

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019010Orig1s038

Trade Name: **Lupron Injection**

Generic Name: **leuprolide acetate**

Sponsor: **AbbVie Endocrine Inc.**

Approval Date: **5/19/2017**

Indications: LUPRON INJECTION (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer.

LUPRON INJECTION is indicated in the treatment of children with central precocious puberty.

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APPROVAL LETTER



NDA 019010/S-038

SUPPLEMENT APPROVAL

AbbVie Endocrine Inc.
Attention: Patti Neall
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Neall:

Please refer to your supplemental New Drug Application (sNDA) dated and received December 8, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron (leuprolide acetate) injection.

We also refer to our letters dated November 14 and December 21, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for GnRH agonists indicated to treat central precocious puberty. This information pertains to the risks of seizures and serious psychiatric adverse events in this patient population.

This supplemental new drug application provides for revisions to the labeling for Lupron, consistent with our November 14 and December 21, 2016, letters and the labeling comments sent to you on February 14, March 7, March 23, and April 12, 2017.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling.

- Revision dates updated to reflect the date of approval of this supplement.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information,

Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We note that Lupron is currently not marketed, and therefore revised carton and container labeling were not submitted. If you resume marketing of this product, you will need to submit a prior approval supplement with revised carton and container labeling as described in our December 21, 2016, Safety Labeling Change Notification letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also remind you of our December 21, 2016, request that for a period of 5 years, you submit all cases of suicidal ideation and behavior, self-injury, or depression reported with Lupron as 15-day alert reports, and that you provide detailed analyses of suicidal ideation and behavior, self-injury, or depression events reported from clinical study and post-marketing reports of suicidal ideation and behavior, self-injury, or depression events as adverse events of special interest in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to our December 21, 2016, letter as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of suicidal ideation and behavior, self-injury, or depression reported with Lupron should also be provided in the periodic safety report.

If you have any questions, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER R PIPPINS
05/19/2017

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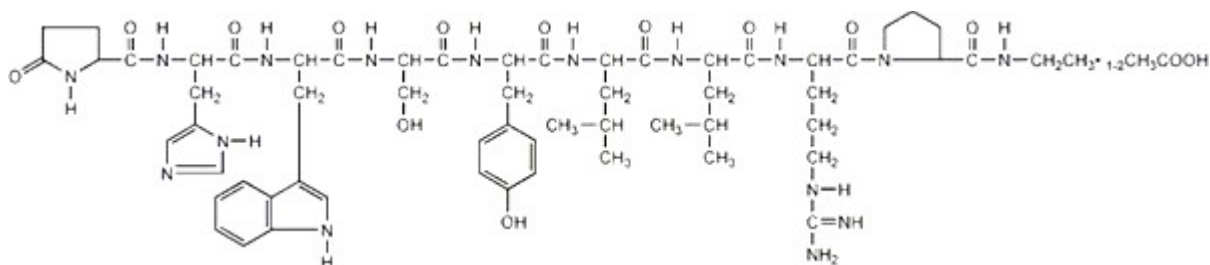
LABELING

LUPRON® INJECTION (leuprolide acetate)

Rx only

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON INJECTION is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after

initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption

Bioavailability by subcutaneous administration is comparable to that by intravenous administration.

Distribution

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Metabolism

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model. In rats and dogs, administration of ¹⁴C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion

Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations

The pharmacokinetics of the drug in hepatically and renally impaired patients has not been determined.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

CLINICAL STUDIES

In a controlled study comparing LUPRON 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years of treatment. The objective response to treatment was also similar for the two groups.

INDICATIONS AND USAGE

LUPRON INJECTION (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer.

CONTRAINDICATIONS

1. LUPRON INJECTION is contraindicated in patients known to be hypersensitive to GnRH, GnRH agonist analogs or any of the excipients in LUPRON INJECTION: Reports of anaphylactic reactions to GnRH agonist analogs have been reported in the medical literature.
2. LUPRON is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON may cause fetal harm when administered to a pregnant woman. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of LUPRON, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Initially, LUPRON, like other LH-RH agonists, causes increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of LUPRON treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON, pregnancy must be excluded (see **CONTRAINDICATIONS** section).

Periodic monitoring of serum testosterone and prostate-specific antigen (PSA) levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** and **ADVERSE REACTIONS** sections).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Effect on QT/QTc Interval

Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Information for Patients

See [INFORMATION FOR PATIENTS](#) which appears after the **REFERENCE** section.

Laboratory Tests

Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and prostate-specific antigen (PSA). In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued.

Drug Interactions

See [CLINICAL PHARMACOLOGY, Pharmacokinetics](#) section.

Drug/Laboratory Test Interactions

Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months

when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

Pregnancy

Teratogenic Effects

Pregnancy Category X

(see **CONTRAINDICATIONS** and **WARNINGS** sections)

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, LUPRON produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in major fetal malformations throughout gestation. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON in rabbits and with the highest dose in rats. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug.

Nursing Mothers

It is not known whether leuprolide acetate is excreted in human milk. LUPRON should not be used by nursing mothers.

Pediatric Use

See labeling for **LUPRON INJECTION for Pediatric Use** for the safety and effectiveness in children with central precocious puberty.

Geriatric Use

In the clinical trials for LUPRON INJECTION, the majority (69%) of subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON in this population.

ADVERSE REACTIONS

Clinical Trials

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (see **WARNINGS** section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of LUPRON INJECTION (leuprolide acetate) versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	LUPRON (N=98)	DES (N=101)
	<u>Number of Reports</u>	
Cardiovascular System		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
Gastrointestinal System		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		

Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
Miscellaneous		
Asthenia	10	10
* Physiologic effect of decreased testosterone.		

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON.

Cardiovascular System—Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System*—Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System*—Libido decrease, Thyroid enlargement; *Musculoskeletal System*—Joint pain; *Central/Peripheral Nervous System*—Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System*—Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*—Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*—Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*—Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

In an additional clinical trial and from long-term observation of both studies, the following additional adverse events (excluding those considered not drug related) were reported for patients receiving LUPRON.

Cardiovascular System—Bradycardia, Carotid bruit, Extrasystole, Palpitations, Perivascular cuffing (eyes), Ruptured aortic aneurysm, Stroke, Tachycardia, Transient ischemic attack; *Gastrointestinal System*—Flatus, Dryness of mouth and throat, Hepatitis, Hepatomegaly, Occult blood (rectal exam), Rectal fistula/erythema; *Endocrine System*—Libido increase, Thyroid

nodule; *Musculoskeletal System*—Ankylosing spondylosis, Arthritis, Blurred disc margins, Bone fracture, Muscle stiffness, Muscle tenderness, Pelvic fibrosis, Spasms/cramps; *Central/Peripheral Nervous System*—Auditory hallucinations/tinnitus, Decreased hearing, Decreased reflexes, Euphoria, Hyperreflexia, Loss of smell, Motor deficiency; *Respiratory System*—Chest tightness, Decreased breathing sounds, Hemoptysis, Pleuritic chest pain, Pulmonary infiltrate, Rales/rhonchi, Rhinitis, Strep throat, Wheezing/bronchitis; *Integumentary System*—Boil (pubic), Bruises, Hives, Keratosis, Mole, Shingles, Spiders; *Urogenital System*—Blisters on penis, Inguinal hernia, Penile swelling, Post void residual, Prostatic pain, Pyuria; *Miscellaneous*—Abdominal distention, Facial swelling/edema, Feet burning, Flu, Eyelid growth, Hypoproteinemia, Accidental injury, Knee effusion, Mass, Pallid, Sallow, Weakness.

