PHARM REVIEW

Takeda-Abbott Research &
Development
Abbott Park, IL

JUN 30 1989

Submission dated: 12-30-88

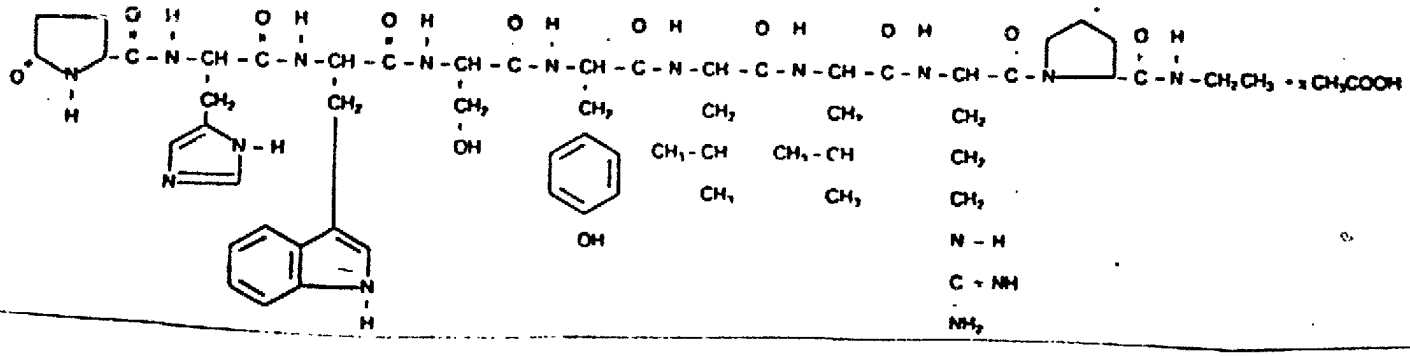
Pharmacology Review of Original NDA

Drug: Lupron depot (Leuprolide acetate for depot suspension), 3.75 mg

Code name: TAP-144-SR, Abbott-43818

Chemical name:
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

Structural formula:



Therapeutic indications: For the treatment of leimyoma uteri (utrine fibroids).

Formulation and dosage: The single dose vial of Lupron Depot contains leuprolide acetate (3.75 mg), purified gelatine (0.65 mg), DL-lactic & glycolic copolymer (33.1 mg), and D-mannitol (6.6 mg). The accompanying ampule of diluent contains carboxy methylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), and water for single monthly IM injection. The content of leuprolide acetate in the TAP-144-SR is therefore 8.5%.

Related INDs and NDAs: IND NDAs 19-010 and 19-732

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH). It is much more potent and has longer T1/2 than the natural hormone. Leuprolide acetate acts as a potent inhibitor of gonadotropin secretion when given on a continuous basis and in therapeutic doses. Following an initial stimulation, chronic administration results in suppression of ovarian and testicular steroidogenesis as long as treatment is continued. Since estrogen stimulates the growth of uterine fibroids, medical therapy is based on the suppression of estrogen production.

Nonclinical Pharmacology and Toxicology studies

This NDA refers to pahrmacology and toxicology data submitted for the approval

of leuprolide acetate injection (NDA 19-010) and for leuprolide acetate for depot suspension (NDA 19-732). New studies submitted with the present submission and discussed below include teratology studies in rabbit and rats, effect on peri and postnatal development of the rat and effect on fertility and general reproduction in the rat. All these studies were conducted in Japan in accordance with the FDA-GLP Regulations (21 CFR 58).

Teratology study of TAP-144-SR in the rabbit- Study No. 567/TE

In this study TAP-144-SR at dose levels of 0.003, 0.03 and 0.3 mg/kg (0.00024, 0.0024 and 0.024 mg/kg as TAP-144) was administered s.c. to rabbits (13-15/g) on day 6 of pregnancy to assess the effect of the drug on fetal development.

Results

Death and abortion: One dam in LD group died on day 16 of pregnancy and another in the same group aborted on day 27 of pregnancy.
No treatment effect was seen in body wt or food consumption.

Autopsy findings: The number of c.l. was increased in the mid and high dose groups(19 and 15 compared to 10 for the controls). The % of dead implants was incrased in the HD group.

Observations of fetuses: Fetal mortality was increased in the mid and high dose groups and fetuses in these groups weighed less when compared to control group. No treatment related changes were seen in the low dose group. There were 112, 109, 67 and 56 fetuses in control and 3 treatment groups resp.

