We will be sending a paper copy of our response to you tomorrow on
October 26, 2001. Attached via secure email is the same response
divided into the following parts:

Cover Letter 26Oct01
Form 356h 26Oct01
Attachment 1 - Newly revised frovelan draft label
Attachment 2 - Side by Side Comparison of Agency's Draft Label and
Applicant's Proposed Label

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Please confirm receipt of secure email.

Best regards,

syd

-----Original Message-----

From: Chen, Lana Y [mailto:CHENLA@cder.fda.gov]
Sent: Tuesday, October 23, 2001 11:25 AM
To: Gilman, Sydney
Cc: Chen, Lana Y
Subject: RE: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes

Syd,

As for question 1, I expect the letter to issue within the week or so; I will update you accordingly. As for question 2, OPDRA expects their final review to be completed within 2 weeks. Preliminary review of the name last year found the _____ name acceptable. As for question 3, I will let you know if there are further questions from the division.

As for your question re: labeling, we'd like to know what your justification is for the multiples of human exposures cited in your labeling under pregnancy: Pregnancy Category C. For example, in the 2nd paragraph, 1st sentence: "When pregnant rats were administered frovatriptan during the period of organogenesis at oral doses of 100, 500 and 1000 mg/kg/day (equivalent to _____ time the exposure to parent drug in humans receiving the MRHD)....." Also, the last sentence of this paragraph.

thanks,
Lana

-----Original Message-----

From: Gilman, Sydney [mailto:Sydney.Gilman@elancorp.com]
Sent: Tuesday, October 23, 2001 9:55 AM
To: 'Chen, Lana Y'
Subject: RE: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes
Importance: High

Lana --

We received the draft copy of the Exec-CAC minutes on Thursday and had the following questions:

1. Anticipated timing for receipt of the final minutes signed off by the Division.

2. Has OPDRA confirmed that _____ is acceptable as the tradename for

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frovatriptan?

3. Elan has responded to questions from Clinical, Nonclinical and Chemistry. Since we have not received any additional questions were are any specific issues that we should discuss or receive in writing prior to the Action Letter due November 8, 2001?

3. Can we begin to work on labeling text prior to the November 8th PDUFA date?

Looking forward to your response.

syd

-----Original Message-----

From: Chen, Lana Y [mailto:CHENLA@cdcr.fda.gov]
Sent: Thursday, October 18, 2001 9:03 AM
To: Sydney Gilman (E-mail)
Cc: Chen, Lana Y
Subject: FW: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes

Syd,

Attached are the Exec CAC mtg minutes from the October 2, 2001. Although sign-off from the division is imminent, I'm forwarding this to you as a courtesy copy.

anks,
ana

-----Original Message-----

From: CDER DocAdmin, DFS
Sent: Friday, October 12, 2001 10:52 AM
To: Atrakchi, Aisar H; Rosloff, Barry N; Chen, Lana Y; Seifried, Adele S; DeGeorge, Joseph J
Subject: DFS Email - N 021006 N 000 AZ 07-May-2001 - Meeting Minutes

This message is automatically generated, Please do not reply to this message

Document room update the following:

	Decision Date	Decision Code
N 021006 N 000 AZ 07-May-2001	12-Oct-2001	NR:NO REPLY NECESSARY

Document Type: Meeting Minutes
Submission Description: NDA 21,006 - Minutes of Exec CAC meeting of 10/02/2001,

Author(s)/Discipline(s)

1. Adele Seifried, UNKNOWN
2. Aisar Atrakchi, PHARMACOLOGIST

Signer(s)

1. Adele Seifried
12-Oct-2001

BEST POSSIBLE COPY

2. Joseph DeGeorge
12-Oct-2001

Supervisory Signer(s)

-
1. Joseph DeGeorge
12-Oct-2001

**APPEARS THIS WAY
ON ORIGINAL**

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: April 11, 2000
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 21-006, N000, Frovatriptan
To: File

Background

The sponsor is Vanguard and the indication is for the acute treatment of migraines. The IND was submitted on 9/30/95 and the NDA was submitted on 1/29/99. A draft report for a 3 month rate study was provided as a major amendment on 1/20/00.

CMC

The application was reviewed by Drs. Heimann and Guzewska. After reviewing the original submission and amendments addressing deficiencies, they concluded that the application was approvable relative to the chemistry issues. The sponsors plans on marketing the 2.5 mg tablet _____

The naming committee felt that the proposed name, _____ was unacceptable because of potential confusion with other Midrin and Maduramycin. Other potential confusion could arise from Cardura and Midamor.

Animal toxicology

The application was reviewed by Drs. Stolzenberg and Fitzgerald. They concluded that the carcinogenicity studies provided with the application were inadequate. The doses for the rat and mouse carcinogenicity studies were based on a > 25 fold AUC. Because the drug tested positive for potential genotoxicity in a human lymphocyte assay, the maximally tolerate dose (MTD) should have been used in carcinogenicity study. This conclusion was supported by the Carcinogenicity Assessment Committee (CAC).

To correct this deficiency, the sponsor initiated a 26 week p53 mouse carcinogenicity study. They also performed a 3 month rat study to demonstrate that the doses used in the

rat carcinogenicity study were adequate. The study needed to show that the highest dose in the rat carcinogenicity study, 85 mg/kg/day, was close to the MTD. Close was defined as being within 2 to 3 times the MTD.

The sponsor noted that in the rat study only "minor focal tubular basophilia/regeneration, similar to that seen in control animals, was found in 150, 255 and 440 mg/kg/day dosed animals. In males dosed at 440 mg/kg/day, the slightly higher incidence of tubular lesions, together with the presence of tubular dilatation in one animal and a slightly reduced incidence of hyaline droplets, were all suggestive of a minor renal effect at this dose level. The kidneys of females dosed at 440 mg/kg/day were not sufficiently different from the controls to be considered affected by treatment."

The executive CAC committee met and reserved final judgement on the adequacy of the rat carcinogenicity study until completion of the p53 mouse study. If the mouse study is positive or equivocal, then the rat carcinogenicity study may need to be repeated using higher doses. If the p53 mouse study was negative, the rat study would not need to be repeated. As explained by Dr. DeGeorge (personal communication), the p53 mouse is a carcinogenicity assay that responds only (as far as we know) to genotoxic carcinogens. A negative study would reduce the chances that the drug is a carcinogen via a genotoxic mechanism. This finding would also suggest that the lower doses used in the rat study were adequate. If the study is equivocal, then further studies may be needed. A positive study would suggest that the drug is a carcinogen in animals. In addition, the executive CAC committee concluded that the MTD for the drug was closer to 255 mg/kg/day. This differs from the conclusions of both the sponsor and the division pharmtox reviewers. Dr. Fitzgerald concluded that the MTD for the rats is closer to 440 for the males and greater than 440 for the females.

The reviewers recommended additional changes to the labeling to reflect the findings of the animal studies.

The drug exhibits a 25 fold selectivity of the 5HT1D over the 5HT1F receptor and a 600 fold selectivity of the 5HT1D over 5HT1B. At therapeutic doses, the sponsor claims that the drug produces constriction of the carotid arteries while having little effect on the coronary arteries. The clinical significance of this finding is unclear. At higher doses, the drug has leads to vasoconstriction of the coronary arteries. The drug was not found to have nociceptive activity in the mouse.

Human Pharmacology and Biopharmaceutics

The application was reviewed by Drs. Sunzel, Mahmood and Tammara. They concluded that regarding PK, the application was acceptable if labeling recommendations were used.

The studies evaluating the effects of hepatic and renal impairment were inadequate. The sample size was too small to assess the effects of renal or hepatic impairment. Also, the

age difference in the control group and the hepatic impaired patients were too large to draw conclusions.

The PK results are summarized as follows: The Cmax is 2 to 4 hours. The absolute bioavailability is 20 to 30%. Tmax was delay 1 hour when dosing followed food. The commercial 2.5 mg dose was bioequivalent to the used in clinical trials. Protein binding is 15%, RBC binding is 60%. Metabolism is by the CYP1A2 pathway. The drug does not induce or inhibit P450. Clearance is decreased in females. The terminal half life is 26 hours, Elderly have a 2 fold increase in AUC and Cmax compared to young and females have a 2 fold increase in AUC and Cmax when compared to males. The desmethyl frovatriptan's half life is 70 to 90 hours in males and females, respectively. Oral contraceptive may inhibit metabolism with a 30% increase in AUC.

Efficacy

The efficacy portion of the application was reviewed by Drs. Oliva and Koti who concluded that there was sufficient evidence to support the claim that the drug is effective for the acute treatment of migraines.

The sponsor provided 5 adequate and well controlled studies, 2, 6, 7, 9 and 14, to support the claim of efficacy for the acute treatment of migraines. All of these studies evaluated the efficacy of the outpatient treatment of at least one moderate to severe headache with a single dose of drug. Only study 09 was conducted outside the US. The studies used a parallel design and the patients were randomized in a double blind fashion. The headache response rate at 2 hours was the primary outcome measure. Rescue was permitted 2 hours after treatment. A responder was defined as someone who had a change in headache pain from moderate or severe to mild or no pain. Incidence of nausea, photophobia and phonophobia at 2 hours following treatment, and time to rescue was determined in each study. The studies are summarized below.

Table 1 Summary of Efficacy Studies

Study	Number treated	Doses studied (mg)	Number of doses	Number of attacks
02	844	0, 2.5, 5, 10, 20 , 40	1	1
14	598	0, 0.5, 2.5, 5	1	1
06	308	0, 2.5	1	3
07	1111	0, 2.5	2 (for recurrence)	3
09	1196	0, 2.5, sumatriptan 100	2 (for recurrence)	3

An additional study, 08, evaluated the efficacy of a second dose taken after non response to the initial dose. All patients received 2.5 mg to treat the initial headache. For those who did not respond to the initial headache, a second dose, was given in a double blind fashion. Non responders were randomize to either an additional dose of drug or placebo was given placebo.