Postmarketing

During postmarketing surveillance which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular System - Hypotension, Myocardial infarction; *Endocrine System* - Diabetes; *Gastrointestinal System* - Hepatic dysfunction; *Hemic and Lymphatic System* - Decreased WBC; *Integumentary System* - Hair growth; *Central/Peripheral Nervous System* - Convulsion, Spinal fracture/paralysis, Hearing disorder; *Miscellaneous* - Hard nodule in throat, Weight gain, Increased uric acid; *Musculoskeletal System* - Tenosynovitis-like symptoms; *Respiratory System* - Respiratory disorders.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON DEPOT and LUPRON INJECTION package inserts for other events reported in the same and different patient populations.

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically. Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Follow the pictorial directions on the reverse side of this package insert for administration.

NOTE: As with all parenteral products, inspect the solution for discoloration and particulate matter before each use.

HOW SUPPLIED

LUPRON INJECTION (leuprolide acetate) is a sterile solution supplied in a 2.8 mL multiple-dose vial. The vial is packaged as follows: 14 Day Patient Administration Kit with 14 disposable syringes and 28 alcohol swabs, NDC 0074-3612-30 and six-vial carton, NDC 0074-3612-34.

Store below 77°F (25°C). Do not freeze. Protect from light; store vial in carton until use.

REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. *Chemotherapy and biotherapy guidelines and recommendations for practice* (2nd Ed.) Pittsburgh, PA: Oncology Nursing Society.

INFORMATION FOR PATIENTS

Be sure to consult your physician with any questions you may have or for information about LUPRON INJECTION (leuprolide acetate) and its use.

WHAT IS LUPRON?

LUPRON INJECTION (leuprolide acetate) is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH) a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH and this leads to events which stimulate the production of sex hormones.

However, when you inject LUPRON INJECTION (leuprolide acetate), the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.

LUPRON must be injected because, like insulin which is injected by diabetics, LUPRON is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LUPRON

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the grey rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use LUPRON. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the 0.2 mL or 20 unit mark.
4. Take cover off needle. Push the needle through the center of the rubber stopper on the LUPRON bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the 0.2 mL or 20 unit mark.
7. Toward the end of a two-week period, the amount of LUPRON left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the 0.2 mL or 20 unit mark.
9. Do this again if necessary to eliminate air bubbles.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.

13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle. Push the plunger to administer the injection.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. **NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.**

SOME SPECIAL ADVICE

- You may experience hot flashes when using LUPRON INJECTION (leuprolide acetate). During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor. Like other treatment options, LUPRON may cause impotence. Notify your doctor if you develop new or worsened symptoms after beginning LUPRON treatment.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- If you have experienced an allergic reaction to other drugs like LUPRON, you should not use this drug.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure LUPRON keeps working for you.
- If you need to use an alternate to the syringe supplied with LUPRON, low-dose insulin syringes should be utilized.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need LUPRON so it will be at the pharmacy when you need it.
- Store below 77°F (25°C). Do not store near a radiator or other very warm place. Do not freeze. Protect from light; store vial in carton until use.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

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Rev. 05/2017

For Pediatric Use

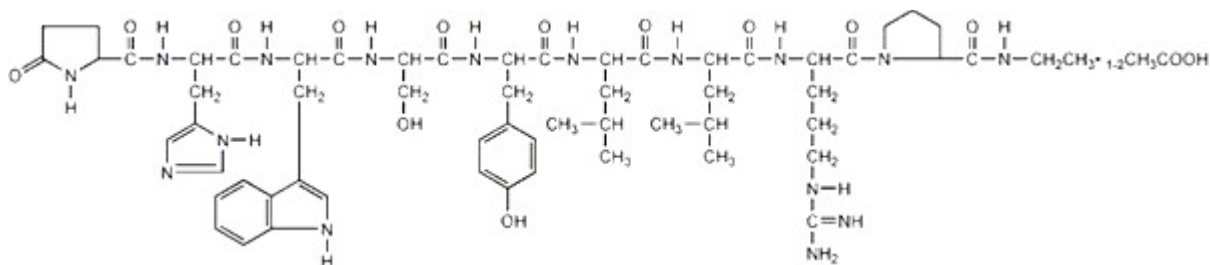
LUPRON® INJECTION

(leuprolide acetate)

Rx only

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON INJECTION is a sterile, aqueous solution intended for daily subcutaneous injection.

It is available in a 2.8 mL multiple dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

CLINICAL PHARMACOLOGY

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

A pharmacokinetic study of leuprolide acetate in children has not been performed.

Absorption

In adults, bioavailability by subcutaneous administration is comparable to that by intravenous administration.

Distribution

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy adult male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Metabolism

In healthy adult male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of ¹⁴C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion

Following administration of LUPRON DEPOT 3.75 mg to three adult patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations

The pharmacokinetics of the drug in hepatically and renally impaired patients has not been determined.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

CLINICAL STUDIES

In children with central precocious puberty (CPP), stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to prepubertal levels in males and females respectively. Reduction of gonadotropins will allow for normal physical and psychological growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprolide acetate.

The following physiologic effects have been noted with the chronic administration of leuprolide acetate in this patient population.

1. **Skeletal Growth.** A measurable increase in body length can be noted since the epiphyseal plates will not close prematurely.

2. **Organ Growth.** Reproductive organs will return to a prepubertal state.
3. **Menses.** Menses, if present, will cease.

INDICATIONS AND USAGE

LUPRON INJECTION is indicated in the treatment of children with central precocious puberty. Children should be selected using the following criteria:

1. Clinical diagnosis of CPP (idiopathic or neurogenic) with onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males.
2. Clinical diagnosis should be confirmed prior to initiation of therapy:
 - Confirmation of diagnosis by a pubertal response to a GnRH stimulation test. The sensitivity and methodology of this assay must be understood.
 - Bone age advanced 1 year beyond the chronological age.
3. Baseline evaluation should also include:
 - Height and weight measurements.
 - Sex steroid levels.
 - Adrenal steroid level to exclude congenital adrenal hyperplasia.
 - Beta human chorionic gonadotropin level to rule out a chorionic gonadotropin secreting tumor.
 - Pelvic/adrenal/testicular ultrasound to rule out a steroid secreting tumor.
 - Computerized tomography of the head to rule out intracranial tumor.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON INJECTION. Reports of anaphylactic reactions to GnRH agonist analogs have been reported in the medical literature.
2. LUPRON is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. (See **PRECAUTIONS, Pregnancy, Teratogenic Effects** section.) The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of LUPRON, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed (see **CLINICAL PHARMACOLOGY** section).

