

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-132/S-015

ADMINISTRATIVE DOCUMENTS



MEMORANDUM

Date: June 30, 2003
From: Armando Oliva, MD
To: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
Subject: Team Leader Memorandum for NDA 20-132 SCF 015, Imitrex Tablets

This NDA supplement contains information for a new fast disintegrating tablet (FDT). The sponsor intends to replace the existing marketed tablet with this new tablet. The submission contains CMC information as well as the results of four studies to show that the FDT is bioequivalent to the currently marketed tablet. Dr. Heimann performed the chemistry review, and Dr. Jackson performed the OCPB review. Both reviewers recommend approval.

The four studies are listed below.

- SUM10948 Pilot relative bioavailability of two FDT vs. currently marketed Imitrex 50mg. Study 948 was used to determine the best sodium bicarbonate formulation for future studies and was not formally reviewed.
- SUM10950 Bioequivalence of FDT vs. Imitrex tablets. Study 950 compared the 50mg and 100mg FDT tablet to the marketed 50mg and 100mg tablets in healthy male and female volunteers in the fasted state.
- SUM10954 Food vs. Fasting study of FDT vs. Imitrex tablets. Study 954 compared the 100mg FDT, both fed and fasted, with the currently marketed 100mg tablet, fed and fasted.
- SUM10961 Bioequivalence of FDT dissolved in water vs. Imitrex tablets. Study 961 compared the 100mg FDT dissolved in water with the currently marketed 100mg tablet.

Dr. Jackson concludes the following:

1. FDT 50mg and 100mg are bioequivalent to the currently marketed 50mg and 100mg tablets, based on C_{max} , $AUC_{0 \rightarrow \infty}$, and $AUC_{0 \rightarrow t}$ under fasting conditions
2. FDT 50mg has a 23% lower C_{max} after food compared to the marketed tablet
3. FDT 50mg has a 15% and 12% higher C_{max} and AUC after food compared to the fasting state for FDT
4. T_{max} tended to be slightly earlier for the FDT compared to the marketed tablet.

I refer the reader to Dr. Jackson's review for the details of the individual studies that were reviewed. All three were traditional PK studies in normal healthy volunteers using a crossover design. I present the highlights in this memo.

Figure 1 shows the concentration vs. time profiles of the 4 tablets tested in the fasted state. As one can see, the curves are almost super-imposable for the 50mg and 100mg FDT and currently marketed tablets. Table 1 shows the various PK parameters in support of bioequivalence in the fasted state. (Both taken from the OCPB review, page 9)

Figure 1: Study 950 – Concentration vs. Time Profiles

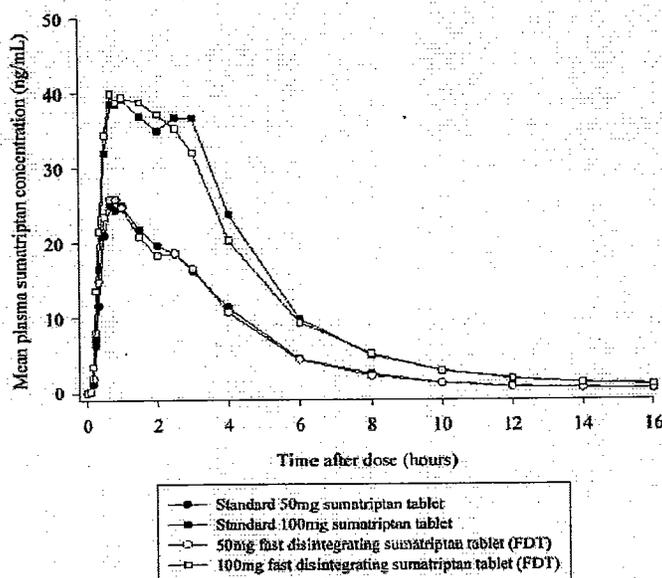


Table 1: Study 950 – Pharmacokinetic Parameters

Parameter [units]	50 mg Standard Tablet [A]	100 mg Standard Tablet [B]	50 mg FDT [C]	100 mg FDT [D]
N	30	31	31	30
Primary				
AUC _(0-∞) [ng.h/mL] ¹	105 (55.6)	167 (50.2)	103 (49.0)	199 (105)
AUC _(0-t) [ng.h/mL]	98.5 (48.5)	190 (106)	97.1 (43.1)	185 (91.3)
C _{max} [ng/mL]	29.1 (12.3)	53.2 (29.0)	30.0 (12.5)	52.2 (21.3)
Secondary				
t _{max} [h] ²	1.00 (0.50 – 4.00)	1.00 (0.50 – 4.00)	0.83 (0.33 – 3.00)	1.00 (0.33 – 3.00)
AUC ₍₀₋₂₎ [ng.h/mL]	37.8 (16.2)	61.2 (24.1)	38.2 (15.8)	64.8 (22.6)