94% of the patients were white with a mean age of 41. 88% were female. The patients had an average of 3.2 headaches per month. 68% had used sumatriptan in the past. 60% of the migraines were accompanied by nausea. Photophobia was reported in 80% of migraines and phonophobia in 67%. Approximately 2/3 of the headaches were rated as moderate at the time of treatment. The results of the 2 hour headache response rates are summarized below.

Table 2 Two hour headache response rate (number of patients exposed) (* p value < 0.05)

Treatment	Study 02	Study 14	Study 06	Study 07	Study 09
Placebo	22% (91)	25% (115)	21% (99)	27% (347)	23% (225)
2.5 mg	42%* (90)	38%* (121)	39%* (73)	46%* (672)	37%* (438)
Sumatriptan 100	NA	NA	NA	NA	47%* (441)
0.5 mg	NA	30% (119)	NA	NA	NA
1.0 mg	NA	26% (109)	NA	NA	NA
5 mg	40%* (91)	37% (115)	NA	NA	NA
10 mg	41%* (177)	NA	NA	NA	NA
20 mg	48%* (178)	NA	NA	NA	NA
40 mg	42%* (192)	NA	NA	NA	NA

In study 08, the sponsor evaluated the efficacy of the a second dose for persistent headache. All patients took an initial dose of 2.5 mg. Patients were randomly given either 2.5 mg or placebo to take for persistent headaches 2 hours after the initial dose. The primary outcome measure was the headache response rate 4 hours following the initial dose. The 4 hour headache response rate for those assigned to 2.5 mg and placebo were 39 and 44% respectively.

A small in patient study was performed in 75 patients with at high risk for CAD (three patients had a history of CAD). The 4 hour headache response rate for the patients randomized to 2.5 mg and placebo were 84 and 79%, respectively. The results of the incidence of the secondary outcome measures are summarized below.

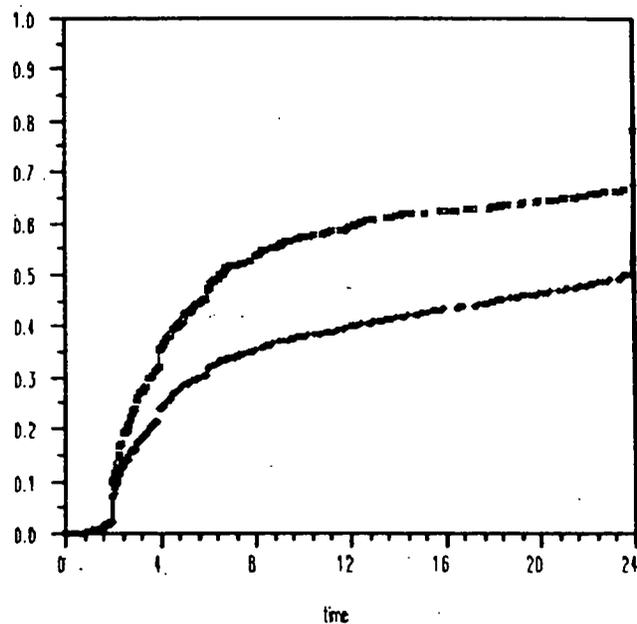
Table 3 Incidence rates for associated symptoms 2 hours after treatment (*p value < 0.05)

Symptom	Dose	Study 02	Study 14	Study 06	Study 07	Study 09
Nausea	2.5mg	36% (90)	44% (121)	43% (188)	43% (677)	51% (441)
	PBO	51% (91)	50% (115)	52% (100)	45% (348)	58% (226)
		p=0.039*	p=0.12	p=0.092	p=0.116	p=0.007*
Photophobia	2.5mg	69% (90)	65% (121)	62% (188)	57%(677)	51% (441)
	PBO	86% (91)	77% (115)	76% (100)	68% (348)	60% (226)
		p=0.007*	p=0.006*	p=0.001*	p<0.001*	p=0.010*
Phonophobia	2.5mg	60% (90)	55% (121)	52% (188)	48% (677)	46% (441)
	PBO	75% (91)	62% (115)	64% (100)	54% (348)	52% (226)
		p=0.044*	p=0.16	p=0.018*	p=0.012*	p=0.16

Analyses were performed to examine differences for sex, race and age. The number of males, non white, elderly was small and it is difficult to assess differences in the groups. The headache response rates were lower in the drug group for patients with either moderate and severe headaches at baseline. Dr. Koti noted in both study 7 and 9 that the differences were associated with nominal p values < 0.05 . In study 6, the difference for the patients with severe pain at baseline were not associated with a p value < 0.05 while those with moderate pain baseline the differences were associated with p values < 0.05 . Headache response rates were generally higher for those headaches treated with drug > 4 hours after the headache started. The opposite was true for patients treated with placebo. The use of SSRIs, non selective MAOI, estrogen or propranolol did not appear to effect the results for the primary outcome.

Dr. Oliva provided a Kaplan Meier plot for time to rescue for 2.5 mg and placebo groups for the combination of studies 2, 14, 6, 7 and 9 in Figure 1 below.

Figure 1 Time to rescue (drug lower curve)



Safety

The safety portion of the application was reviewed by Dr. Oliva who concluded that the safety data did not demonstrate specific safety issues that would suggest that the drug is significantly different from previously approved triptans.

Approximately 3000 patients were exposed to at least a single dose of 2.5 mg or higher in the controlled and open label clinical studies. About 1200 were exposed to placebo. 482 were exposed to 100 mg of sumatriptan. In regards to information on long term safety,

258 patients treated, on average, 2 or more headaches per month for 6 months. 184 of these patients treated, on average, 2 or more headaches per month for 12 months. In over 75% of the attacks, patients used one or two doses of the drug.

The most common adverse events that had a higher incidence compared to placebo in the controlled clinical trials are summarized in the table below. These events appeared to be dose related.

Table 4 Common Adverse Events

Event	Frovatriptan 2.5mg	PBO
Dizziness	7.9%	5.3%
Fatigue	5.3%	2.3%
Paresthesia	4.1%	2.4%
Headache	4.1%	2.6%
Flushing	3.5%	2.0%
Temp change sens.	3.3%	2.3%
Dry mouth	3.1%	1.4%
Chest Pain	2.4%	1.3%
Throat Tightness	1.6%	0.1%

There were few serious adverse events in either the placebo or drug groups. One patient died. The death was related to sepsis from an infected foot ulcer which was present prior to treatment. One of the 16 subjects exposed to daily doses in a phase 1 study developed elevated liver function tests 5 days after receiving 40 mg bid. Approximately 5% of patients dropped out for adverse events during the long term study, 5 for chest pain. 4.6% of the 496 patients in the long term study had chest pain. Two dropout for chest pain.

In labs, vital signs and ECGs in the majority of studies were not collected close to the time of dosing. The number of patients with predefined "clinically noteworthy values" was similar for those receiving placebo and drug. When vital signs were checked during dosing, the BP, in general, was slightly higher in the drug treated subjects. Only one change was fulfilled the criteria for being clinical noteworthy. This was in a subject hypertension and who had an elevated BP at baseline. For ECGs, one patient had developed Q waves since the baseline ECG and one developed new anterolateral T wave abnormalities. These patient shad not had any symptoms. When ECGs were checked during the time of dosing, the patients did not experience chest pain. The incidence for evidence of ischemia on Holter was similar between the drug and placebo groups.

Comments

The sponsor has provided adequate evidence to support the conclusion that 2.5 mg of the drug is effective for the acute treatment of migraines. The findings were not as robust as with the currently approved migraine treatments in that not all secondary outcome measures in all studies were associated with p values < 0.05. In labeling the sponsor should include the two hour headache response rates for 2.5 mg and placebo for studies

02, 14, 06, 07 and 09. They should also provide Kaplan-Meier curves for the time to response to 2 hours following dosing and the time to rescue to 24 hours following dosing.

For the dosing and administration section, the 2.5 mg dose should be recommended. It should also be mentioned that the data suggested that doses beyond 2.5 mg did not provide additional benefit and there was evidence from one study that a second dose to treat persistent pain was not effective. We have allowed sponsors to recommend additional doses without evidence for efficacy as long as there was sufficient evidence for safety. The sponsor will need to provide additional evidence for the safety of repeated doses of the drug for the treatment of recurrent migraines prior to including it in labeling.

The adverse event profile for this drug appears to be similar to other triptans. The sponsor has not provided sufficient information to exclude the contraindications and warnings described in labeling for other triptans.

The major outstanding issues are the adequacy of the carcinogenicity evaluation and long term safety. The adequacy of the carcinogenicity studies are in question and interpretation of the results are controversial. See Dr. Fitzgerald's memo for a complete discussion of this issue. Basically, the sponsor is conducting a 6 month p53 mouse study to investigate this issue further. If the study is negative, the existing carcinogenicity studies may be adequate. If the p53 study is equivocal, an additional 2 year rat carcinogenicity study may need to be performed. A positive study would suggest that the drug is a carcinogen in animals.

Recommendations

I recommend that the NDA not be approved at this time because there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed [314.125(b)(4)]. This recommendation is based on two issues. One is the lack of an adequate animal carcinogenicity studies. The other is the lack of sufficient long term safety data. To remedy the situation, the sponsor will need to provide adequate studies evaluating the carcinogenicity potential of the drug. Specifically, they will need to provide the results from the 6 month p53 mouse study

Second, the sponsor will need to provide safety data from 300 to 600 patients who have used the recommended dose to treat, on average, 2 or more migraines a month for 6 months. This data is currently being collected.

The sponsor also needs to address the inadequacy of the studies evaluating the effects of hepatic and renal impairment on drug metabolism, issues related to the drug name, and the plan for conducting studies in adolescents. Finally, the clinical site inspection results are pending.

/S/

Randy Levin, M.D.
Neurology Team Leader

JUL - 2 19

NDA 21-006

Executive Director, Regulatory Affairs

Dear _____

Please refer to your pending January 29, 1999 new drug application submitted, on behalf of Vanguard Medica, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Miguard™ (frovatriptan succinate) Tablets.