Psychiatric events have been reported in patients taking GnRH agonists, including leuprolide acetate. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with LUPRON (see **ADVERSE REACTIONS**).

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

Noncompliance with drug regimen or inadequate dosing may result in inadequate control of the pubertal process. The consequences of poor control include the return of pubertal signs such as menses, breast development, and testicular growth. The long-term consequences of inadequate control of gonadal steroid secretion are unknown, but may include a further compromise of adult stature.

PRECAUTIONS

Patients with known allergies to benzyl alcohol, an ingredient of the vehicle of LUPRON INJECTION, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Information for Caregivers

Prior to starting therapy with LUPRON INJECTION, the parent or guardian must be aware of the importance of continuous therapy. Adherence to daily drug administration schedules must be accepted if therapy is to be successful. Irregular dosing could restart the maturation process.

- During the first 2 months of therapy, a female may experience menses or spotting. If bleeding continues beyond the second month, notify the physician.
- Any irritation at the injection site should be reported to the physician immediately. If the child has experienced an allergic reaction to other drugs like LUPRON, this drug should not be used.
- Report any unusual signs or symptoms to the physician, like continued pubertal changes, substantial mood swings or behavioral changes.
- Inform caregivers that symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression, have been observed in patients receiving GnRH agonists, including leuprolide acetate. Alert caregivers to the possibility of development or worsening of psychiatric symptoms, including depression, during treatment with LUPRON (see **WARNINGS** and **ADVERSE REACTIONS**).
- Inform caregivers that reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions may be at increased risk (see **WARNINGS**).

Laboratory Tests

Response to leuprolide acetate should be monitored 1-2 months after the start of therapy with a GnRH stimulation test and sex steroid levels. Measurement of bone age for advancement should be done every 6-12 months.

Sex steroids may increase or rise above prepubertal levels if the dose is inadequate (see **WARNINGS** section). Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels.

Drug Interactions

See **CLINICAL PHARMACOLOGY, Pharmacokinetics** section.

Drug/Laboratory Test Interactions

Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses of 0.6 to 4 mg/kg (>100 times the clinical doses of 7.5 to 15 mg/month based on body surface area). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testes interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at daily dose as high as 60 mg/kg (>5000 times the clinical doses based on body surface area). Adult patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery. However, following a study with leuprolide acetate, immature male rats demonstrated tubular degeneration in the testes even after a recovery period. In spite of the failure to recover histologically, the treated males proved to be as fertile as the controls. Also, no histologic changes were observed in the female rats following the same protocol. In both sexes, the offspring of the treated animals appeared normal. The effect of the treatment of the parents on the reproductive performance of the F1 generation was not tested. The clinical significance of these findings is unknown.

Pregnancy

Teratogenic Effects

Pregnancy Category X

(see **CONTRAINDICATIONS** section)

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/1200 to 1/12 the human pediatric dose) to rabbits, LUPRON produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON in rabbits and with the highest dose in rats.

Nursing Mothers

It is not known whether leuprolide acetate is excreted in human milk. LUPRON should not be used by nursing mothers.

Geriatric Use

See labeling for LUPRON INJECTION for the pharmacokinetics, efficacy and safety of LUPRON in this population.

ADVERSE REACTIONS

Clinical Trials:

Potential exacerbation of signs and symptoms during the first few weeks of treatment (see **PRECAUTIONS** section) is a concern in patients with rapidly advancing central precocious puberty.

In two studies of children with central precocious puberty, in 2% or more of the patients receiving the drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Reactions considered not drug related are excluded.

	<u>Number of Patients</u> <u>N = 421 (Percent)</u>	
Body as a Whole		
General Pain	12	(3)
Headache	11	(3)
Injection Site Reactions Including Abscess*	37	(9)
Cardiovascular System		
Vasodilation	9	(2)
Integumentary System (Skin and Appendages)		
Acne/Seborrhea	13	(3)
Rash Including Erythema Multiforme	12	(3)
Psychiatric System		
Emotional Lability	19	(5)
Urogenital System		
Vaginitis/Vaginal Bleeding/Vaginal Discharge	13	(3)
* Most events were mild or moderate in severity.		

In those same studies, the following adverse reactions were reported in less than 2% of the patients.

Body as a Whole - Aggravation of preexisting tumor and decreased vision, Allergic Reaction, Body Odor, Fever, Flu Syndrome, Hypertrophy, Infection; *Cardiovascular System* - Bradycardia, Hypertension, Peripheral Vascular Disorder, Syncope; *Digestive System* - Constipation, Dyspepsia, Dysphagia, Gingivitis, Increased Appetite, Nausea/Vomiting; *Endocrine System* - Accelerated Sexual Maturity, Feminization, Goiter; *Hemic and Lymphatic System* - Purpura; *Metabolic and Nutritional Disorders* - Growth Retarded, Peripheral Edema, Weight Gain; *Musculoskeletal System* - Arthralgia, Joint Disorder, Myalgia, Myopathy; *Nervous System* - Hyperkinesia, Somnolence; *Psychiatric System* - Depression, Nervousness; *Respiratory System* - Asthma, Epistaxis, Pharyngitis, Rhinitis, Sinusitis; *Integumentary System (Skin and Appendages)* - Alopecia, Hair Disorder, Hirsutism, Leukoderma, Nail Disorder, Skin Hypertrophy; *Urogenital System* - Cervix Disorder/Neoplasm, Dysmenorrhea, Gynecomastia/Breast Disorders, Menstrual Disorder, Urinary Incontinence.

Laboratory: The following laboratory events were reported as adverse reactions, antinuclear antibody present and increased sedimentation rate.

Postmarketing

During postmarketing surveillance, which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported. Localized reactions including induration and abscess have been reported at the site of injection. Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular System – Hypotension, Pulmonary embolism; *Gastrointestinal System* – Hepatic dysfunction; *Hemic and Lymphatic System* – Decreased WBC; *Integumentary System* – Hair growth; *Psychiatric adverse events*: Emotional lability, such as crying, irritability, impatience, anger, and aggression, has been observed with GnRH agonists, including leuprolide acetate (see **WARNINGS**); Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists, including leuprolide acetate, in children treated for central precocious puberty. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

Central/Peripheral Nervous System – Peripheral neuropathy, Convulsion, Spinal fracture/paralysis, Hearing disorder; *Miscellaneous* – Hard nodule in throat, Weight gain, Increased uric acid; *Musculoskeletal System* – Tenosynovitis-like symptoms; *Respiratory System* – Respiratory disorders; *Urogenital System* – Prostate pain.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The

leuprolide-treated group had lower bone density scores than the nontreated control group. The effects on bone density in children are unknown.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON INJECTION and LUPRON DEPOT package inserts for adverse events reported in other patient populations.