- Actual number of subjects with sufficient data for analysis A (N = 23), B (N = 21), C (N = 24), D (N = 23);
- Median (range)
- FDT = Fast disintegrating tablet

Study 954, the food study, provided some interesting results (Table 2, taken from the OCPB review, table 8, page 13).

Table 2: Study 954 – Pharmacokinetic Parameters

Parameter [units]	100 mg Standard Tablet [A]-after food	100 mg FDT Tablet [B]-after food	100 mg FDT Tablet [C]-fasted
N	28	29	27
AUC _(0-∞) [ng.h/mL] _a	265 (69)	254 (64)	218 (55)
AUC ₍₀₋₁₎ [ng.h/mL]	258 (71)	246 (65)	213 (52)
C _{max} [ng/mL]	77.1 (21.7)	59.6 (18.0)	50.8 (14.4)
AUC ₍₀₋₂₎ [ng.h/mL]	85.4 (34.6)	66.1 (35.6)	61.8 (19.0)
t _{max} * [h]	1.50 (0.58 4.00)	2.00 (0.50 4.00)	2.00 (0.50 3.98)

A (n = 26), B (n = 28), C (n = 26)
 * Median (range)
 FDT = fast disintegrating tablet

It shows that the C_{max} of the FDT after food is *higher* compared to FDT fasted, but *lower* compared to the currently marketed tablet in the fed state. The AUC of the FDT after food is also higher compared to FDT fasted, but is about the same as the currently marketed tablet in the fed state.

I find this observation interesting because of the following statement that currently exists in the pharmacokinetics section of approved Imitrex tablet labeling:

Food has no significant effect on the bioavailability of sumatriptan, but delays the T_{max} slightly (by about 0.5 hours).

The results of this study are incompatible with this statement. This statement implies that the C_{max} of the currently marketed tablet is similar both in the fed and fasted state. If this is true, it is impossible for the FDT to have a *higher* C_{max} in the fed state compared to fasted while at the same time have a *lower* C_{max} compared to the currently marketed tablet after food.

Either, the current statement in labeling is wrong, or the results of the current study cannot be true. By every indication, study 954 is a valid study. I discussed this discrepancy with Dr. Baweja. He looked at the original sumatriptan application. He tells me that this statement is based on data using higher doses than what are currently approved, and we cannot, in retrospect, assure the quality of that data or its relevance to lower doses.

Therefore, in order for the results of the current study to be true (and consistent with study 950 which shows bioequivalence in the fasted state), there must exist an even larger

they are proportional to the 50mg tablet and the kinetics are linear between 25mg and 100mg, and the dissolutions are similar, OCBP opines that the in vivo bioequivalence requirement for the 25mg FDT tablet can be waived.

Safety

Since the PK studies used approved doses, and the FDT is bioequivalent to the currently marketed tablet, I did not expect an unusual safety profile for the FDT and did not perform an exhaustive review of the safety data generated by these small PK studies. In general, the adverse events reported by subjects taking the FDT were similar in number and nature compared to those reported by subjects taking the currently marketed tablet. There appeared to be a dose-related increase in AE's, as is seen with the approved sumatriptan tablets. There were no deaths and no serious adverse events. There were two adverse dropouts (coughing/respiratory disorder, and severe headache/nausea/vomiting). The majority of the AE's were mild in intensity (82%).

The sponsor submitted a 4-month safety update on 6/19/03. Although the PK studies were completed at the time of the original submission, there were two studies using the FDT which were referenced in the original submission only in a table contained in an appendix (studies ' _____ and _____) _____

_____ . However, the safety data available from these two studies indicate that there were no deaths, or serious adverse events. There was one adverse dropout of a patient who experienced depression and withdrew from the study prior to taking any study medication.