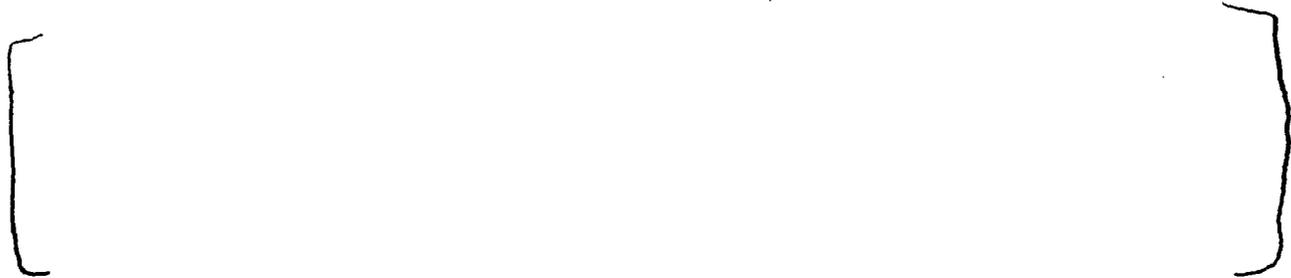
We also refer to your submission dated June 8, 1999.

We are reviewing the Chemistry section of your submission and have the following comments and information requests:

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WITHHOLD 6 PAGE (S)



We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Lana Chen, Pharm.D., Regulatory Management Officer, at 36(301) 594-2850.

Sincerely,

/S/

Maryla Gzewska Ph.D.
Chemistry Team Leader, Neurology Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 21-006

Drug: Frovatriptan (VML 251)
Sponsor: _____ for Vanguard
Date: April 28, 1999
Conversation Between: Agency: L Chen, RPh, G Fitzgerald, PhD, R Levin, MD,
S Stolzenberg, PhD

Firm: _____
Vanguard: P. Sugden, S. Waterman, M. Pue, C. Powell,
P. Astbury, P. Buchan

Telephone #: _____, participant code # 549487

Purpose:

The Agency requested this teleconference to inform the Firm that the carcinogenicity studies submitted to NDA 21-006 used inadequate doses. The Firm was previously informed of this, under IND _____ in June 1996 as per recommendation of the Exec CAC. The firm was advised of their option to present their case to the Full CAC (to be convened upon their request). Alternatively, the Firm could opt to conduct two carcinogenicity studies with appropriate doses.

The Firm indicated their need for internal discussion, and that a response would be communicated to the Agency shortly.



Lana Chen, R.Ph.

cc: Orig IND
HFD-120

HFD-120/Levin
/Fitzgerald/Stolzenberg
/Chen

Final: 7/2/1999

APPEARS THIS WAY
ON ORIGINAL



NDA 21-006

NOV 30 1999

INFORMATION REQUEST LETTER

[]
Executive Director, Regulatory Affairs
[]

Chen

Dear _____

Please refer to your pending January 29, 1999 new drug application submitted, on behalf of Vanguard Medica, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Miguard™ (frovatriptan succinate) Tablets.

We also refer to your submission dated September 29, 1999.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

[

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We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information

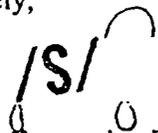
NDA 21006

Page 3

reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Lana Chen, Pharm.D., Regulatory Management Officer, at 36(301) 594-2850.

Sincerely,


Maryla Guzewska, Ph.D.

Chemistry Team Leader, Neurology Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Chen

NDA 21-006

[]

MAR 24 1999

Dear _____

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Miguard (frovatriptan) tablets

Therapeutic Classification: Standard (S)

Date of Application: January 29, 1999

Date of Receipt: January 29, 1999

Our Reference Number: 21-006

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 29, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 29, 1999 and the secondary user fee goal date will be January 29, 2000.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-006

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, contact Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/s/ 3/23/89

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Fax

To: Dr. Maria Sunzel

From: _____

Fax: (301) 594-2859

Pages:

Phone: (301) 594-5563

Date: 10/21/99

Re: Response to teleconference of 21-sept-99 **CC:**

Urgent For Review Please Comment Please Reply Please Recycle

Attached is a copy of the response to the issues raised in the teleconference with Vanguard representatives and you.

I will be sending this as well as the data via courier, but I wanted to get this information to you today.

Yours truly,

NDA 21-006 US Agent

APPEARS THIS WAY
ON ORIGINAL

FROVATRIPTAN NDA

**Response to questions raised by FDA Biopharmaceutics Reviewers on
21/09/99**

1. *There were a number of analytical and validation reports referenced in the human pharmacokinetic study reports which could not be located in the dossier. Could Vanguard provide these or indicate where in the application they are located:-*

i) *Report No: VML 251/96/01
Analytical report 1165/71/1010 could not be located.*

Analytical report 1165/71/1010 was re-issued as analytical report 1165/73, and is included as Appendix 28 to study report VML 251/96/01 (see Volume 1.072, p. 297 of NDA).

ii) *Report No: 1165/24
Analytical report — 1165/30 and validation reports 1165/29/1010 and — 1165/31/1010 could not be located.*

Validation reports 1165/29/1010 and 1165/31/1010 can be found in Volume 1.052 of the NDA, on pages 1 and 263 respectively. The analytical report — 1165/30 was included unnumbered as Appendix 30 to report 1165/24 and can be found in Volume 1.060 on page 94. ...

iii) *Report No: 1165/42
Analytical report — 1165/44/1010 could not be located.*

Analytical report — 1165/44/1010 was included unnumbered, as Appendix 27 to report 1165/42. It can be found in Volume 1.068, page 281 of the NDA.

iv) *Report No: 1165/62
Analytical report — 1165/65/1010 could not be located.*

Analytical report — 1165/65/1010 was included unnumbered as Appendix 22 to report 1165/62. It can be found in Volume 1.086, page 239 of the NDA.

v) *Report No: VML 251/96/03
Analytical report — 1165/85/1010 could not be located.*

Analytical report — 1165/85/1010 was re-issued as report 1165/82 and is included as Appendix 39 to report VML 251/96/03. It can be found in Volume 1.075, page 278 of the NDA.

2. *Thirty-two subjects were recruited into the comparative bioavailability study 1165/62, but pharmacokinetic data were analysed for only 24. FDA would like to see the analysis of the pharmacokinetic data on all 32 subjects*

We regret that we are unable to comply with this request. Plasma levels of frovatriptan were not measured in samples from the remaining eight subjects, and the samples from these subjects were destroyed on completion of the study report.

Sample size calculations were performed prior to the start of the study. These showed that 23 subjects would be required to detect a difference of greater than 20% in AUC with 80% power and a 5% level of significance. (See page 24 of the study report.) It was decided to recruit 32 subjects to balance the study and to allow for dropouts. In accordance with a protocol amendment, plasma levels of frovatriptan were measured only for the first 24 subjects that completed the study; hence no selection of subjects with regard to pharmacokinetic analysis took place. Moreover the number of subjects in the analysis was in agreement with the initial sample size calculation.

3. *Please provide individual pharmacokinetic parameters for all female subjects who were included in the comparative analysis of subjects who were taking oral contraceptives (OCs) and those who were not.*

Please find enclosed a disc containing the individual pharmacokinetic parameters for all subjects included in the analysis of a possible interaction with OCs. Please note that we have identified three subjects (#1, #8 and #17) from study VML 251/97/05 who were originally assigned to the OC group and who were in fact on Depo Provera. These patients have been assigned to the non-OC users group in the enclosed data sets. New versions of figures X and Y from the Human Pharmacokinetics and Biopharmaceutics section of the NDA (see Volume 1.051, pages – and –), with these subjects correctly assigned to their appropriate group, are presented in Attachment 1 to this letter. In addition it was discovered while reviewing this database that the data from patient #10 in study VML251/96/12 had been omitted from the database because the patient did not complete the iv treatment. We have amended the Excel file (S96_12.XLS) containing the individual subject pharmacokinetic data for that study, to include the values from this subject, and enclose the updated file on disc. The following figures and tables from the Human Biopharmaceutics and Pharmacokinetics section of the FDA have also been updated to include this subject, and revised versions are included in Attachment 2.

Tables 6-2, 6-19, 6-28 and 6-29
Figures 6-29, 6-30, 6-41, 6-42 and 6-43

-
4. *Please provide individual tablet dissolution data for a representative batch of the formulation to be placed on the market.*

Please find in Attachment 3 individual tablet dissolution times for batch SB001 of frovatriptan 2.5 mg tablets. Data are presented both at initial release and after storage under ICH conditions for up to 12 months.

APPEARS THIS WAY
ON ORIGINAL

Barry N. Rosloff, Ph.D.
11/5/01

NDA 21-006 (Frovatriptan) – Supervisory Pharmacologist Memo

The relevant issues regarding the approvability of this NDA have been previously addressed in the numerous primary reviews (Dr. Stolzenberg) and CAC meetings, and in the supervisory memo of Dr. Fitzgerald (4/7/00). The primary reviewer and exec CAC concluded that if a valid p53 mouse study of frovatriptan were negative, no further testing for carcinogenic potential was necessary. Such a p53 mouse study has now been performed and reviewed (review by Dr. Atrakchi of 9/24/01; exec CAC minutes of meeting of 10/2/01) and was considered negative regarding genotoxic carcinogenic effects. The NDA is now approvable.

Barry N. Rosloff

APPEARS THIS WAY
ON ORIGINAL

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

DATE: April 7, 2000

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

TO: NDA 21-006
Miguard™, frovatriptan succinate
Vanguard Medica Ltd. (England)
2.5 mg. Tablets of base

SUBJECT: Pharmacology/Toxicology Team Leader Memo

Frovatriptan is _____; triptan series; the others are Imitrex (sumatriptan), Zomig (zolmitriptan), Amerge (naratriptan), Maxalt (rizatriptan) _____. Like the others, it is indicated for the acute treatment of migraine with or without aura in adults. Unlike the other drugs in this class, frovatriptan is metabolized primarily by CYP1A2, and as such is not subject to drug interaction problems, since few drugs are metabolized by that isozyme.