OVERDOSAGE

In rats, subcutaneous administration of 125 to 250 times the recommended human pediatric dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials using leuprolide acetate in adult patients, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

LUPRON INJECTION can be administered by a patient/parent or health care professional.

The dose of LUPRON INJECTION must be individualized for each child. The dose is based on a mg/kg ratio of drug to body weight. Younger children require higher doses on a mg/kg ratio.

After 1-2 months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, sex steroids, and Tanner staging to confirm downregulation.

Measurements of bone age for advancement should be monitored every 6-12 months. The dose should be titrated upward until no progression of the condition is noted either clinically and/or by laboratory parameters.

The first dose found to result in adequate downregulation can probably be maintained for the duration of therapy in most children. However, there are insufficient data to guide dosage adjustment as patients move into higher weight categories after beginning therapy at very young ages and low dosages. It is recommended that adequate downregulation be verified in such patients whose weight has increased significantly while on therapy.

As with other drugs administered by injection, the injection site should be varied periodically.

Discontinuation of LUPRON INJECTION should be considered before age 11 for females and age 12 for males.

The recommended starting dose is 50 mcg/kg/day administered as a single subcutaneous injection. If total downregulation is not achieved, the dose should be titrated upward by 10 mcg/kg/day. This dose will be considered the maintenance dose.

Follow the pictorial directions on the reverse side of this package insert for administration.

NOTE: As with other parenteral products, inspect the solution for discoloration and particulate matter before each use.

HOW SUPPLIED

LUPRON INJECTION (leuprolide acetate) is a sterile solution supplied in a 2.8 mL multiple-dose vial. The vial is packaged as follows: 14 Day Patient Administration Kit with 14 disposable syringes (Use the syringes supplied with LUPRON INJECTION) and 28 alcohol swabs, NDC 0074-3612-30 and six-vial carton, NDC 0074-3612-34.

Store below 77°F (25°C). Do not freeze. Protect from light; store vial in carton until use.

REFERENCES

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INSTRUCTIONS FOR USE

LUPRON INJECTION (loo-pron in 'jekSH(ə)n) (leuprolide acetate)

Read the Instructions for Use before you start using LUPRON INJECTION and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Your doctor should show you how to draw up LUPRON INJECTION and give the injection the right way before you inject the first time.

Do not share your syringes with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

Supplies you will need for the LUPRON INJECTION:

- 1 vial of LUPRON INJECTION
- a sterile 1 ml syringe (See Figure A)
- a 27 gauge, ½ inch sterile needle
- 1 cotton gauze
- 2 alcohol swabs
- 1 puncture resistant sharps container (See “Disposal of used syringes, needles, and vials”)



Figure A

Preparing the LUPRON INJECTION

Step 1.

Wash hands thoroughly (See Figure B) and dry them with a clean towel.



Figure B

Step 2.

- Check the liquid in the container. It should look clear. Do not use if it is not clear or if it has particles in it.
- If using a new vial, flip off the plastic cover to expose the grey rubber stopper.
- Use an alcohol swab to clean the metal ring and the grey rubber stopper on the medicine vial every day, just before you use it (See Figure C).

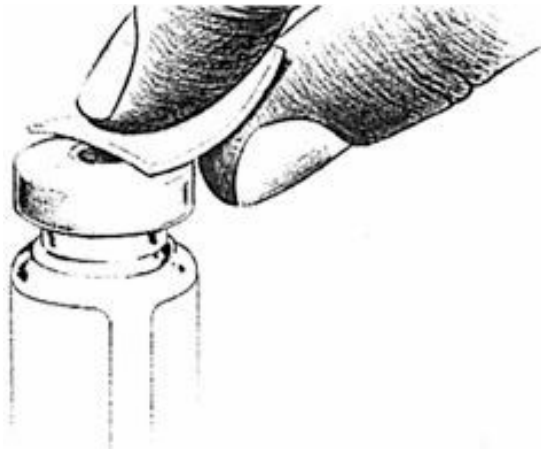


Figure C

Step 3.

Remove outer wrapping from 1 syringe (See Figure D).

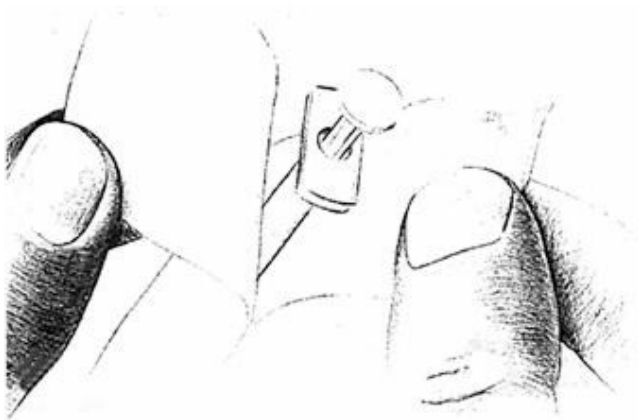


Figure D

Step 4.

- Remove outer wrapping from 1 needle.
- Place needle on top of syringe and turn it forward (clockwise) until it is tight and firmly attached (See Figure E).

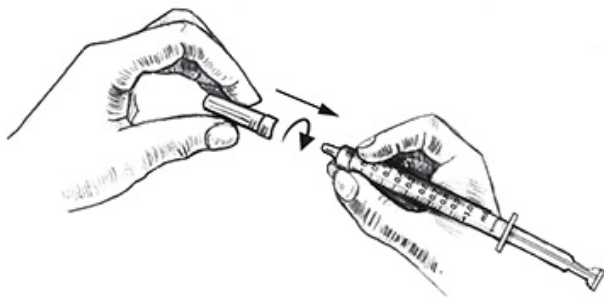


Figure E

Step 5.

Pull the syringe plunger back until the tip is at the proper mark for the prescribed dose (See Figure F).



Figure F

Step 6.

Uncover needle by pulling the cap straight off (See Figure G). **Do not** touch the needle.

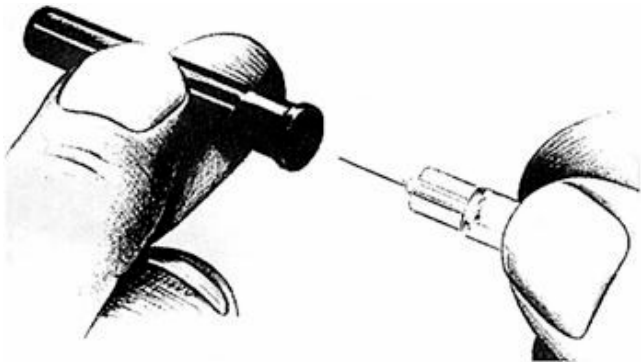


Figure G

Step 7.

- Place the vial on a clean flat surface.
- Push the needle through the center of the rubber stopper on the vial (See Figure H).
- Push the plunger all the way in to inject air into the vial.



Figure H

Step 8.

- Keep the needle in the vial.
- Lift the vial and turn it straight upside down.
- Check to see that the needle tip is in the liquid (See Figure I).

