CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708

PHARMACOLOGY REVIEW(S)

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NDA 20-708

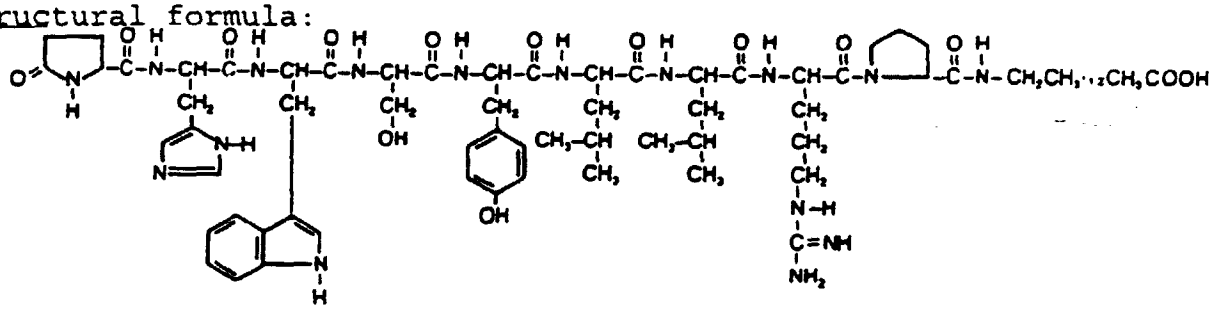
TAP Pharmaceuticals, Inc.
Deerfield, IL

Submission dated: 3-6-1996 Received at HFD-580: 3-7-1996

Pharmacology Review of NDA Supplement

Drug Product:

Established name: leuprolide acetate for depot suspension
Proprietary name: Lupron Depot-3 month 11.25 mg
Code name: TAP-144-SR; Abbott-43818
Chemical name: 5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.
Structural formula:



Molecular formula: C59 H84 N16 O12 CH3COOH
Molecular wt: 1209.42 (free base); 1269.46 (mono-acetate)

Components, composition and dosage form of TAP-144-SR(3M) injection (11.25 mg):

TAP-144-SR(3M)(11.25 mg)		TAP-144-SR(3M) vehicle		
Ingredient	Per vial	Ingredient	per ampule	per use
Leuprolide acetate	11.25mg	Mannitol	mg	mg
polylactic acid	mg	CMC-Na	mg	mg
D-mannitol	mg	Polysorbate80	mg	mg
Total	mg	Acetic acid	appropriate amount	
		H2O for injec	ml	ml

Dosage form: Sterile depot suspension for injection

Route of administration: intramuscular injection

Strength: 11.25 mg

Indication: Management of endometriosis and with iron for the preoperative hematologic improvement of anemia caused by uterine fibroids.

Leuprolide acetate, the active drug used in this new formulation is the same as approved for sponsor's NDAs 19-010, 19-732, 20-011, 19-943, 20-263, and 20-517. The drug product in this application is the same as Lupron Depot-3 Month 22.5 mg approved under NDA 20-517 for palliative treatment of advanced prostate cancer.

Non-clinical pharmacology and toxicology: All preclinical pharmacology and toxicology has been referred to previously approved NDAs mentioned above.

The sponsor has stated that this drug development of 3 Month Depot was reviewed in 1991 with representatives from Division of Metabolism and Endocrine Drug Products (Dr. Fourcroy and Dr. Rarick) and the Division of Biopharmaceutics, who agreed upon a PK/PD study for the use of this product for the management of endometriosis and uterine fibroids as currently approved under NDA 20-011 and 19-943.

The sponsor has now submitted a clinical/statistical data which includes comparison of efficacy and safety with historical data from Lupron Depot 3.75 mg clinical studies in patients with endometriosis and uterine fibroids.

Results of clinical study: results of PK/PD study (M94-139) indicated that the Lupron Depot - Month 11.25 mg formulation produces hormonal and menstrual suppression comparable to that of Lupron Depot 3.75 mg.

Therapeutic advantages of 11.25 mg Depot formulation over 3.75 mg Depot formulation: Sponsor has suggested that the 11.25 mg

formulation with dosing interval of 3 months, should lead to increased patient acceptance of the dosing schedule. Also this dosing interval would be appropriate with regard to the respective treatment duration currently approved for endometriosis (six months) and uterine fibroids (three months).

Labeling: Labeling for the present formulation is similar to the approved labeling for 3.75 mg Lupron Depot- 1 month formulation and is presented as combined labeling for 3.75 and 11.25 formulations.

Recommendations: Based on extensive preclinical and clinical experience on the safety and efficacy of Lupron Depot along with results of the clinical PK/PD study conducted in support of its proposed use for the management of endometriosis and for the preoperative hematologic improvement of anemia caused by uterine fibroids, Pharmacology considers it safe and recommends approval of Lupron Depot 11.25 mg for the proposed indications.

Krishan L. Raheja 9/17/96
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A Jordan
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Original NDA 20-708 s
HFD-345
HFD-580
HFD-580/A.Jordan
HFD-580/K.Raheja, 9-17-1996, N20-708s