External observation of fetuses: revealed that mean frequencies of malformation was 0, 0.8, 1.1 and 4.8 % for the control and 3 treatment groups. The number of fetuses affected were 0, 1, 1 and 2 resp in the 4 groups. The malformations consisted of encephalomeningocele, microphthalmia and thoraco-abdominal fissure.

The mean frequencies of major skeletal abnormalities was 0, 0, 7.5 and 13.3 %. These consisted of segmentation defect of thoracic and /or lumber vertebrae, fusion of thorac vertebrae bodies, abnormal caudal vertebrae, fusion of rib and sternal fissure. The number of fetuses affected in the 4 treatment groups were 0, 0, 3 and 6 resp. The mean frequency of minor abnormalities was also increased in the high dose group.

The mean frequencies of major visceral abnormalities were 0.7, 4.2, 12.9 and 4.8 % and consisted of hydrocephaly, abnormal lobation of the liver and lung, retroesophageal rt. subclavian artery and abnormal cauda vena cava. The number of fetuses affected were 1, 5, 4 and 3 resp. in the 4 groups.

Thus the incidence of total major abnormalities was recorded in 1, 6, 8 and 11 fetuses in the control and 3 treatment groups.

Teratological study of TAP-144-SR in the rat- Study No. 475/TE

Wistar pregnant rats (39-40/g) were administered on day 6 of pregnancy TAP-144-SR at dose levels of 0.03, 0.1 and 0.3 mg/kg (0.0024, 0.008 and 0.024 mg/kg as TAP-144) to assess the effect of the drug on fetal development and reproductive ability of F1 animals. 23-24 were autopsied on day 20 of pregnancy and remaining 15-16 females were allowed to deliver.

Results

Observations on groups for autopsy on day 20 of gestation: No deaths occurred in dams in any group. The number of c.l. was increased in dosed groups compared to controls.

Fetuses: The number of dead implants/number of c.l. was increased in the HD group compared to the controls (17.4% vs 5.7%) A slight decrease in the number of ossified sacro-caudal vertebrae (indication of degree of ossification) was observed in the middle and high dose groups compared to with the control group.

Groups for post-natal observations: Dams- No death occurred in any group. Prolonged delivery time was obsrved in one HD group and slight extention of gestation period in all treated groups. Also death of all fetuses in 2/16 dams and death of all the newborn on day 2 of 2/14 dams were reported in HD group.

F1 pups: No treatment related effect on the morphological development of the pups was observed. Degree of ossification was not affected by treatment. No behavioral changes were seen as a result of treatment.

Reproductive performance of F1 animals: The copulation rate, conception rate, gestation period, and general signs in F1 animals were comparable in all groups. No treatment related external, visceral or skeletal abnormalities occurred in the F2 pups.

Effect of TAP-144-SR on peri- and post-natal development of the rat-prenatal treatment

TAP-144-SR was administered s.c. as single dose at 0.3 mg/kg (0.0024 mg/kg as TAP-144)to Wistar rats (16 treated and 15 controls) on day 15 of gestation. Fetuses were delivered on day 21 of gestation and fostered by untreated dams. The effect of drug on growth, morphologic development, behavior and reproductive performance of the offspring was studied.

Results: No deaths occurred in either group. One treated dam aborted on day 19 of gestation. Treatment had no effect on b.wt. of treated dams, number of implantation sites, number of live or dead fetuses, morphological development or behavioral changes of F1 pups before or after weaning. Sporadic findings of adhesion of spleen and the liver or hydronephrosis seen at autopsy of F1 animals was considered not treatment related.

Study on reproductive performance of F1 animals showed no sig. differences between the treated and the control groups in b.wt. changes, clinical signs, days required until mating, copulation rate, conception rate, gestation period, number of implants, number of newborns (F2), number of live F2 pups. No visceral or external abnormalities were observed in F2 pups.

Effect of TAP-144-SR on postnatal development of the rat- Study No. 565/PE

Doses of 10 and 100 mg/kg of TAP-144-SR (0.8 and 8 mg/kg of TAP-144) were administered s.c. to Wistar rat dams (23-24/g) on the day they gave birth. The effect of drug on nursing in the dams, and on the growth, morphologic development and behavior of the newborn were studied. Autopsy was performed on each dam after her pups were weaned.