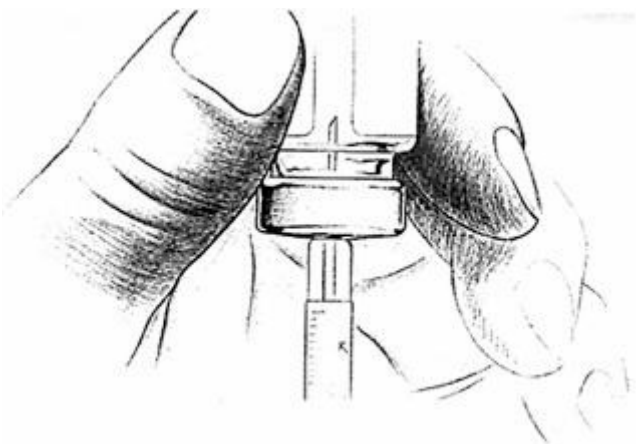


Figure I

Step 9.

- With the needle tip still in the liquid, slowly pull back the plunger until syringe fills to the proper mark (See Figure J).
- If any bubbles appear in the syringe, remove them by pushing the plunger up slowly.

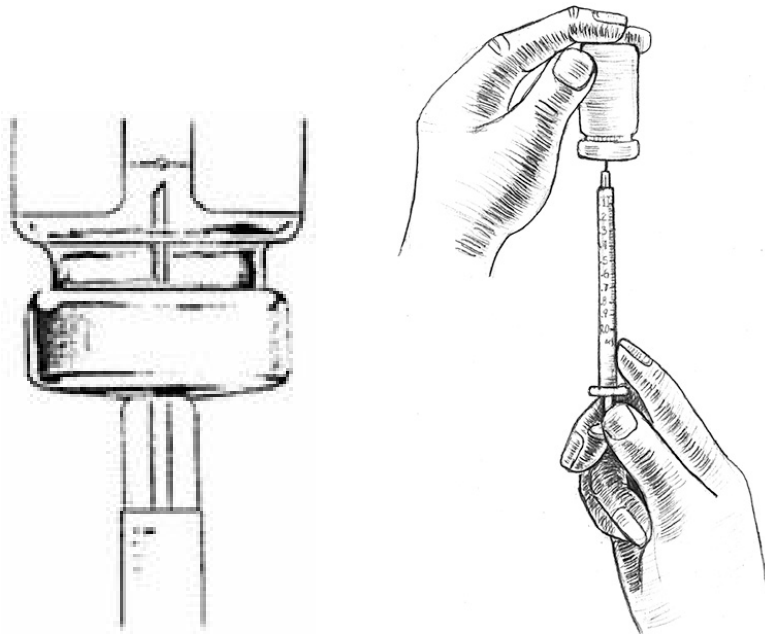


Figure J

Giving LUPRON INJECTION

Step 10.

- Choose a different injection site each day.
- Clean the injection site with a new alcohol swab.
- Hold the skin fold between your thumb and your index finger or as you were instructed by your doctor.
- Insert the needle straight into the skin quickly, as shown by your doctor in a 90° angle (See Figure K).
- Push the plunger to inject the medicine.



Figure K

Step 11.

- Remove the needle at the same angle it was inserted (90°) (See Figure L).
- Wipe the skin with a cotton gauze.



Figure L

Disposal of used needles, syringes, and vials

Step 12.

- Put the used needles, syringes, and vials in a FDA-cleared sharps disposal container right away after use (See Figure M). **Do not** throw away (dispose of) loose needles, syringes, or vials in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and vials. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.



Figure M

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: May, 2017

MEDICATION GUIDE
LUPRON INJECTION (loo-pron in 'jekSH(ə)n)
(leuprolide acetate)

What is the most important information I should know about LUPRON INJECTION?

- During the first 2 months of treatment, LUPRON INJECTION can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including vaginal bleeding, breast development, and growth of testicles, if:
 - your child does not receive their LUPRON INJECTION according to the doctor's prescribed schedule every time or
 - your child does not receive the right amount of LUPRON INJECTION

Call your child's doctor if these signs continue after the second month of treatment with LUPRON INJECTION.

- Some people taking gonadotropin releasing hormone (GnRH) agonists like LUPRON INJECTION have had new or worsened mental (psychiatric) problems. Mental (psychiatric) problems may include emotional symptoms such as:
 - crying
 - irritability
 - restlessness (impatience)
 - anger
 - acting aggressive

Call your child's doctor right away if your child has any new or worsening mental symptoms or problems while taking LUPRON INJECTION.

- Some people taking GnRH agonists like LUPRON INJECTION have had seizures. The risk of seizures may be higher in people who:
 - have a history of seizures

- have a history of epilepsy
- have a history of brain or brain vessel (cerebrovascular) problems or tumors
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs)

Seizures have also happened in people who have not had any of these problems. **Call your child's doctor right away if your child has a seizure while taking LUPRON INJECTION.**

What is LUPRON INJECTION?

LUPRON INJECTION is a prescription gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).

LUPRON INJECTION should not be taken if your child is:

- allergic to GnRH, GnRH agonist medicines, or any ingredients in LUPRON INJECTION. See the end of this Medication Guide for a complete list of ingredients in LUPRON INJECTION.
- pregnant or becomes pregnant. LUPRON INJECTION can cause birth defects or loss of the baby. If your child becomes pregnant call your doctor.

Before your child receives LUPRON INJECTION, tell the doctor about all of your child's medical conditions, including if they:

- have a history of mental (psychiatric) problems.
- have a history of seizures.
- have a history of epilepsy.
- have a history of brain or brain vessel (cerebrovascular) problems or tumors.
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs).
- are breastfeeding or plan to breastfeed. It is not known if LUPRON INJECTION passes into breast milk.

Tell your doctor about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will your child receive LUPRON INJECTION?

- Your child's doctor should do tests to make sure your child has CPP before treating with LUPRON INJECTION.
- LUPRON INJECTION should be given exactly as the doctor tells you to give it. See detailed "Instructions for Use" at the end of this Medication Guide for information about the right way to give LUPRON INJECTION.
- LUPRON INJECTION is injected under your child's skin and may be given by your child, a parent, a caregiver or a health professional.
- Keep all scheduled visits to the doctor. If scheduled doses are missed, your child may start having signs of puberty again. The doctor will do regular exams and blood tests to check for signs of puberty.

What are the possible side effects of LUPRON INJECTION?

LUPRON INJECTION may cause serious side effects. See "What is the most important information I should know about LUPRON INJECTION?"

The most common side effects of LUPRON INJECTION include:

- injection site reactions such as abscess
- pain throughout body
- headache
- acne or red, itchy, rash, and white scales (seborrhea)
- serious skin rash (erythema multiforme)
- mood changes
- swelling of vagina (vaginitis), vaginal bleeding, and vaginal discharge

These are not all the possible side effects of LUPRON INJECTION.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LUPRON INJECTION?