In summary, the safety profile seen in these studies are similar to that seen with the currently marketed tablets and I see no new safety signal.

Labeling

The sponsor proposes the following changes to labeling:

Pharmacokinetics: The mean maximum concentration following oral dosing with 25 mg is 18 ng/mL (range, 7 to 47 ng/mL) and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. This compares with a C_{max} of 5 and 16 ng/mL following dosing with a 5- and 20-mg intranasal dose, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The bioavailability is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption. The C_{max} is similar during a migraine attack and during a migraine-free period, but the T_{max} is slightly later during the attack, approximately 2.5 hours compared to 2.0 hours. When given as a single dose, sumatriptan displays dose proportionality in its extent of absorption (area under the curve [AUC]) over the dose range of 25 to 200 mg, but the C_{max} after 100 mg is approximately 25% less than expected (based on the 25-mg dose).

_____ A food effect study involving administration of IMITREX

Tablets 100 mg to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased by 15% and 12%, respectively, when administered in the fed state.

I find these changes acceptable.

Dr. Heimann recommends the following sentence at the end of the description section. I find this change acceptable and the sponsor has already agreed to them.

Each tablet also contains the inactive ingredients croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium bicarbonate.

In summary, I recommend approval of this application based on the finding of bioequivalence between the FDT and the currently marketed tablets.

Armando Oliva, M.D.
Neurology Team Leader

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/s/

Armando Oliva
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MEDICAL OFFICER

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MEMORANDUM

Date: November 3, 2003
From: Martha R. Heimann, Ph.D., Chemistry Reviewer, HFD-120
Through: Maryla Guzewska, Ph.D., Chemistry Team Leader, Neurology Drugs, HFD-120
To: NDA 20-132/S-015
Subject: Completion of Methods Validation for Imitrex® (sumatriptan succinate) Tablets

NDA 20-132/SCF-015, which provided for reformulation of Imitrex Tablets and new HPLC methods for *Assay* and *Drug related impurities* was approved, prior to completion of methods validation, on June 30, 2003. The methods validation assignment was sent to the Philadelphia District Laboratory. Validation studies were completed by the laboratory on October 7, 2003.

The Philadelphia District laboratory found the *Assay* and *Drug related impurities* procedures to be suitable for regulatory purposes.

The methods have been verified by an FDA laboratory. These are now the regulatory methods.

Martha R. Heimann, Ph.D.

Attachment: (paper copy to archival NDA only)
Philadelphia Laboratory Validation Report

cc: Orig., NDA 20-132
HFD-120/Division File
HFD-120/MGuzewska/initialed MG 11/3/03
HFD-120/MHeimann
HFD-120/PM/LChen

Filename: C:\DATA\WORD\#NDA\N21-231\21231MV_COMPLETE_MEMO.DOC

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/s/

Martha Heimann

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CHEMIST

Methods Validation complete. Paper copy initialed by M. Guzewska
on 11/3/03

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-132/S-015

CORRESPONDENCE



NDA 20-132\S-015

INFORMATION REQUEST LETTER

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Mary-Kaye Whisler, Ph. D.
Assistant Director, CMC New Submissions
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Whisler:

Please refer to your February 28, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imitrex® (sumatriptan succinate) Tablets.

We also refer to your submission dated March 14, 2003, May 16, 2003 and May 23, 2003.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1) With regard to regulatory specifications for the drug product we have the following concerns:
 - a) You propose deletion of the current regulatory _____ procedure for identification of sumatriptan and addition of a non-specific procedure for identification by _____
_____. No justification for use of a less specific procedure was provided.
 - b) For the proposed — identification procedure, you state that "This test may be performed as described below or concomitantly with either the uniformity of dosage units or the dissolution test." No test procedure is described.
- 2) _____
_____ Based on the statistical analysis and the available primary and supportive stability data we will accept a tentative 24 month expiration dating period. _____
- 3) The post-approval stability protocol should be amended to specify that the first three production batches of each strength will be placed on stability.
- 4) The *How Supplied* section (last sentence) of the package insert should be revised to read:

-
- 5) Please provide an estimated time frame for replacement of the current approved products with the sumatriptan succinate FDT formulations. Specifically, how long would be there two products in commercial distribution?

If you have any questions, call Lana Chen, Regulatory Management Officer, at (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

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Maryla Guzewska
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