No dams died and no clinical abnormalities were observed. All pups from one dam in the HD group died on day 2. At autopsy wt of ovaries and uterus were found lower and that of mammary glands slightly increased in both dosed groups compared to controls. Dilated cecum was seen in 2 dams in each treated group and a mammary tumor was reported in one HD dam.

No effect of treatment was observed on morphologic development of F1 pups. Abnormalities of kidney, ureter, bladder or adreanl defects were seen in treated groups but because of their low frequency were considered incidental. Degree of ossification was not affected by treatment. The absolute but not relative testes wt increased in the 10 mg/kg dose group and wet wt of the uterus increased in the 100 mg/kg dosing group. A tendency for delayed negative geotaxis was observed in males of both dosing groups only on day 5 after birth and not on days 10 and 15.

Effect of TAP-144-SR on fertility and general reproductive performance of the rat- Study No 455/FE.

Three experiments were conducted to determine the effects of TAP-144 on the gonadal function, secretion of sex hormones, reproductive performance of both sexes and effect on the development of fetuses.

In study 1, drug was administered to male rats (30/g) at dose levels of 0, 0.3, 3,0 and 30.0 mg/kg (0.024, 0.24 and 2.4 mg/kg as TAP-144) every 4 wks for 12 wks.

Ten rats/g were sacrificed at the end of 12 wk treatment period and the remaining 20/g were mated with untreated females at various time intervals (1-7 wks) after the end of treatment.

At 12 wk sacrifice atrophy of the testes and a decrease in the weights of testes and other reproductive organs was observed at each dose level. Serum testosterone levels were 3.1, 2.6, 1.6 and 1.1 ng/ml for the control and 3 treated groups resp. The values for FSH for the 4 groups were 196, 282, 152 and 46 ng/ml and for LH 42, 38, 27 and 15 ng/ml resp.

In the high dose group, copulation rate and implantation was decreased in the second and the third wk of mating, suggesting that fertility was reduced by repeated mating. The sponsor stated that similar effect was seen in the untreated rats. This was returned to normal by the 5th wk after final dosing. In the low and mid dose groups, no adverse effects on copulation and fertilization were noted.

No sig. difference was noted between the treated and the control groups in mortality, number of live fetuses, sex ratio, body wt. or external, skeletal or visceral abnormalities of the live fetuses. 15 wks after beginning of the mating, the wts. of the testes and epididymides of animals in the mid and high dose groups were still slightly lower than the controls.

In the second study, doses of 0, 0.3, 3 and 30 mg/kg (0.024, 0.24 and 2.4 mg/kg as TAP-144) were administered s.c. to female rats (30/g) once 4 wks before mating. In the high dose a narrowed vagina and loss of vaginal folds were observed. The estrous cycle was arrested after treatment in all groups and number of days until estrus occurred after arrest were dose dependent. Wt

of the ovaries and uterus was decreased in HD group, ovaries in mid dose group and no effect in the low dose group. Serum hormone levels were affected only in the high dose group. Estradiol was decreased in the high dose group compared to controls (44 vs 72 ng/ml). LH level was increased (42 vs 62 ng/ml) and FSH level was decreased (147 vs 50 ng/ml).

In the mid and high dose groups the number of copulations and the duration until conception was greater than in the controls. Although all animals in the high dose became pergnant eventually, 15 of 20 did not become pregnant after first copulation. Autopsy on day 20 of gestation showed a dose-related decrease in number of c.l. (16, 15, 14 and 13 for the control and 3 treatment groups) and implants (14, 14, 10 and 10). Implantation rate was reduced in the mid and high dose groups. No abnormality occurred in the low dose group. In the high dose group, number of live fetuses was decreased but no sig. differences were observed in fetal mortality between the treated and the control groups. No treatment-related abnormalities were seen on exteral, skeletal and visceral exam. There was no difference in the number of sacro-caudal vertebrae ossified between the treated and control groups.

In the third study, doses of 0.1, 0.3 and 1 mg/kg (0.008, 0.024 and 0.08 mg/kg as TAP-144) were administered s.c. on day 0 of pregnancy to 20 rats/g. One dam in the high dose group had vaginal bleeding on day 10 of gestation. Decrease in body wt of dams in the high dose group was considered to be due to marked decrease in fetal wts in this group. No differences were seen in mid and low dose groups. In the high dose group there was increased number of c.l. but decreased implantation rate. These changes were considered due to ovulation or corpora etriticum after dosing in 8 of 19 animals and there were no sig. differences between number of implants between the high dose and controls. No adverse effects were seen in other groups.