- Store LUPRON INJECTION below 77°F (25°C).
- **Do not** freeze LUPRON INJECTION.
- Protect LUPRON INJECTION from light.
- Store LUPRON INJECTION in the original carton until ready for use.

Keep LUPRON INJECTION and all medicines out of the reach of children.

General information about the safe and effective use of LUPRON INJECTION.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LUPRON INJECTION for a condition for which it was not prescribed. Do not give LUPRON INJECTION to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about LUPRON INJECTION that is written for health professionals.

What are the ingredients in LUPRON INJECTION?**LUPRON INJECTION daily administration:**

Active Ingredients: leuprolide acetate

Inactive Ingredients: sodium chloride, USP for tonicity adjustment, benzyl alcohol, NF as a preservative, and water for injection. The pH may have been adjusted with sodium hydroxide, NF and /or acetic acid, NF.

Manufactured for:

AbbVie Inc.

North Chicago, IL 60064

By Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

For more information, call 1-800-633-9110.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: May, 2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
019010Orig1s038

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Division of Metabolism and Endocrinology Products (DMEP)

Application: NDA 019010/S-038

Name of Drug: Lupron (leuprolide acetate) injection

Applicant: AbbVie Endocrine Inc.

Background and Summary

On October 28, 2016, Safety Labeling Change (SLC) Notification letters were issued to the application holders for the following products: Lupron Depot PED (leuprolide acetate) depot suspension/injection (NDA 020263), Supprelin LA (histrelin acetate) subcutaneous implant (NDA 022058), and Synarel (nafarelin acetate) nasal solution (NDA 019886). The SLC Notification letters required the applicants of these products to revise their prescribing information (PIs) with language regarding the risk of seizures in central precocious puberty (CPP) patients treated with GnRH agonists. See Dr. Jennifer Pippins's review dated October 28, 2016, for additional details. Due to an administrative oversight, the SLC Notification letter for Lupron (leuprolide acetate) injection (NDA 019010), which is also approved to treat CPP, was issued on November 14, 2016. Because Lupron is not currently marketed, SLC Notification letters were issued concurrently by the Office of Generic Drugs (OGD) to ANDA holders for leuprolide products.

The application holders for Lupron, Lupron Depot PED, and Supprelin LA submitted supplements in response to the SLC Notification letters. (b) (4)

However, there was not sufficient time to reach agreement with all of the applicants on the content of labeling prior to issuance of a second SLC, as described below.

On December 21, 2016, SLC Notification letters were issued to the application holders for all GnRH agonist products with approved indications to treat CPP (the same products that were involved with the SLC for seizures described above). These SLC Notification letters required the applicants of these products to revise their PIs with language regarding the risk of serious psychiatric adverse events in CPP patients treated with GnRH agonists. In addition, the SLC Notification letters required the applicants to develop a new Medication Guide (MG) for each of the products. See Dr. Pippins's review dated December 21, 2016, for additional details. Because of the requirement for a new MG for each product, the carton and container labeling was also required to be revised to include a prominent and conspicuous instruction to authorized dispensers to provide a MG to each patient to whom the drug is dispensed

The supplements submitted in response to these SLCs are listed in the table below. Note that the applicant for Lupron and Lupron Depot PED submitted supplements in response to the first SLC and amended those supplements with their response to the second SLC. The applicants for Supprelin LA and Synarel submitted separate supplements in response to each SLC.

Applicant	NDA	Product
AbbVie Endocrine Inc.	NDA 019010/S-038	Lupron (leuprolide acetate) injection
	NDA 020263/S-042	Lupron Depot PED (leuprolide acetate) depot suspension/injection
Endo Pharmaceuticals Solutions, Inc.	NDA 022058/S-014	Supprelin LA (histrelin acetate)
	NDA 022058/S-015	subcutaneous implant
G.D. Searle LLC., a subsidiary of Pfizer Inc.	NDA 019886/S-033	Synarel (nafarelin acetate) nasal solution
	NDA 019886/S-035	

The Office of Prescription Drug Promotion (OPDP) reviewed the proposed labeling for each product. Their review filed on March 6, 2017, included no comments for the prescribing information and noted that they would contribute to the review of the MGs that would be filed by the Division of Medical Policy Programs (DMPP), who filed a review on March 16, 2017. This review also included proposed revisions to the Instructions for Use (IFU) for Lupron and Synarel; these comments were the result of a collaborative review with the Division of Medication Error and Prevention Analysis (DMEPA). For Lupron, DMPP and DMEPA requested changes to update the IFU to current patient labeling standards; these comments were provided to the applicant as requested changes, which were not required under section 505(o)(4) of the FDCA. For Synarel, DMPP and DMEPA removed some information that was redundant with the new MG; therefore these were considered required changes under section 505(o)(4) of the FDCA. It should be noted that the new MG for Supprelin LA will replace the currently-approved patient package insert (PPI).

The applicants' proposed PIs and DMPP's recommended changes for the applicants' MGs and IFUs were reviewed by Dr. Pippins, along with the clinical team, and the applicants were asked to make revisions.

Materials Reviewed

This labeling review compared the following labeling for Lupron (leuprolide acetate) injection:

Labeling Reviewed	Final Proposed Labeling Submission Date	Currently Approved (supplement and date)
Prescribing Information	May 3, 2017	NDA 019010/S-037
Instructions for Use		July 10, 2014

Review

The prescribing information and Instructions for Use were compared to the currently approved versions, using the Microsoft Word electronic comparison function. A PDF copy of this comparison document is appended to this review. The changes in the proposed labeling are consistent with the SLC-required changes, as documented in the November 14 and December 21, 2016, SLC Notification letters and the labeling comments issued on February 14, March 7, March 23, and April 12, 2017. Other minor formatting revisions have been made throughout the labeling; all of these changes are acceptable.

Recommendations

The prescribing information and Instructions for Use described above and the final proposed Medication Guide submitted on May 3, 2017, were reviewed and found acceptable by Dr. Jennifer Rodriguez Pippins. The supplement is ready for approval.

Lupron is currently not marketed, and therefore revised carton and container labeling were not submitted. The approval letter should include instructions to the applicant that if they resume marketing of this product, they will need to submit a prior approval supplement with revised carton and container labeling as described in the December 21, 2016, Safety Labeling Change Notification letter.

The revision dates in the final PI, IFU, and MG, should be revised to reflect the approval date of the supplement prior to attachment to the approval letter.