The pharmacology and toxicology data submitted to this NDA have been reviewed by Dr. Sidney Stolzenberg who recommends in his main review that the NDA not be approved because the doses selected for the carcinogenicity studies were based on the AUC option, which is not appropriate because frovatriptan produced a positive response in the human lymphocyte assay. In a subsequent review he considers that a second rat study may not be required (see page 5 of this memo).

There have been three Executive-CAC meetings and one full CAC meeting to address the issues of genotoxicity, dose selection and validity of the mouse and rat carcinogenicity studies, plus a meeting of the E-CAC to approve the protocol for a p53 mouse study. The minutes of those meetings are attached to this memo (attachments 1 through 5). Following is a summary of the sequence of events and discussion of issues relating to the conduct, review and evaluation of the carcinogenicity studies and the human lymphocyte genotoxicity assay.

The protocol for the rat two year carcinogenicity study was submitted for CAC concurrence on March 19, 1996, with the high dose chosen based on an AUC which would be at least 25 times the human AUC. This option is available for use for non-

genotoxic drugs. That study was initiated three weeks later, on April 12, 1996, using doses of 8.5, 27 and 85 mg/kg/day, even though there had not been an opportunity yet to provide input from the E-CAC. On June 19, 1996 the sponsor was notified that the CAC could not provide concurrence for the doses selected because of insufficient data. Specifically, the committee asked for data to support the claim that the increase in chromosomal aberrations obtained in the human lymphocyte assay was not relevant because the results were seen at cytotoxic doses. As an alternative, the sponsor was informed that a 90 day dose ranging study with pharmacokinetic data could be conducted to support the proposed doses. On August 15 and September 17, 1996 a three month and a six month dose ranging rat study were initiated, using doses of 10, 100 and 1000 mg/kg/day. On June 27, 1996 an 84 week mouse carcinogenicity study was started (the standard duration is 104 weeks), with doses of 4, 13 and 40 mg/kg/day; the protocol had not been submitted to the FDA for concurrence.

After the NDA was submitted (January 29, 1999) the mouse and rat carcinogenicity studies were taken to the E-CAC on April 27, 1999. That committee agreed that the drug is genotoxic, that the doses chosen for the mouse and rat carcinogenicity studies were inadequate, and that the studies should be repeated. They suggested that a full CAC meeting should be held to discuss whether traditional, transgenic, or a combination of both types of studies should be conducted. That meeting was held on July 29, 1999 with the sponsor in attendance. Because the sponsor still contended that the positive response in the human lymphocyte assay resulted from excess cytotoxicity and should not be considered evidence for genotoxicity, that issue, as well as the adequacy of doses, was discussed. During the course of the meeting, the sponsor acknowledged that frovatriptan was positive in the human lymphocyte assay. Therefore, it would be necessary to establish that a maximally tolerated dose (MTD) had been used in the carcinogenicity studies, since multiples of human exposure cannot not be used to select the high doses for a genotoxic drug. The sponsor conceded that the mouse study was inadequate and should be repeated, but continued to consider that the rat study had reached an MTD and was an adequate study (see minutes for details of their arguments). In that study there was no drug related effect on body weight and no drug related organ histopathology. Fourteen of 19 members of the committee voted that an MTD was not reached in the rat study (4/19 said an MTD was reached in males, 1/19 was not sure). The committee suggested that repeating the three month study could potentially demonstrate that the doses used in the current study were within a reasonable range (2- to 3-fold) of the MTD. The already submitted rat dose ranging studies used a middle dose of 100 (a NOEL) and a high dose of 1000. It was suggested that intermediate doses should be examined.

On August 27 and September 17, 1999 the sponsor submitted plans for addressing the issues raised by the CAC. They presented a theory that the positive result in the human lymphocyte assay may have resulted from co-culture with erythrocytes and not from any effect of the drug. The original assays had been performed using whole

blood. This is a common procedure, and, in fact, the method for conducting this assay described in the OECD guideline indicates that either whole blood or separated lymphocytes may be used. The sponsor, citing a 1985 reference¹, proposed that chemicals such as frovatriptan may bind to erythrocytes, damaging membranes and releasing heme, and the heme may then initiate peroxidative damage to other cells, indirectly causing chromosome damage. A protocol was submitted which would compare the effects of whole blood and separated lymphocytes in the human lymphocyte assay. In case that study did not support their theory that the positive genotoxicity finding which had been observed was an artefact, the sponsor also initiated a 13 week study in rats with four doses between the previously studied 100 and 1000 mg/kg/day. The goal was to try to determine whether or not the already conducted rat carcinogenicity study is adequate based on an MTD endpoint. They also stated that they had initiated a 4 week dose ranging study in mice to determine the doses to be used in a definitive mouse p53 assay. The results of the dose ranging study and the protocol for the p53 study were submitted on December 10, 1999 and taken to the E-CAC on January 18, 2000, at which time the definitive study had already been initiated. The CAC had comments concerning doses and transfer of satellite animals to the main study, which were transmitted to the sponsor.

Draft reports of the purified human lymphocyte assay and the three month study in rats were submitted on January 21, 2000. The lymphocyte assay definitively demonstrated that frovatriptan causes chromosomal aberrations in that system unrelated to the presence of heme (see attachment 6). There was a statistically significant increase in the percentage of aberrant cells in the assays, both with whole blood and with separated lymphocytes ($p < 0.01$). With this clearly positive result in one assay of the three which constitute the required standard genotoxicity test battery, "an in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in vitro mouse lymphoma tk assay"², it is not appropriate to use multiples of human exposure for determination of the high doses in the carcinogenicity studies. Therefore, the standard to be met for determining whether or not the rat carcinogenicity study is an adequate study is that a maximally tolerated dose must have been used³.

The newly submitted three month rat study, which was designed to try to determine that the high dose used in the carcinogenicity study was within 2 to 3 times the MTD, was taken to the E-CAC on March 14, 2000. That study used doses of 150, 255 (3x the

1. R. Munday, Toxicity of Aromatic Disulphides. II. Intraerythrocyte Hydrogen Peroxide Formation and Oxidative Damage by Aromatic Disulphides, Journal of Applied Toxicology, Vol. 5, No. 6, page 409, 1985.

2. ICH Guidance for Industry, S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals, July 1997.

3. ICH Guidance for Industry, Dose Selection for Carcinogenicity Studies of Pharmaceuticals, March, 1995.

high dose in the carcinogenicity study), 440 and 750 mg/kg/day. There were two deaths at 440 mg/kg, one male during week one and one female during week four, and no deaths at 750 mg/kg. The observed deaths were apparently not drug related, and may have been gavage accidents. The only toxicities in that study which could possibly be used to determine a maximum tolerated dose are those which occurred in kidney (other toxicity findings are summarized in attachment 7).

Incidence of selected microscopic findings in the kidney – terminal kill												
Tissue and finding	No. examined:	Males					Females					
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F	
		C	150	255	440	750	C					250
Kidney		10	10	10	9	10	10	10	10	9	10	
focal tubular basophilia/regeneration	Grade -	6	6	4	2	0	8	6	5	4	7	
	1	3	3	6	6	2	2	4	5	5	1	
	2	1	0	0	1	4	0	0	0	0	0	
	3	0	0	0	0	3	0	0	0	0	1	
	4	0	1	0	0	1	0	0	0	0	1	
tubular dilatation	Grade -	10	10	10	8	5	10	10	10	9	8	
	1	0	0	0	1	3	0	0	0	0	2	
	2	0	0	0	0	2	0	0	0	0	0	
granular casts	Grade -	10	10	10	9	7	10	10	10	9	9	
	1	0	0	0	0	2	0	0	0	0	0	
	2	0	0	0	0	1	0	0	0	0	1	
hyaline droplets	Grade -	1	1	2	3	5	10	10	10	9	10	
	1	7	9	8	4	3	0	0	0	0	0	
	2	2	0	0	1	2	0	0	0	0	0	
	3	0	0	0	1	0	0	0	0	0	0	

Key: "-" = finding not present, 1 = minimal, 2 = slight, 3 = moderate, 4 = moderately severe

If one examines this table of renal toxicities, It is clear that the effects are not striking at doses below 750 mg/kg. The sponsor's summary of those findings includes the following statements:

"In the kidney, there was a clear increase in incidence and severity of focal tubular basophilia/regeneration in males dosed at 750 mg/kg/day but an increase only of the severity of the lesions in females dosed at 750 mg/kg/day. — Minor cases were seen as small foci of affected tubules in the cortex, whilst in the more severe cases there were multiple fine wedges of affected tubules extending from the outer cortex to the outer medulla, often with associated tubular dilatation and intraluminal granular casts. — Minor focal basophilia/regeneration, similar to that seen in control animals was found in 150, 255 and 440 mg/kg/day dosed animals. In males dosed at 440 mg/kg/day, the slightly higher incidence of tubular lesions, together with the presence of tubular dilation in one animal and a slightly reduced incidence of hyaline droplets, were all suggestive of a minor renal effect at this dose level. The kidneys of females dosed at 440 mg/kg/day were not sufficiently

different from the controls to be considered affected by treatment.”

It should be noted that, in the three and six month rat studies which were conducted after the initiation of the two year study but prior to this study, there were no effects at the middle dose of 100 mg/kg, but at 1000 mg/kg there was also renal tubular basophilia/regeneration at three months and tubular nephropathy at six months. These findings occurred in both males and females (see attachment 8). In the six month study, 3 of 20 high dose males and 1 of 20 high dose females died during weeks 3, 5, 19 and 23. The sponsor considered those deaths to be related to renal toxicity; however, there was no conclusive evidence to support that claim. The occurrence of 10% mortality in a six month study is not unusual, and probably indicates that 1000 mg/kg/day was an MTD for that study.