The mortality rate, the number of live fetuses or sex ratio was not affected by treatment. In the mid and high dose groups, fetal wts were lower and number of sacro-caudal vertebrae ossified were decreased compared to the control (6.2, 5.3 and 2.7 resp for 3 treated groups vs 6.4 for the controls). No sig differences in the type and frequencies in the external, skeletal or visceral abnormalities were reported.

Summary: Except for for some treatment- related increase in the mean frequencies of malformations and skeletal abnormalities in the rabbit teratology study, no unexpected findings were observed in the rabbit and rat teratology studies, treatment effect on peri- and post-natal development as well as effect on fertility and general reproductive performance in the rat.

No-effect dose level of TAP-144-SR was reported to be 0.003 mg/kg (0.0024 mg/kg as TAP-144) in the rabbit and 0.03 mg/kg in the rat teratology studies. Also with prenatal treatment a dose of 0.3 mg/kg had no advaerse effect on the growth of pups and 100 mg/kg administered during lactation had no effect on nursing ability of dams or the growth of their pups.

Administration of TAP-144-SR to male and female rats before mating caused atrophy of the reproductive organs and suppression of reporductive performance which are known effects of LHRH agonists and these changes were largely reversible on cessation of treatment.

Comments: Adequate statements regarding carcinogenesis, mutagenesis and impairment of fertility as well as regarding adverse reactions have been included in the labeling section. However, subsection on pregnancy has been omitted even though teratogenic effect was seen in rabbit teratology study.

Recommendations: The preclinical studies submitted in support of NDAs 19-010 and 19-732 demonstrate reasonable safety for the drug and Pharmamcology has no objection to the approval of Lupron Depot (leuprolide acetate for depot suspension) for the treatment of leiomyoma uteri (uterine fibroids). However, the sponsor should be informed to modify the labeling section to include appropriate pregnancy category since there exists a distinct possibility that pregancy could occur during treatment with Lupron depot.

Krishan L. Raheja 5/15/89
Krishan L. Raheja, DVM, PhD

A Jordan
6/30/89

Original NDA 19-943
HFD-345
HFD-510
HFD-510/A.Jordan
HFD-502/J.Weissinger
HFD-510/Raheja, 5-15-89, Wang # 0506p

NDA 20-011

Takeda-Abbott Research &
Development
Abbott Park, IL

Submission dated: 8-31-89

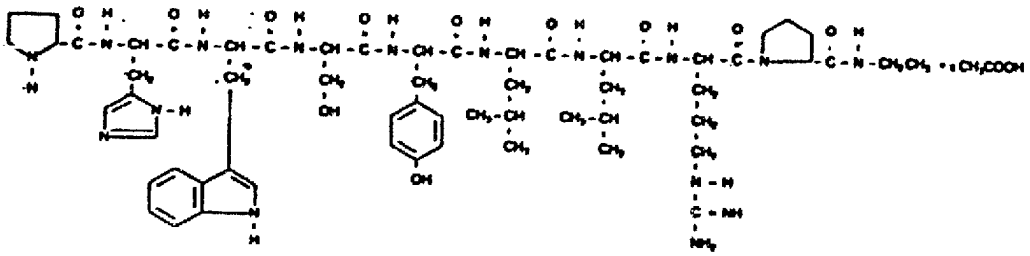
Pharmacology Review of Original NDA for Lupron Depot

Drug: Lupron depot (Lupron acetate for depot suspension), 3.75 mg

Code name: TAP-144-SR, Abbott-43818

Chemical name:
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl- L-seryl-L-tyrosyl-L-D-leucyl-L-leucyl- L-arginyl-N-ethyl-L-prolinamide acetate.

Structural formula:



Therapeutic indications: For the treatment of endometriosis for a period of 6 months. Depot could be used for sole therapy or as adjunct to surgery.

Formulation and dosage: see pharmcology review of NDA 19-943 of 12-30-88.

Related INDs and NDAs: IND NDAs 19-010, 19-732 and 19-943.

Nonclinical pharmcology and toxicology: Reviewed under NDAs 19-010, 19-73[illegible] and 19-943.