Reviewed by: Elisabeth A. Hanan, M.S., Regulatory Project Manager for Safety
(see appended signature page)

Concurrency by: Pamela Lucarelli, Chief, Project Management Staff

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/s/

ELISABETH A HANAN
05/17/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 17, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products
Application Type and Number:	NDA 019010/S-038, NDA 020263/S-042, NDA 022058/S-014 and S-015
Product Name and Strength:	Lupron (leuprolide acetate) injection Lupron Depot PED (leuprolide acetate) depot injection Supprelin LA (histrelin acetate) subcutaneous implant
Product Type:	Single
Rx or OTC:	RX
Applicant/Sponsor Name:	Abbvie Inc. and Endo Pharmaceuticals Solutions Inc.
Submission Date:	November 17, 2016, November 29, 2016, December 8, 2016, January 23, 2017, January 17, 2017, February 21, 2017, March 1, 2017 and March 14, 2017
OSE RCM #:	2017-206
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 REASON FOR REVIEW

On October 28, 2016 and December 21, 2016 the Agency issued a Safety Labeling Change (SLC) notification to Abbvie for Lupron and Lupron Depot-PED (NDA 019010/S-038 and NDA 020263/S-042) and to Endo Pharmaceuticals Solutions for Supprelin LA (NDA 022058/S-014 and S-015). The SLC required the Sponsors to make changes to the Warnings, Precautions and Adverse Reaction sections of the prescribing information (PI) to include language regarding seizures and serious psychiatric adverse events. In addition, the notification on December 21, 2016 requested the development of a Medication Guide (MG) and revisions to the carton and container labels to include these new warnings and safety information.

The Division of Metabolic and Endocrine Products requested we review the proposed PI, MG and carton and container labels to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicants submitted Changes Being Effected supplements for Lupron (NDA 019010/S-038), Lupron Depot-PED (NDA 020263/S-042) and Supprelin LA (NDA 022058/S-014 and S-015) in response to a SLC notification to include language regarding seizures and serious psychiatric adverse events in the PI. In addition, they submitted a Prior Approval Supplements for the creation of a Medication Guide and revisions to the carton and container labels to include a statement alerting the dispenser to provide the Medication Guide while dispensing the drug products.

We note that Abbvie stated they no longer market Lupron (NDA 019010/S-038) in the U.S. and the last annual report showed no domestic distribution of the product, therefore, no carton and container labels were submitted for Lupron. In addition, for Lupron Depot-PED Abbvie stated they only submitted the draft carton label for one of the strengths and after approval all additional dosage strengths will be updated with the statement “Dispense the accompanying Medication Guide to each patient”.

DMEPA evaluated the submitted PIs, container labels and carton labeling and MGs for areas of vulnerability in regards to medication error.

We identified areas in the Lupron Depot-PED and Supprelin LA labels and labeling that can be improved to increase readability and prominence of important information. Specifically, we note information in the Lupron Depot-PED MG which lacks relevance for patient understanding and may lead to compliance error. Moreover, on the Supprelin LA carton and container label, the MG statement lacks prominence and may be overlooked. We provide recommendations to the Division in Section 4.1 and to the Applicant, in Section 4.2, to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

The revised PIs for Supprelin LA, Lupron and Lupron Depot-PED are acceptable from a medication error perspective. The MG for Supprelin LA and Lupron, as well as the submitted container label for Lupron Depot-PED are also acceptable from a medications error perspective. DMEPA identified areas in the Lupron Depot-PED MG and Supprelin LA carton and container labels that can be improved to promote the safe use of the product. We provide our recommendation in Section 4.1 and Section 4.2 to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Lupron Depot-PED Medication Guide

1.



4.2 RECOMMENDATIONS FOR ENDO PHARMACEUTICAL SOLUTIONS, INC

We recommend the following be implemented prior to approval of Supprelin LA (NDA 022058/S-014 and S-015):

A. Carton Label

1. Increase the prominence of the medication guide dispensing instruction by moving the statement up on the principal display panel (PDP) or increasing the

font size of the statement; thus increasing its prominence and reinforcing the directions to the provider.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Supprelin LA that Endo Pharmaceuticals Inc. submitted on January 17, 2017, February 21, 2017 and November 29, 2016.

Table 2. Relevant Product Information for Supprelin LA	
Initial Approval Date	05/03/2007
Active Ingredient	Histrelin acetate
Indication	for the treatment of children with central precocious puberty (CPP)
Route of Administration	Subcutaneous Implant
Dosage Form	Implant
Strength	50 mg
Dose and Frequency	1 implant every 12 months (65 mcg histrelin delivered per day over 12 months)
How Supplied	supplied in a corrugated shipping carton that contains 2 inner cartons: a small one for the vial containing the SUPPRELIN LA implant, which is shipped with a cold pack inside a polystyrene cooler that must be refrigerated upon arrival, and a larger one comprising the Implantation Kit, which must <i>not</i> be refrigerated, for use during insertion or removal of SUPPRELIN LA
Storage	2-8 °C (36-46 °F); Excursion permitted to 25 °C (77 °F) for 7 days. Do not freeze. Protect from light

Table 2.1 presents relevant product information for Lupron that Abbvie submitted on XXXX.

Table 2.1 Relevant Product Information for Lupron Depot-PED	
Initial Approval Date	4/16/1993
Active Ingredient	leuprolide acetate
Indication	treatment of children with central precocious puberty
Route of Administration	Intramuscular
Dosage Form	Prefilled syringe
Strength	7.5 mg, 11.25 mg, 15 mg, 30 mg
Dose and Frequency	<ul style="list-style-type: none">LUPRON DEPOT-PED is administered as a single intramuscular injection. The starting dose 7.5 mg, 11.25 mg, or 15 mg for 1-month administration is based on the child's weight.

	<ul style="list-style-type: none"> LUPRON DEPOT-PED is administered as a single intramuscular injection. The doses are either 11.25 mg or 30 mg for 3-month administration.
How Supplied	1- month and 3-month single prefilled syringe kit
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

Table 2.2 presents relevant product information for Lupron that AbbVie submitted on XXXX.

Table 2.1 Relevant Product Information for Lupron	
Initial Approval Date	4/9/1985
Active Ingredient	leuprolide acetate
Indication	palliative treatment of advanced prostatic cancer
Route of Administration	Subcutaneous
Dosage Form	Solution for Injection
Strength	2.8 mL/ vial
Dose and Frequency	1 mg daily
How Supplied	14 Day Patient Administration Kit with 14 disposable syringes and 28 alcohol swabs and six-vial carton
Storage	Store at 25°C (77°F); protect from light, do not freeze

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 13th, 2017, we searched the L:drive and AIMS using the terms, Supprelin LA, Lupron Depot-PED and Lupron to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 4 previous reviews and we confirmed that our previous recommendation were implemented or considered.

Rahimi, L. Label and Labeling Review for (Lupron Depot-PED (NDA 020263).. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 30. RCM No.:2015-2393.

Vee, S. Label and Labeling Review for (Lupron Depot-PED (NDA 020263). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 SEPT 12. RCM No.:2012-1357.

McMillan, T. Label and Labeling Review for(Lupron Depot-PED (NDA 020263). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 01 AUG 2011. RCM No.: 2011-2437.

Hamilton-Stokes, D. Label and Labeling Review for Lupron Depot-PED (NDA 020263). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2007 OCT 30. RCM No.: 2007-2058.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Supprelin LA labels and labeling submitted by Endo Pharmaceuticals Inc on January 17, 2017.