In Dr. Stolzenberg's March 23, 2000 review of the rat three month study, he concludes that 255 mg/kg in males and 440 mg/kg in females may be the MTD. He bases this primarily on some evidence that there is increasing systemic exposure to frovatriptan over time, which he believes will result in increased severity of renal lesions after chronic dosing. Although there may be some increase in blood levels, I do not believe that there is sufficient information to suggest that it will be at a significant rate beyond week 12. Dr. Stolzenberg also concludes that there is little to be gained by an additional rat carcinogenicity study if the p53 assay is negative, an issue which I discuss in the Evaluation section below.

The Conclusions and Recommendations put forth in the E-CAC report, after the March 14 meeting, are that:

“---- the MTD for males may be around 255 mg/kg/day, but for females exceeded 440 mg/kg/day (more than the 2 to 3-fold times the high dose used in the carcinogenicity study). Looking at all factors, the high levels of exposure after treatment with frovatriptan, the type of carcinogenic risk of clinical significance from an intermittently used product, the ongoing mouse p53 study, the committee concluded that the rat carcinogenicity, in conjunction with the previously conducted mouse study and an adequate and clearly negative p53 mouse study would constitute an adequate assessment of the carcinogenic potential of frovatriptan. They recommended that a rat carcinogenicity study need not be repeated provided there is a clearly negative study in the p53 mouse. If the p53 study is positive or equivocal, a rat carcinogenicity study may be necessary to draw an adequate conclusion regarding the carcinogenic potential of frovatriptan.”

Evaluation

After careful examination of the renal toxicity data, it is impossible for me to reach the same conclusion as the E-CAC with respect to what constitutes an MTD in the rat

study. It appears to me that the maximum tolerated dose in females is near 750 mg/kg, and in males it is probably between 440 and 750 mg/kg. These doses are approximately 9 times and >5 times the high dose of 85 mg/kg which was used in the rat carcinogenicity study, and not the 2 to 3 fold higher that is usually considered to be within an acceptable range by CDER. The committee also considered that there were high levels of exposure after treatment with frovatriptan, a factor which cannot be considered for a genotoxic drug according to ICH guidance, and that migraine represents an intermittent use product, a consideration which has not been invoked for all other intermittent-chronic use migraine drugs. The mouse study, which was only 84 weeks in duration rather than two years, and which used very low doses, as a predictor of carcinogenic potential.

A study in the p53 mouse is ongoing, and when that study is completed, presuming that it will be an acceptable study, one of the two required carcinogenicity studies will be available. The committee recommended that if the p53 study is positive or equivocal, a rat study may be needed to draw adequate conclusions regarding the carcinogenic potential of frovatriptan.

Recommendation

This NDA should not be considered approvable until the p53 mouse study is submitted and an appropriate MTD carcinogenicity study has been conducted in rats.

/S/
Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
4/14/00

NDA 20-016
c.c.\HFD-120
Katz/Levin/Oliva/Stolzenberg/Fitzgerald/Chen
\HFD-100
Temple

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENTS

Executive CAC
June 11, 1996

Committee:

James Farrelly, PhD, HFD-530, Acting Chair
Alex Jordan, PhD, HFD-580
Charles Resnick, PhD, HFD-110
Glenna Fitzgerald, PhD, HFD-120
Sharon Olmstead, HFD-006, Exec Sec

(Freed; HFD-120)

VML 251

Vanguard Medica Ltd

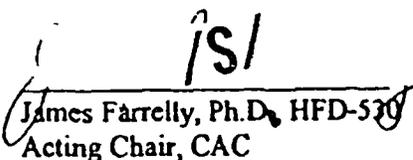
The sponsor proposed a 2-year oral gavage carcinogenicity study in rats using 8.5, 27, and 85 mg/kg/day based on a 28-day toxicity study (HD 500 mg/kg). AUC multiples were provided for weeks 1 and 4. The sponsor believes the increased plasma levels reported over time in the 28-day study support the HD selection. Data from a 10-day toxicity study (100, 600, 1000, and 2000 mg/kg/day) reported 1 death at 1000 mg/kg but no deaths at 2000 mg/kg, although the dose was lowered to 600 mg/kg. The sponsor claims that the metabolism of the product is similar in humans and rats without providing supporting data. The sponsor also claimed that the increase in chromosomal aberrations reported with human lymphocytes was at cytotoxic doses. This claim could not be substantiated since data were not provided.

The committee expressed concern with the lack of data to support both the dose selection for the 2-year carcinogenicity and the other claims made by the sponsor. The committee agreed that a 90-day dose-ranging study with PK data would clarify the proposed dose selection. However, the committee felt the sponsor might be able to justify the dose selection with additional data.

Recommendations:

The data provided (28-day toxicity study) to support the proposed 2-year rodent carcinogenicity study were not sufficient for the committee to provide a recommendation on the dose selection. The committee suggested the following:

1. Information should be provided to justify the 25-fold AUC difference at 85 mg/kg. Data to support the sponsor's claim that the metabolism of the drug is similar in rats and humans (e.g., metabolite profiles) should be provided. The sponsor should also provide data to support their claim that an increase in chromosomal aberration with human lymphocytes was observed at cytotoxic doses.
2. Or the sponsor may conduct a 90-day dose-finding study with pharmacokinetic data to support the proposed dose range for the carcinogenicity study.


James Farrelly, Ph.D., HFD-530
Acting Chair, CAC

cc: IND file
Division file
HFD-120/GFitzgerald/LFreed
CAC file

Executive CAC Minutes

April 27, 1999

Committee: Abby Jacobs, Ph.D., HFD-024, Acting Chair
Joseph Contrera, Ph.D., HFD-900, Member
Ronald Steigerwalt, Ph.D., HFD-510, Alternate Member
Aisar Atrakchi, Ph.D., HFD-120, Acting Team Leader for G. Fitzgerald
Sidney Stolzenberg, Ph.D., HFD-120, Presenting Reviewer

Author of Draft Minutes: Sidney Stolzenberg, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 21-006

Drug Name: frovatriptan succinate monohydrate (Miguard™), 2.5 mg tablet

Sponsor: Vanguard Medica Ltd. (England)

Sponsor's Contact: _____

Background

The executive-CAC met on 6/11/96 to decide on the adequacy of doses selected in the protocol for a 2-year rat carcinogenicity study; the highest dose of 85 mg/kg/day was based on the AUC ratio option. Sponsor claimed (1) the induction of chromosome aberrations in cultured human lymphocytes occurred only at concentrations that were cytotoxic, which negated the positive findings, and (2) the metabolism in humans and rats were basically similar. The committee recommended either of two alternatives to the sponsor: (1) provide adequate documentation to support their claims, or (2) perform a 3-month dose-finding study to determine the MTD. The reviewing pharmacologist (Lois Freed, PhD) also informed the sponsor that their positive findings in the lymphocyte test cannot be discounted because the reduction in mitotic index (MI) observed was not $\geq 90\%$, and that their carcinogenicity test would therefore have to be based on MTD. Subsequently, Dr. Rosalie Elespuru, a genotoxicity expert with CDRH, told Dr. Freed that even if the reduction in MI exceeded 90%, so long as there are sufficient metaphases to conduct chromosomal analyses, positive findings cannot be discounted. Sponsor also believed that the mutagenicity was due to impurities, but in two additional human lymphocyte tests with more highly purified preparations of frovatriptan, increases in chromosome aberrations due to the presence of frovatriptan were still evident. Mutagenicity in E.coli WP2 uvrA pKM101 was also clearly evident in the first Ames test performed but was equivocal in two other tests performed with preparations that were more highly purified.

The claim that the metabolism in humans and rats were basically similar and that unchanged compound and metabolic products in rat blood would adequately exceed human blood levels is acceptable.

Doses selected for the rat (and the mouse) carcinogenicity tests submitted with this NDA were based on a 25-fold multiple of the AUC, but this option is not appropriate for a genotoxic compound. The FDA's previous recommendations for the rat study had been ignored.

Rat Carcinogenicity Study

The study design involved daily oral gavage treatment of 60 rats/sex/group (CrI:CDBR strain) with doses of 8.5, 27 and 85 mg/kg/day for 104 weeks. There were 2 control groups of 60 rats/sex/group that received vehicle by gavage. The NOAEL observed in both a 3-month dose-finding study (dosing initiated on 8/15/96) and in a 6-month study (dosing initiated on 9/17/96)

was 100 mg/kg/day; the next highest dose of 1000 mg/kg/day in both studies caused renal lesions, with 10% mortality attributed to renal lesions in the 6-month study. Thus, the highest dose in the carcinogenicity test was even below the NOAEL.

Tentative Results: In males, there was an increase in incidence of pituitary adenomas at mid dose (n.s.) and high dose ($P < 0.01$). There was also a decrease in survival to terminal kill at low ($P < 0.05$) and high ($P < 0.01$) doses. Sponsors attributed the higher mortality rate at high dose to pituitary adenoma but did not explain the cause for the higher mortality at low dose, where increased incidence of pituitary adenomas was not found. In treated females, there was an increased incidence of adrenal medullary tumors, but no effect drug treatment on survival. Final evaluation of the results awaits the CDER statistical review.

Mouse Carcinogenicity Study

The study design involved daily oral gavage treatment of 50 mice/sex/group (CrI: CD-1 (ICR) BR strain) with doses of 4, 13 and 40 mg/kg/day for 78 weeks; dosing was initiated on 6/27/96. There were 2 control groups of 50 mice/sex/group that received vehicle by gavage. The NOAEL observed in a 3-month dose-finding study (dosing initiated on 10/18/95) was 500 mg/kg/day, the highest dose tested. Thus, the highest dose selected in the carcinogenicity test was considerably below the NOAEL.

Results: No treatment related increased incidence of tumors of any kind were noted in males or females. Except for red extremities at mid and high doses for no more than a few hours after dosing each day, there were no compound related effects on any parameters measured, including morbidity, mortality, body weight, food consumption, hematology, gross and microscopic pathology.

The recommendation by the presenting reviewer was that both the rat and mouse carcinogenicity studies be repeated.

Conclusions and Recommendations by the Executive-CAC:

The committee agreed that the drug was genotoxic.

