CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708/S-005

ADMINISTRATIVE DOCUMENTS

CSO REVIEW OF DRAFT LABELING

NDA 20-708/S-005 Lupron Depot 3-month (leuprolide acetate for depot suspension) 11.25 mg

Submission Date: February 10, 1999

MATERIAL REVIEWED
Prescribing Information (PI).

Background:
The sponsor has submitted a pharmacodynamic/pharmacokinetic study of Lupron Depot 3.75 mg and 11.25 mg in patients with endometriosis to fulfill a Phase 4 commitment. Additional changes have been made from the original draft labeling submitted with this supplement in response to a teleconference with the sponsor dated February 1, 1999.

Prescribing Information

CLINICAL PHARMACOLOGY section, **"Pharmacokinetics"** subsection, *"Metabolism"* subheading

This subheading has been revised to include a new second paragraph, and replacing a proposed new second paragraph, as requested in a teleconference held February 1, 1999. The new second paragraph reads:

CLINICAL STUDIES section,

Endometriosis subsection,

A new terminal sentence has been added to the first paragraph which reads:

Uterine Leiomyomata (fibroids) subsection

The fourth paragraph has been revised to add a new second sentence which reads:

The fifth paragraph has been revised to add a new third sentence which reads:

PRECAUTIONS section, subsection **6.**

The first word of the first sentence has been revised from

ADVERSE REACTIONS section,

Paragraph 5 has been revised from an original terminal sentence which read:

To:

In addition, Table 3 has been deleted.

CHANGES IN LABORATORY VALUES DURING TREATMENT section, **"Lipids"** subsection

A new terminal paragraph has been added which reads:

A new subsection entitled **"Chemistry"** has been added which reads:

No other changes have been made to this revised draft labeling.

/S/

Christina Kish, CSO 2/10/99

cc:
Orig. NDA
HFD-580
HFD-580/SAllen/JSafran/MMann
HFD-580/CKish/2.10.99/n20708rv.5

Patent Certification

This is to certify that the patent information for the new patent nos. 5,631,020, 5,631,021, 5,643,607 and 5,716,640 which cover the method of manufacturing of Lupron Depot, the subject of this supplemental application has been submitted to the agency previously.

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
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NDA 20-708/S-005
Lupron Depot
TAP Holdings, Inc.

Division Director Memo

The action letter for this application will be signed in the Division. Therefore, a Division Director's Memo is not required.

FEB - 2 1999

Group Leader Memorandum

NDA:	**20-708**
Serial#:	**167**
Drug:	**Lupron Depot®** **Leuprolide acetate depot suspension**
Indication:	**Labeling to Describe Results from a Phase IV Pharmacokinetic/Pharmacodynamic Study Comparing 3.75 mg Lupron Depot® monthly to 11.25 mg Lupron® every 3 months in Patients with Endometriosis**
Dose:	**3.75 mg Lupron Depot®** **11.25 mg Lupron Depot®**
Formulation:	**Suspension**
Route of Administration:	**Intramuscular injection**
Related Products:	**Nafarelin Acetate** **Goserelin Acetate** **Histerelin Acetate**
Applicant:	**Tap Holdings, Inc.**
Original Submission:	**4/3/98**
Review Completed:	**1/21/99**
Date of Memorandum:	**1/21/99**

Background

This application is a labeling supplement based on a phase IV study which was done to demonstrate the pharmacokinetic and pharmacodynamic comparability of two already approved formulations of leuprolide acetate: 3.75 mg (given monthly) and 11.25 mg (given every 3 months). The monthly formulation was approved in October of 1980, and the 3-monthly formulation was approved in March of 1997. Each product is approved for the treatment of endometriosis, and for the treatment of anemia associated with uterine fibroids. The sponsor would like to use the data from the phase IV study to add labeling claims about the comparable pharmacokinetics and pharmacodynamics of each product.

Clinical Trial Data

The sponsor completed a single trial comparing the pharmacokinetic and pharmacodynamic activity of the once-monthly (3.75 mg) versus the 3-monthly (11.25 mg) formulations of leuprolide acetate depot suspension. Twenty patients were randomized to the 3.75 mg dose group, and 21 were randomized to the 11.25 mg dose

group. Efficacy parameters included clinical assessments of patient pain, patient pain evaluations, menstrual suppression, estradiol levels, and pharmacokinetic parameters. Overall, the two formulations of leuprolide acetate had comparable efficacy regarding these clinical and pharmacokinetic endpoints. In addition, the safety profiles of each drug formulation were comparable.

Review of this study led to some interesting concerns regarding loss of bone mineral density (BMD) as an adverse effect related to treatment. On average, the mean loss in BMD from baseline to the end of treatment (month 6) was 3.0% in the 3.75 mg arm versus 2.8% in the 11.25 mg arm. While this data was comparable with earlier results, it was concerning that some patients in each treatment arm lost as much as 7.3% of their BMD after 6 months of treatment. Only 23 patients had follow-up BMD scans obtained after 6 additional months of post-treatment follow-up. Of these, 17 of 23 (74%) had BMD measurements that remained below baseline levels; and six of these 17 subjects actually had continued to lose BMD (anywhere from 0.1% to 1.0%) between the end-of-treatment assessment and the 6 month follow-up assessment.

Conclusions

The data in this submission support that the two formulations of leuprolide acetate are comparable regarding their efficacy and pharmacokinetic parameters in patients with endometriosis. Safety profiles were also similar with each formulation. Concerns exist about the current labeling, especially regarding BMD loss. Loss of BMD following Lupron therapy may be substantial, and it may continue despite cessation of therapy. I agree with the medical officers' proposed revisions to labeling as outlined in their review, and I agree with the approval of this NDA supplement.

/S/ M.D. 3/2/99

Marianne Mann, M.D.
Deputy Director, HFD-580

cc:
NDA 20-708
Rarick/Mann/Allen/Safran/HFD-580

NDA 20-708/S-005
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TAP Holdings, Inc.

Pharmacology

This application did not require a Pharmacology Review.

NDA 20-708/S-005
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Chemistry Review

This application did not require a chemistry review.

NDA 20-708/S-005
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EER

This application did not require an EER.

NDA 20-708/S-005
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Microbiology

This application did not require a microbiology review.

NDA 20-708/S-005
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DSI Audits

Clinical Audits are not required, this is a biopharmaceutic trial to obtain data to update their **CLINICAL PHARMACOLOGY** section.

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Advisory Committee

This application was not the subject of an Advisroy Committee.

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Federal Register Notice

This application was not the subject of a Federal Register Notice.

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Advertising Material

Advertising Material has not been submitted for this application.

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Integrated Summary of Safety

An integrated summary of safety is not required, only one trial was performed.