Recommendations: The preclinical studies submitted in support of NDAs 19-010, 19-732 and 19-943 demonstrated reasonable safety for the drug. Based on those studies pharmacology previously recommended approval of NDA 19-94[illegible] for the treatment of leiomyoma uteri with 3.75 mg depot formulation . Pharmacology recommends approval of the present NDA 20-011 for the treatment of endometriosis with Lupron depot formulation as used under NDA 19-943.

Krishan L. Raheja 9/15/89
Krishan L. Raheja, DVM, PhD

Original NDA 20-011
HFD-345
HFD-510
HFD-510/A.Jordan
HFD-502/J.Weissinger
HFD-510/Raheja,9-14-89, TAP144SR.End

A Jordan
9/15/89

4-7-94

NDA 19-943

TAP Pharmaceuticals Inc.
Deerfield: IL

Submission dated: 3-30-1994 Received at HFD-510: 3-31-1994

Pharmacology Review of Resubmitted NDA

Drug: Leuprolide acetate for depot suspension (USP/USAN), Lupron Depot 3.75 mg (proprietary name), TAP-144-SR, Abbott-43818 (Code names)

Dosage form: Sterile depot suspension for injection

Strength: 3.75 mg

Dosage: When mixed with 1 ml of diluent, Lupron Depot is administered as a single monthly injection.

Route of administration: intramuscular injection

Proposed indications: Lupron Depot 3.75 mg is indicated for 3 months of therapy in the preoperative management of uterine leiomyomata to improve hematologic status and for up to 6 months to reduce uterine/myoma volume and associated symptoms when surgery is delayed.

Related INDs and NDAs: IND (Lupron Depot), NDA 19-010 (Lupron Injection s.c. for the palliative treatment of prostate cancer was approved in April 1985), NDA 19-732 (Lupron Depot 7.5 mg for the palliative treatment of advanced prostate cancer was approved on January 26, 1989), NDA 20-011 (Lupron Depot 3.75 mg for the management of endometriosis was approved on October 22, 1990), NDA 20-263 (Lupron Depot-PED 7.5 mg, 11.25 mg and 15 mg for the treatment of central precocious puberty was approved on April 16, 1993) and NDA 19-943 (Lupron Depot 3.75 mg for management of uterine fibroids) was originally submitted on December 30, 1988.

The present NDA was originally submitted in December 1988 and following an Advisory Committee vote (October, 1989) was voluntarily withdrawn in December 1989. Based on recommendation of the Advisory Committee and discussions with the DMEDP, Protocol M90-411 was developed to evaluate Lupron Depot and iron vs iron alone in improvement of hematologic status of patients with iron deficiency anemia secondary to menorrhagia induced by uterine fibroids.

Preclinical Pharmacology and toxicology: The present submission refers to all the preclinical data submitted under original NDA 19-943 of December 30, 1988. Copies of the reviews of the original NDA 19-943 as well as that of NDA 20-011 (for the formulation under review but for different indication) are attached.

Clinical studies: Submission also contains results of 3 studies (M86-034, M86-049 and M86-062) which were previously submitted with the original NDA 19-943 submision along with results of new study M90-411.

Labeling: Labeling for Lupron Depot 3.75 mg for the present indication i.e. management of uterine fibroids, has been combined with the labeling for management of endometriosis (NDA 20-011). Thus most of the general information and the information on endometriosis is from the labeling approved for NDA 20-011 (Lupron Depot 3.75 mg).

It should however, be pointed out that under combined labeling figure 1 on page 37 (volume 1.1), showing percent of patients with symptoms at baseline, final treatment visit, and after 6 and 12 months of follow-up is in very small print and is not legible.

Note: The sponsor has modified the original pregnancy category labeling and classified as category X as recommended by Pharmacology in review of the original NDA 19-943 submission.

Recommendations: The drug product described in this NDA, Lupron Depot 3.75 mg is approved for the indication of management of Endometriosis (NDA 20-011). Based on the data submitted with the original NDA 19-943 submission of 12-30-1988, Pharmacology had recommended approval of the Lupron Depot 3.75 mg for the management of uterine fibroids. Pharmacology reaffirms its recommendation for approval.

Krishan L. Raheja 4/7/94
Krishan L. Raheja, DVM, PhD

A Jordan
4/12

Original NDA 19-943
HFD-345
HFD-510
HFD-510/A.Jordan
HFD-510/L.Rarick
HFD-502/A.Taylor
HFD-510/Raheja, 4-7-94, N19943.R