The committee concurred that the dose selection for the already conducted rat and mouse carcinogenicity studies had been inadequate and discussed various options.

Subsequent Note added in comment: The committee will defer to the full CAC for recommendations on whether traditional, transgenic, or a combination of both types of studies might be desirable. Because the decision to request repetition of carcinogenicity studies has serious repercussions in terms of time and money, such decisions are usually discussed and voted on at a full CAC.

The sponsor can be informed that the need for repetition of carcinogenicity studies conducted in support of N21-006 will be discussed at an upcoming full CAC meeting. The sponsor can choose to attend and make a presentation at this meeting.

/S/

5/11/99

Abigail Jacobs, Ph.D.
Chair, Executive CAC

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/Division File, HFD-120
/GFitzgerald, HFD-120
/SStolzenberg, HFD-120
/LChen, HFD-120
/ASeifried, HFD-024

APPEARS THIS WAY
ON ORIGINAL

**Full CAC – NDA 21,006, Frovatriptan
July 29, 1999**

Attendees:

FDA: Joseph DeGeorge (HFD-024), Adele Seifried (HFD-024), Charles Resnick (HFD-110), Tom Papoian for Al DeFelice (HFD-110), Glenna Fitzgerald (HFD-120), Sid Stolzenberg (HFD-120), Paul Roney (HFD-120), Linda Fosson (HFD-120), Roswitha Kelly (HFD-120), David McGuinn for Paul Andrews (HFD-150), Abebayo Laniyonu for Nakissa Sadrieh (HFD-160), Dou Lucy Jean (HFD-170), Yash Chopra for Jasti Choudary (HFD-180), Ron Steigerwalt (HFD-510), Terry Peters for Bob Osterberg (HFD-520), Ita Yuen for James Farrelly (HFD-530), Paul Brown for Abby Jacobs (HFD-540), Andrea Weir (HFD-550), Mark Vogel (HFD-570), C. Joseph Sun (HFD-570), Laurie McLeod for Alex Jordan (HFD-580), Owen McMaster for Ken Hastings (HFD-590), Charles Anello (HFD-700), Joseph Contrera (HFD-901).

Vanguard: Chris Powell, Sally Waterman, John Ashby, Gary Williams, George Shopp, _____ Martin Rue, Rand Ashbury, Linda Fradkin, and Peter Bucher.

Author of Draft: Adele Seifried

The following information reflects a summary of the Committee's discussion and its recommendations. Detailed study information can be found in the reviewer's background document and sponsor's background package.

NDA 21,006

Sponsor: Vanguard Medica Ltd. (England)

Drug: MIGARD (frovatriptan succinate monohydrate)

Indication: Acute treatment of migraine

Background

A protocol for a 2-year rat carcinogenicity study in which the doses proposed were 8.5, 27 and 85 mg/kg/day, was submitted to FDA on March 19, 1996. The high dose was based on the "AUC ratio option" derived from blood levels observed during Weeks 1 and 4 of a 28-day rat study and blood levels in humans receiving a therapeutic dose of 2.5 mg. This dose was expected to result in systemic exposure, based on AUC, that would be ≥ 25 times higher than in humans.

The protocol for this 2-year rat study was submitted to the division and the executive-CAC met on 6/11/96 to evaluate the acceptability of the dose selection. The sponsor had indicated that (1) the metabolism of the product was similar in rats and humans, and (2) the drug was not, in their view, genotoxic. They acknowledged that a positive response was obtained in the in vitro human lymphocyte test, but claimed that the

increase in chromosomal aberrations occurred only at cytotoxic concentrations, which in their evaluation negated the positive findings.

In the view of the executive CAC, neither of the two claims by the sponsor were substantiated by the supporting data that had been submitted. Given the positive finding in the standard ICH genotoxicity battery and the absence of toxicity in the dose ranging study, the executive-CAC concluded that the data provided were not sufficient for the committee to provide concurrence on the doses selected or a recommendation for a 2-year rat study. The committee suggested two possible options: (1) provide adequate data to support their claims, or, (2) conduct a 90-day dose-finding study for the purpose of basing the doses selected on MTD.

As evidence of excessive toxicity in the genotoxicity study, the sponsor cited a reduction in the mitotic index (MI). The reduction in MI was 64% in the original preparation and subsequently never exceeded 69% with all other preparations tested in which evidence of a genotoxic effect occurred. The genotoxic response occurred in the absence of S9 (Aroclor 1254-induced rat liver), but not in its presence. The degree of MI reduction under these conditions, however, is not viewed as a basis for negating a positive response in this test system. Cytotoxicity should, by current standards, approximate 50% for a valid study and MI reduction may also be related to cell cycle delay rather than with cytotoxicity.

NDA 21-006 for frovatriptan was submitted to FDA-CDER on January 29, 1999. Upon reviewing the data for this NDA, we found that the doses for the rat carcinogenicity study (8.5, 27 and 85 mg/kg/day) were the same as originally proposed by the sponsor. It was also noted that the treatment of the rats for the carcinogenicity test had been initiated on 4/12/96, approximately three weeks after the protocol had been submitted to FDA and two months before the executive-CAC meeting of 4/12/96. Dosing for the mouse carcinogenicity test was initiated on June 27, 1996, but a protocol for the mouse study had not been submitted to FDA.

Dosing for the 3- and 6-month rat studies that could have contributed to the carcinogenicity study dose selection were initiated on August 15, and September 17, 1996, respectively, by which time the rat carcinogenicity test had been in progress for over 4 months.

The Executive-CAC met on April 27, 1999, to evaluate the adequacy of the completed 2-year rat and 84-week mouse carcinogenicity studies for frovatriptan (NDA 21-006). The committee agreed that the drug was positive in the genotoxicity study and that dose selections for both carcinogenicity studies should not be based on AUC ratios. The sponsor was informed of this recommendation and was invited to participate in a full CAC meeting to discuss the acceptability of the carcinogenicity studies.

Since the conduct of the original positive genotoxicity assay, two additional preparations of frovatriptan have been tested for induction of chromosome aberrations in cultured human lymphocytes. Positive responses for genotoxicity were also observed with these preparations.

Based on metabolism and toxicokinetic data submitted with the NDA, the sponsor has established that metabolic pathways are basically similar for the rat and human, although differences in pharmacokinetics may exist. The parent compound and virtually all metabolites identified in the blood of rats would be expected to be present at concentrations that are substantially higher than in humans receiving a clinical dose.

Other issues:

The current standard duration of the mouse carcinogenicity studies is 104 weeks, while the sponsor's study was of 84 weeks duration.

In a bacterial reverse mutation assay (Ames Test), one of the frovatriptan preparations was mutagenic for *E coli* WP2 uvra pKM 101, also in the absence of S9 but not in its presence. Other preparations were not found to be positive in this assay, but there may have been a trend towards a positive result.

Sponsor's Presentation:

Dr. Chris Powell discussed the clinical use, chemical structure, genotoxicity, and mouse and rat carcinogenicity, and gave overall conclusions for Vanguard.

Genotoxicity:

Chromosome aberration tests were positive only at significant levels of mitotic inhibition, in the absence of S9, at 20 hours but not at 44 hours. It was noted that the concentration tested as positive was approximately 24,500 fold human plasma levels. The aberrations were only gaps and breaks. (Breaks alone were also positive.) They concluded from the totality of data that there was not biologically relevant genotoxicity.

Therefore, they concluded that the use of multiples of clinical exposure is an acceptable basis for the selection of high doses for the carcinogenicity studies.

(Discussion: It was noted that the multiple of exposure concentrations were not considered in evaluation of the relevance of genotoxicity findings (particularly in vitro findings) unless the mechanism of the genotoxicity were clearly identified and could be ruled out as occurring at lower exposure multiples.)

Mouse Carcinogenicity Study:

Mouse carcinogenicity studies were done at dose levels of 4, 13, and 40 mg/kg/day, with mean daily AUC ratios at the top dose of greater than 100 and mean monthly AUC ratios greater than 4,000 on the basis of one migraine attack a month. There was no effect on the incidence of neoplasia.

(Discussion: It was noted that the monthly comparative ratio was not considered appropriate as the clinical indication did not limit use to once monthly and that the one month exposure comparison did not consider the likely total months of exposure in the mouse versus the patient population. Also, the exposure ratios did not take into account the different proportions of parent versus metabolites across species that would reduce the ratio by approximately 1/3.)

Rat Carcinogenicity Study:

Dose levels were 8.5, 27, and 85 mg/kg/day; mean daily AUC ratio was greater than 165 at the top dose. No increase of malignant tumors was seen; and there was an increase in benign pituitary and adrenal tumors. The sponsor indicated that the doses used were likely within several fold of an MTD based on renal toxicity in decedents and lower overall survival in the HD and LD group.

(Discussion: The same issues as discussed above for exposure in mouse apply to rat. When all rats were included in the assessment of renal toxicity, not only decedents, there was no association of toxicity with drug treatment and survival in the MD group was unaltered by drug treatment, calling into question whether there was evidence of drug toxicity in the study.)

Sponsor's Conclusions:

Overall conclusion was that there is no biologically relevant genotoxicity, thus multiples of clinical exposure should thus be considered acceptable.

The bioassays are adequate to assess potential carcinogenicity

The limited tumor findings are not considered evidence of relevant human risk and the results of the studies support the proposed clinical use of frovatriptan.

During questioning, the sponsor stated that the rat bioassay high dose produced minimal toxicity which they believed indicated that the dose tested was within one dose multiple of the MTD. They doubted the clinical significance of additional information

from further testing in the rat. On the mouse bioassay, the sponsor felt that higher doses could have been used, but that those chosen were adequate (based on exposure multiples). If an additional mouse bioassay is requested by the agency, the sponsor requests that it be a conventional bioassay so that results can be compared with existing data and so that the existing data for dose setting could be used. They also felt that there is more historical data to aid in interpretation of results. The sponsor further requested that any additional requirements be post-approval requirements.

