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APPLICATION NUMBER: NDA 20-353/S-001

ADMINISTRATIVE DOCUMENTS

MAR 20 1996

NDA 20-353

LABELING REVIEW OF NDA

NDA 20-353(S001)

Submission Date: February 15, 1996
Admendment date: March 5 and 11, 1996
Review Date: March 11, 1996

Applicant: Elan Pharmaceutical Research Corp.
1300 Gould Drive
Gainesville, Georgia 30504-3947

Applicant's Representative: Sharon L. Hamm, Pharm. D., R.Ph.
(770) 534-8239

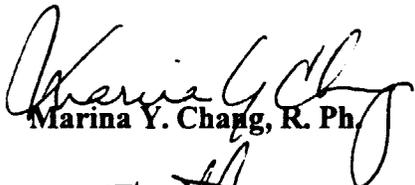
Drug: NAPRELAN (naproxen sodium tablets) CONTROLLED-
RELEASE TABLETS, 375 mg, 500 mg and 750 mg.

Pharmacologic Category: NSAID

Submitted: Draft package insert labeling.

Reviewer's Comment: The supplement was originally submitted on February 15, 1996 requesting and expedited review for the deletion of "Due to the gastric pH elevating effects of H2-blockers, sucralfate, and intensive antacid therapy, concomitant administration of NAPRELAN is not recommended." in PRECAUTIONS, Drug Interactions section. The removal of this statement has been reviewed and concurred by the Division of Pharmaceutical Evaluation-III.

Recommendation: Approval letter should be sent.


Marina Y. Chang, R. Ph.


James Witter, M.D.

NDA 20-353

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cc: NDA 20-353
HFD-550 —
HFD-550/MO
HFD-550/SChem/CYaciw
HFD-550/SPharm/CChen
HFD-550/Clin/MChang
HFD-550/CSO/SLin
HFD-550/RJoyce RLF 3/20/90

2035301. WAF

MEMO

To: Sue-Ching Lin, CSO
From: E. Dennis Bashaw, Pharm.D. *EDB*
Date: Friday, March 1, 1996
Subject: Napreelan®, NDA 20-353

While preparing the proposed package insert for Napreelan¹ tablets the sponsor, inadvertently, incorporated the following text from the Naprosyn-EC² package insert:

"Due to the gastric pH elevating effects of H₂-blockers, sucralfate, and intensive antacid therapy, concomitant administration of Napreelan is not recommended."

In a telefax of 2/15/96, Elan requested that this text be deleted from the final approved labeling as it does not apply to their product. In order to evaluate their request, the original reviewer of Napreelan was contacted and a copy of his original review was obtained.

First of all it must be noted that even for Naprosyn-EC this comment was based on theoretical concerns. The concern being that these agents could cause a rapid release of naproxen in the stomach, due to the pH sensitive nature of the coating, rather than in the lower GI tract as designed. No specific studies were done with either H₂-blockers, sucralfate, and intensive antacid therapy for the Naprosyn-EC NDA.

By contrast Napreelan is a controlled release formulation of naproxen that was designed, to some extent, to have a pH independent rate of release. In support of this position two types of studies were performed by the sponsor: 1) a food/fasting trial using the FDA high fat breakfast, and 2) in vitro dissolution testing.

In the food/fasting trial, a total of 24 male subjects received the following three treatments in random order:

- a. Naproxen immediate release tablets-fasted
- b. Napreelan-fasted
- c. Napreelan-fed

The results of this trial are summarized below:

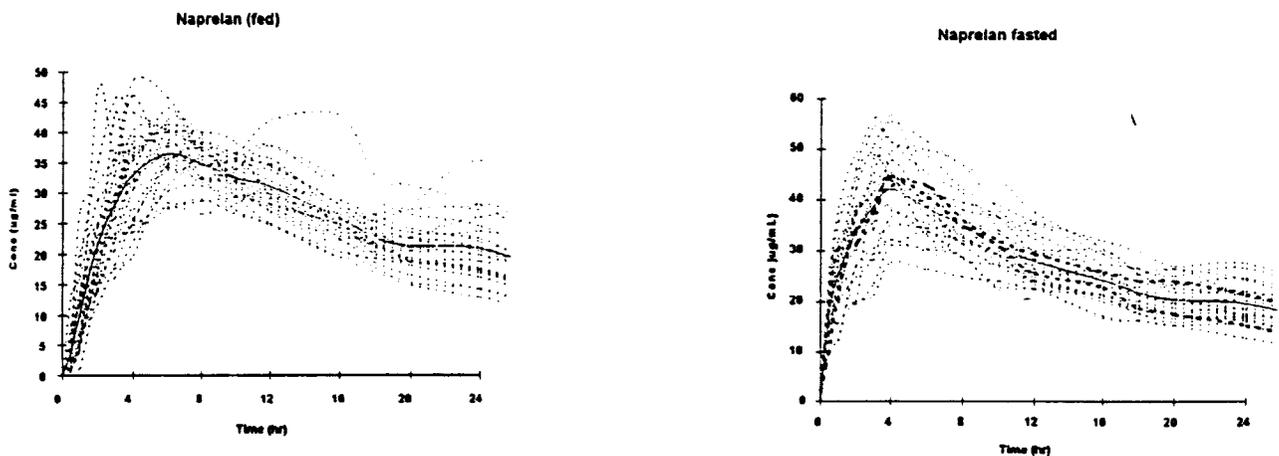
¹ Napreelan is a registered trademark for naproxen controlled release tablets by Elan.

² Naprosyn-EC is a registered trademark for enteric coated naproxen tablets by Roche Pharmaceuticals.

Study 0191001
Naprelan Fed vs. Fasted
(Geometric Mean)

	Naproxen-IR	Naprelan (fasted)	Naprelan (Fed)	90% Confidence Intervals (Naprelan fed vs. fasted)
AUC(0-inf)	1096.48	1096.48	1071.52	95.5-100.0
Cmax(ug/ml)	81.28	42.66	38.9	85.1-97.7
Tmax(hrs)	—	4.13	7.42	n.a.

Reproduced below is a representation of the individual data from this trial:



As one of the primary effects of food is to raise the gastric pH to near neutral levels the lack of a statistically significant difference in either AUC or Cmax suggests that the dosage form is somewhat "pH independent".

As for the in vitro studies, the sponsor conducted a number of in vitro dissolution experiments using various lots of drug and media. The dissolution specification as proposed and accepted by the FDA is as follows:

The mean results of comparative dissolution testing is presented below using a range of dissolution media.

The results of comparative pH dissolution testing suggests that the dissolution of naproxen from the Naprelan dosage form is somewhat pH dependent. At pH's below 4 the solubility of naproxen, due to naproxen's K_a , is very low. With increasing pH there is a definite increase in the observed dissolution rate. It should be noted, however, that even in pH 7.2 media the percent dissolved for Naprelan tablets does not reach the level of naproxen immediate release tablets until 2 hours after dosing. This represents an almost 3 fold increase in dissolution time and suggests that some component of the release mechanism of naproxen from the Naprelan dosage form is somewhat resistant to pH.

Conclusion

After reviewing the material contained in the original NDA review for this product, it is this reviewer's opinion that the sentence in the label, "*Due to the gastric pH elevating effects of H_2 -blockers, sucralfate, and intensive antacid therapy, concomitant administration of Naprelan is not recommended.*" should be removed from the Naprelan label as being inappropriate. Concurrence with this finding was obtained in a meeting on March 1, 1996 with Dr. Nicholas Fleischer, Dir. Div. of Pharmaceutical Evaluation-III.

CC: NDA 20-353 (ORIG),
HFD-550/DIV File
HFD-550/CSO/Lin
HFD-850 (Drug, Chron Files)
HFD-880(Fleischer)
HFD-860 (Malinowski)
HFD-550(Bashaw)
HFD-344(Viswanathan)
HFD-205.