FDA's Presentation:

Dr. Sid Stolzenberg's presentation made the following points:

The tables presented by Dr. Powell (at this meeting) for kidney histopathology findings in the carcinogenicity study (to support their view that they were close to an MTD) were based on decedent animals. The effects were no longer apparent when based on all 60 animals in each dose group. These tables had not previously appeared in the report.

In the 2-year Rat study, the length of the study and animals surviving were adequate. Body weight decrease of more than 10% at HD was not achieved, and severe clinical signs of pharmacological effects were not apparent. As a result, it is not clear what dose represents an MTD. The high dose should have been based on MTD instead of AUC given the positive finding in the genotoxicity battery. The genotoxicity finding should not be dismissed as resulting from inappropriate levels of toxicity.

The 84-week mouse study was not in accord with current standards for study duration. There were not adequate body weight decreases, nor severe clinical signs of pharmacological effects, nor indications of drug-related toxicity of any kind to suggest that an MTD was used or approximated.

He also pointed out that the Exec CAC agreed that the drug was genotoxic in the assays conducted and that the doses selected for the rat and mouse studies were thus inadequately selected.

Summary of Discussion:

Joe DeGeorge went over the guidance on using AUC to calculate the doses. The guidance indicates that only drugs not positive in the standard genotoxicity assays are considered for dose selection using kinetic endpoints. In discussion one of the sponsor's consultants indicated that although he did not believe the studies indicated that the drug was genotoxic, he acknowledged that the assay was positive and that further follow-up studies could be conducted to better evaluate the basis of the response. The sponsor acknowledged the positive findings and asked that the remaining discussion be focused on what additional studies should be done, given that

their drug has been judged to be positive in genotoxicity testing.

The question was posed how to rule out a genotoxic contribution to the tumor response already observed in the rat when both the rat and the mouse studies may not have comprehensively evaluated the tumorigenic potential of the drug. It was acknowledged by members of the CAC that if positive findings had not been observed in the genotoxicity studies there would be less concern for the tumor response observed and the dose selection could have been viewed as adequate based on multiples of the AUC.

The sponsor expressed the opinion that a 2-year mouse assay would be most informative (already have an 18-month mouse study). It was questioned as to how this would help to explain the genotoxic contribution to the carcinogenic action of the drug already observed in the rat albeit at possibly inadequate doses. It was noted that the 2-year study results could not be combined with the 84-week study results to determine a no effect level if the 2-year study were positive. It was also noted that the dose range study is conducted for one month, and the final results available within nine months for transgenic assays compared to the nearly three years it would take to conduct and complete a standard 2-year mouse study.

The sponsor suggested that *in vivo* clastogenicity assays may be more useful to define the scope of the genotoxicity problem. They suggested that an *in vivo* micronucleus in rat or *in vivo* chromosome analysis in bone marrow might be useful additional tests to explore the relevance of the genotoxicity and carcinogenicity observed at the doses tested in rat. It was noted that we already have results from two different genotoxicity studies; the clastogenicity study is clearly positive and the Ames test for mutagenicity could be viewed as equivocal.

Although the drug clearly does not meet the criteria to use AUC to select doses, it could be concluded that the doses used in the rat study are close enough due to the trend for reduced survival in the LD and MD and the renal toxicity, etc. The CAC was asked to consider this in addressing the questions. After additional discussion on the possible use and value of alternative carcinogenicity assays and experience in similar situations, the committee addressed the questions presented.

The vote and summary of comments follows:

Questions - Carcinogenicity Assessment Committee

- 1. Please provide your interpretation of the results of the 3 *in vitro* chromosomal aberration assays in human lymphocytes, addressing the following points:**
 - a) Do you believe that the inhibition of mitotic index was excessive (64% to 69%), thereby invalidating the assays? At the high dose, or all doses?**

this shows that the MTD is close to the high dose tested, then the study may be considered adequate.

- There was no evidence that the study was close to the MTD. The effect on survival seen only in males at LD and HD was probably random.

4. If you conclude that frovatriptan is genotoxic, and that the carcinogenicity studies have not been conducted at doses that constitute an MTD or other acceptable endpoint, what do you recommend?

- The male arm of the rat study is OK/ the sponsor could choose an alternative mouse or 2-year mouse study.
- Another mouse study should be done; the p53 study would be most informative. If either study conducted is negative, accept overall results as an adequate assessment of carcinogenicity.
- Either repeat both the rat and mouse 2-year studies at MTD doses or do P53 mouse, if it is negative, accept as an adequate assessment of carcinogenicity (non-genotoxic carcinogen with adequate exposure margin)
- Since the sponsor agreed to perform another mouse carcinogenicity study, they should consider doing a P53 or neonatal mouse assay to address whether the positive findings in the genotoxicity assay is relevant to carcinogenesis. If it is a non-genotoxic carcinogen (only positive in rat while negative in alternative assays), the rat carcinogenicity study would not need to be repeated as there is an adequate margin of exposure to assess human risk.
- Conduct 2 appropriate studies to assess carcinogenicity.
- An alternative mouse carcinogenicity study could be conducted to determine if the compound is a genotoxic carcinogen. If 2-year mouse is done, additional genotoxicity data is needed to dismiss the relevance of positive genotoxicity findings in relation to the positive findings in rats. This should include a 28-day repeat dose micronucleus/chrom ab assay and in vitro human lymphoblastoma assay. Any positives in these assays would raise additional concern.

a) Should 3-month dose ranging studies be repeated? Note that the 3- and 6-month rat studies that were submitted used doses of 10, 100 and 1000 mg/kg/day with 100 being a NOAEL and the 3-month mouse study used 5, 50 and 500 mg/kg/day with 500 being a NOAEL.

Yes (11); No (4)

Comments:

- It is possible that repeating the 3-month studies (rat, mouse) could demonstrate that the current studies were within a reasonable range of the MTD and the studies done may be an adequate assessment of the carcinogenicity of the drug based on the

findings observed in the study(s).

- 3-month studies should be performed using dose levels of approximately 125, 250, 500, and 1000 mg/kg/day in both rat and mouse
- The sponsor could use the 6-month data to support an MTD; clearly 1000 exceeds the MTD so it's not unreasonable to select 500 as the MTD. (There would be no need to repeat range-finding study if 500-600 mg/kg is used as the highest dose; the MTD is somewhere between 100 and 1000.)

b) Would you recommend 2 bioassays or a rat bioassay and a mouse alternative model? (votes)

(Answers assume doses used in rat are not found to be close enough based on dose ranging study)

- Either is okay (5)
- Alternative plus 2 year rat (5)
- Alternative only, no need to do rat (4)
- Two standard assays (2)
- No further testing is needed (2)

c) If you recommend a mouse alternative model, which one do you recommend?

- P53 (8) – would address potential genotoxicity and carcinogenic potential
- One that detects genotoxic carcinogens (2)

/S/
8/22/99
Joseph J. DeGeorge, Chair

cc:

/Division File, HFD-120, NDA 21-006
/GFitzgerald, HFD-120
/SStolzenberg, HFD-120
/AChen, HFD-120
/ASeifried, HFD-024

Executive CAC Minutes
January 18, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Alexander Jordan, Ph.D.
Ronald Steigerwalt, Ph.D., HFD-510, Alternate Member
Glenna Fitzgerald, Ph.D., HFD-120, Team Leader
Sidney Stolzenberg, Ph.D., HFD-120, Presenting Reviewer
Author of Draft: Sidney Stolzenberg, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 21-006

Drug Name: frovatriptan succinate monohydrate (Miguard™), 2.5 mg tablet

Sponsor: Vanguard Medica Ltd. (England)

Sponsor's Contact: _____

Background: Sponsor had agreed to perform a mouse p53 bioassay to satisfy the preclinical deficiencies for this NDA. An NDA amendment was received by CDER on 12/10/99, which contained the summary of results for a dose-finding study in the wild type C57B1/6 mouse and a protocol for the definitive study in the p53 heterozygous C57 B1/6 mouse.

Doses used in the dose-finding study were 200, 400, 800/600, and 1600 mg/kg/day. There were 6/sex in treated and control groups and 18/sex in the satellite, frovatriptan-treated groups, which were used for toxicokinetics. Blood samples from animals in the satellite groups had been obtained on Day 28 of treatment.

A dose of 1600 mg/kg was acutely lethal, with the majority of males and females dying within the first 24 hours of dosing. At 800 mg/kg/day, 3/24 males and 1/24 females died during the first 2 days of dosing so that the dosing was lowered to 600 mg/kg/day on the 3rd day. An additional male and 2 additional females died after the dosage had been lowered to 600 mg/kg/day. No other dose limiting effects, such as body weight gain, clinical pathology, clinical signs or target organ histopathology, were observed.

In the protocol for the definitive 6-month study with p53+/- mice, doses proposed were 20, 62.5, 200 and 625 mg/kg/day, with groups of 15/sex/group in the main study and 18/sex/group in the satellite toxicokinetic study.

On December 21, 1999, Dr. Chris Powell, toxicologist for the sponsor, had been informed by e-mail that arrangements had been made for an executive-CAC meeting on January 18, 2000 to decide on the adequacy of the doses for the proposed protocol. Shortly after the New Year, Dr. Powell informed the reviewing pharmacologist by telephone that Vanguard Company officials had decided to initiate the p53-mouse study according to their originally proposed protocol, without awaiting comment from the

executive-CAC. Within a few days after initiation of dosing, 2 animals on high dose had already died.

The Executive-CAC could not concur with the doses being used by the sponsor in their ongoing 6-month study with the p53 mouse because of deaths in the dose-finding study at 800/600 mg/kg/day (and further confirmed in the main study at 625 mg/kg/day). The Committee would have concurred with a high dose of 400 mg/kg/day and raised concerns for the dose spread of the existing study design.

Recommendations:

Given that the study had already been initiated, it is suggested that the sponsor lower the 625 mg/kg/day dose to 400 mg/kg/day immediately, provided there is still adequate survival. It is further recommended that this dose level be supplemented with animals being treated for kinetic assessments at the 625 mg/kg dose level. It is also important to know if there are deaths at the 200 mg/kg/day dose because the doses may have to be scaled back even further.

The Committee stressed that such detailed toxicokinetics, as proposed in the protocol, is not needed at all dose levels.

The Committee recommended that the sponsor provide the report of the supplementary human lymphocyte chromosomal aberration assay that contributed to their scientific rationale for use of the p53 assay.

ISI - 1/21/00
Joseph DeGeorge, Ph.D.
Chair, Executive CAC

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- /SStolzenberg, HFD-120
- /CSO/PM, HFD-120
- /ASeifried, HFD-024

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**Executive CAC Minutes
March 14, 2000**

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Nakissa Sadrieh, Ph.D., HFD-160, Alternate Member
Glenna Fitzgerald, HFD-120, Team Leader
Sidney Stolzenberg, Ph.D., HFD-120, Presenting Reviewer
Author of Draft Minutes: Sidney Stolzenberg, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 21-006

Drug Name: frovatriptan succinate monohydrate (Miguard™), 2.5 mg tablet
Sponsor: Vanguard Medica Ltd. (England)

Background

At a meeting of the full CAC on 7/29/99, it was agreed that the AUC option was not valid for selection of the highest doses in the rat and mouse carcinogenicity studies because the drug was clastogenic in cultured human lymphocytes. Highest doses should have been based on the MTD. Sponsor was given various options for correcting these deficiencies. They chose to perform a 26-week p53 mouse carcinogenicity study and a second 3-month rat dose-finding study. If the dose-finding study demonstrated that the MTD is within 2-3 times the highest dose used in the previously performed 2-year rat carcinogenicity test (85 mg/kg/day), it was agreed that a second 2-year rat study would not be required (See minutes of meeting on 7/29/99, by A. Seifried). The occurrence of treatment-related renal lesions was considered to be a dose limiting effect because compound-related deaths attributed to nephropathy were observed at 1000 mg/kg/day in the 26-week rat study. Renal lesions of similar incidence and severity were also seen at 1000 mg/kg/day in a 13-week study, but deaths had not yet occurred by 13 weeks.

Three-Month Rat MTD-Finding Study

The study design involved daily oral gavage treatment of 10 rats/sex/group (CrI:CD(SD)IGBR strain) with doses of 0, 150, 255, 440 and 750 mg/kg/day for 13 weeks. An additional satellite study for toxicokinetics consisted of 9/sex/group

Results: (limited to mortality and compound related effect on target organs)

Mortality: In both the main and satellite studies, there were 3 deaths at 440 mg/kg/day (1 male, 2 females) and 1 male at 150 mg/kg/day. Causes of deaths could not be determined, but were not associated with renal or other target organ lesions. There were no deaths at 250 or 750 mg/kg/day.

Histopathology of Target Organs

In kidneys, an increase in incidence and severity of focal tubular basophilia/regeneration in 750 mg/kg/day treated males (8/10) was clearly evident, but only a small increase in number of females (2/10) with a moderate or severe lesion, was seen. In males at 440 mg/kg/day, there was only 1 of 9 with a renal lesion that was slightly more severe than controls. In females at 440 mg/kg/day, no effect on renal histopathology was evident. The dose of 440 mg/kg/day is 5.2-fold higher than 85 mg/kg/day (highest dose in the rat carcinogenicity study) and does not meet CAC's criteria (of within 2 to 3 fold) for acceptability of the 2-year study.

In addition to the routine kidney histopathology, bromodeoxyuridine (BrdU) was administered by mini-osmotic pump for the final week to 5/sex/group of the satellite study. In both sexes, an increase in labeling of the renal papilla was limited to 750 mg/kg/day. In S3 proximal tubules, a dose-related increase in labeling index was seen in all male treated groups (not in females).

A prominent zona glomerulosa (minimal to slight effect) was seen in some animals of all treated male groups, but only at high dose in females. The presenting reviewer initially dismissed the adrenal histopathology findings as being relevant for estimating the MTD because it was not considered as a possible dose limiting effect either by the sponsor or the reviewer. In the meeting it was pointed out that adrenal cortical hormones and urinary excretion of the drug may have an influence on renal histopathology and that this may be a signal for the later occurring renal toxicity. It was also noted that this relationship was tenuous based on the information available.

Substantial bioaccumulation of frovatriptan with increased time of administration has been repeatedly shown to occur. Based on blood AUC levels found on Day 1, Week 5 and 12 in the MTD-finding study, sponsor estimated that the blood AUC levels found for the 255 mg/kg group after 52 weeks would be about the same as that found for 440 mg/kg/day after 12 weeks. However, there was no convincing data to show that blood AUC levels would continue to rise beyond 12 weeks at the extent predicted by the sponsor. Ratios of rat:human blood AUC levels for frovatriptan were high, even after a single dose at 150 mg/kg/day in the present study and at 85 mg/kg/day in the carcinogenicity study.

Sponsor concluded that the NOEL for the MTD-finding study was 150 mg/kg/day, based on BrdU labeling of kidneys in males, but did not specify an MTD.

Conclusions and Recommendations by the Executive-CAC:

The committee indicated that the MTD for males may be around 255 mg/kg/day, but for females exceeded 440 mg/kg/day (more than 2 to 3-fold times the high dose used in the carcinogenicity study). Looking at all factors, the high levels of exposure after treatment with frovatriptan, the type of carcinogenic risk of clinical significance from an intermittently used product, and the ongoing p53 mouse study, the committee concluded that the rat carcinogenicity study, in conjunction with the previously conducted mouse study and an adequate and clearly negative p53 mouse study would constitute an

adequate assessment of the carcinogenic potential of frovatriptan. They recommended that a rat carcinogenicity study need not be repeated provided there is a clearly negative study in the p53 mouse. If the p53 study is positive or equivocal, a rat carcinogenicity study may be necessary to draw an adequate conclusion regarding the carcinogenic potential of frovatriptan.

Regarding the ongoing p53 study, the committee suggested that the sponsor should consider moving animals at high dose from the satellite toxicokinetic study to the main study, so that the total number in the high dose group would be 20/sex or more. This could be helpful in making sure that the study is adequate. The committee advised that assignment of the extra animals to the main study should be done by randomization early in the study.

ISI - 03/17/00
J. DeGeorge

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/SStolzenberg, HFD-120
/LChen, HFD-120
/ASeifried, HFD-024
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TABLE 2 - MEAN CHROMOSOMAL ABERRATIONS AND MITOTIC INDICES

Treatment		Mean % Aberrant Cells Excluding Gaps	Mean % Mitotic Index
Whole blood			
Solvent Control	10 µl/mL	0.50	9.4
Mitomycin C	0.2 µg/mL	40.00**	4.7Δ
Frovatriptan			
	1000 µg/mL	6.00**	6.8
	500 µg/mL	1.00	6.5
	50 µg/mL	0.50	8.2
Separated lymphocytes			
Solvent Control	10 µl/mL	4.00	5.1
Mitomycin C	0.2 µg/mL	48.00**	1.4Δ
Frovatriptan			
	500 µg/mL	12.00**	2.8
	250 µg/mL	6.00	4.8
	50 µg/mL	6.50	4.2

** Statistically significant increase in the percentage of aberrant cells at $p < 0.01$ using Fisher's Exact Test (one-sided).

Δ Positive control mitotic index and % aberrant cells are determined from a single culture.

Incidence of selected microscopic findings in the adrenal - terminal kill

Tissue and finding		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Adrenal prominent zona glomerulosa	No. examined:	10	10	10	9	10	10	10	10	9	10
	Grade -	10	3	3	0	0	10	10	10	9	5
	1	0	7	7	9	9	0	0	0	0	4
	2	0	0	0	0	1	0	0	0	0	1
medullary atrophy	Grade -	10	10	10	4	0	10	10	10	4	0
	1	0	0	0	5	8	0	0	0	5	2
	2	0	0	0	0	2	0	0	0	0	8

Key: "-" = finding not present, 1 = minimal, 2 = slight

Incidence of selected microscopic findings in the thyroid - terminal kill

Tissue and finding		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Thyroid follicular cell hypertrophy	No. examined:	10	10	10	9	10	10	10	10	9	10
	Grade -	9	10	8	7	4	9	9	8	8	3
	1	1	0	2	2	4	1	1	2	1	5
	2	0	0	0	0	2	0	0	0	0	2

Key: "-" = finding not present, 1 = minimal, 2 = slight

APPEARS THIS WAY
ON ORIGINAL

3-Month Dose-Finding Study (Report No 1165/80-1050). Doses administered were 0, 10, 100 & 1000 mg/kg/day in groups 1-4, respectively.

Incidence and severity of tubular basophilia/regeneration in the kidney									
Tissue and finding		Group and sex							
		1M	2M	3M	4M	1F	2F	3F	4F
Kidney	Number examined	10	10	10	10	10	10	10	10
	Number with tubular basophilia/regeneration	1	2	3	8	2	2	3	10
	Grade								
	1	1	2	3	3	2	2	3	3
	2	0	0	0	2	0	0	0	5
	3	0	0	0	3	0	0	0	2

Key : Grade 1 = minimal, 2 = slight, 3 = moderate

6-Month Rat Study (Report No 1165/33-1050). Doses administered were 0, 10, 100 & 1000 mg/kg/day in groups 1-4, respectively.

Incidence of selected histopathology findings in the kidney - terminal kill									
Tissue and finding		Group and sex							
		1M	2M	3M	4M	1F	2F	3F	4F
Kidney	Number examined	20	20	19	15	20	18	19	19
Tubular nephropathy	Grade -	20	20	19	3	20	18	19	11
	1	0	0	0	4	0	0	0	2
	2	0	0	0	1	0	0	0	2
	3	0	0	0	6	0	0	0	3
	4	0	0	0	1	0	0	0	1

Key: Grade - = finding not present, 1 = minimal, 2 = slight, 3 = moderate, 4 = marked.

APPEARS THIS WAY
ON ORIGINAL