- Container labe
- Carton labeling
- Medication Guide
- Prescribing Information

G.2 Label and Labeling Images

Prescribing Information:

<\\cdsesub1\evsprod\nda022058\0078\m1\us\draft-pi-tracked.pdf>

<\\cdsesub1\evsprod\nda022058\0076\m1\us\draft-pi-tracked.pdf>

Medication Guide:

<\\cdsesub1\evsprod\nda022058\0076\m1\us\draft-medguide-tracked.pdf>

 (b) (4)

Container label:



Carton labeling:

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Lupron Depot-PED (NDA 020263/S-042) labels and labeling submitted by AbbVie Inc on November 17, 2016, January 23, 2017, March 1, 2017 and March 14, 2017.

Prescribing Information & Medication Guide:

<\\cdsesub1\evsprod\nda020263\0102\m1\us\114-labeling\draft-labeling\draft-labeling-text\neg-lbl-5092.pdf>

<\\cdsesub1\evsprod\nda020263\0101\m1\us\114-labeling\draft-labeling\draft-labeling-text\neg-lbl-5248.pdf>

<\\cdsesub1\evsprod\nda020263\0100\m1\us\dn3785v2-lupron-depot-ped-redline-pm-adr-seizures-2017jan11.pdf>

<\\cdsesub1\evsprod\nda020263\0099\m1\us\dn3785v1-lupron-depot-ped-redline-pm-adr-seizures-2016-oct-3.pdf>

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Container label:

(b) (4)

G.3 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Lupron (NDA 019010/S-038) labels and labeling submitted by AbbVie Inc on December 8, 2016, January 23, 2017, March 1, 2017 and March 14, 2017 .

Prescribing Information and Medication Guide:

<\\cdsesub1\evsprod\nda019010\0057\m1\us\114-labeling\draft-labeling\draft-labeling-text\neg-lbl-5134.pdf>

<\\cdsesub1\evsprod\nda019010\0056\m1\us\114-labeling\draft-labeling\draft-labeling-text\neg-lbl-5247.pdf>

<\\cdsesub1\evsprod\nda019010\0054\m1\us\114-labeling\draft-labeling\draft-labeling-text\neg-lbl-5134.pdf>

<\\cdsesub1\evsprod\nda019010\0051\m1\us\114-labeling\draft-labeling\draft-labeling-text\neg-lbl-5134.pdf>

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

IDALIA E RYCHLIK
03/20/2017

HINA S MEHTA
03/20/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 16, 2017

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Meena Ramachandra, PharmD
Regulatory Reviewer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): LUPRON INJECTION (leuprolide acetate)
LUPRON DEPOT-PED (leuprolide acetate for depot suspension)
SUPPRELIN LA (histrelin acetate) subcutaneous implant
SYNAREL (nafarelin acetate) nasal solution

Application Type/Number: NDA 019010/ S-038
NDA 020263/S-042
NDA 022058/S-014, S-015
NDA 019886/S-033, S-035

Tracked Safety Issue (TSI) Number: 1404 and 1405

Applicant: AbbVie Endocrine Inc.
Endo Pharmaceuticals
G.D. Searle LLC

1 INTRODUCTION

On October 28 and December 21, 2016, the Division of Metabolic Endocrinology Products (DMEP) issued safety labeling change (SLC) Notification letters for all gonadotropin releasing hormone (GnRH) agonists currently approved to treat central precocious puberty. These SLCs required that the New Drug Application (NDA) holders add language to the prescribing information (PI) regarding seizures (TSI 1404) and serious psychiatric adverse events (TSI 1405). The letters issued on December 21, 2016, also required that the NDA holders develop a Medication Guide (MG) for each of the approved products to include the new safety information. The approved products included: LUPRON INJECTION (leuprolide acetate), LUPRON DEPOT-PED (leuprolide acetate for depot suspension), SUPPRELIN LA (histrelin acetate) subcutaneous implant, and SYNAREL (nafarelin acetate) nasal solution. SUPPRELIN LA (histrelin acetate) subcutaneous implant and SYNAREL (nafarelin acetate) nasal solution had approved patient labeling, which were converted to MGs. LUPRON INJECTION (leuprolide acetate) and LUPRON DEPOT-PED (leuprolide acetate for depot suspension) did not have approved patient labeling. DMEP received supplements for all of the products. These supplements included proposed revisions to the Prescribing Information that incorporated the new safety information.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on February 1, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guides (MG) and Instructions for Use (IFU) for LUPRON INJECTION (leuprolide acetate), LUPRON DEPOT-PED (leuprolide acetate for depot suspension), SUPPRELIN LA (histrelin acetate) subcutaneous implant, and SYNAREL (nafarelin acetate) nasal solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft LUPRON INJECTION (leuprolide acetate) MG and IFU received on March 1, 2017, and received by DMPP and OPDP on March 3, 2017.
- Draft LUPRON INJECTION (leuprolide acetate) Prescribing Information (PI) received on March 1, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 3, 2017.
- Draft LUPRON DEPOT-PED (leuprolide acetate for depot suspension) MG received on March 1, 2017, and received by DMPP and OPDP on March 3, 2017.
- Draft LUPRON DEPOT-PED (leuprolide acetate for depot suspension) Prescribing Information (PI) received on March 1, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 3, 2017.

- Draft SUPPRELIN LA (histrelin acetate) subcutaneous implant MG received on January 17, 2017, and received by DMPP and OPDP on February 14, 2017.
- Draft SUPPRELIN LA (histrelin acetate) subcutaneous implant Prescribing Information (PI) received on January 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 14, 2017.
- Draft SYNAREL (nafarelin acetate) nasal solution MG received on January 17, 2017, and received by DMPP and OPDP on February 14, 2017.
- Draft SYNAREL (nafarelin acetate) nasal solution Prescribing Information (PI) received on January 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 14, 2017.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MGs and IFU documents using the Arial font, size 10.

In our collaborative review of the MGs and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MGs and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MGs and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MGs and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MGs and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MGs and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
03/16/2017

AMANPREET K SARAI
03/16/2017

MEENA RAMACHANDRA
03/16/2017

MARCIA B WILLIAMS
03/16/2017

LASHAWN M GRIFFITHS
03/16/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 6, 2017

To: Elisabeth Hanan, Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Focused Review of Labeling

LUPRON DEPOT-PED (leuprolide acetate for depot suspension)
Injection, Powder, Lyophilized, For Suspension
NDA 020263/S-042

LUPRON (leuprolide acetate) Injection
NDA 019010/S-038

SUPPRELIN LA (histrelin acetate) subcutaneous implant
NDA 022058/S-014, S-015

SYNAREL (nafarelin acetate) Nasal Solution
NDA 019886/S-033, S-035

On February 1, 2017, DMEP consulted OPDP to conduct a focused review of the draft Package Insert (PI) and Medication Guide (MG) for LUPRON DEPOT-PED (leuprolide acetate for depot suspension), LUPRON (leuprolide acetate) Injection, SUPPRELIN LA (histrelin acetate) subcutaneous implant and SYNAREL (nafarelin acetate) nasal solution. The focus of this labeling review is a new safety labeling change (SLC) requiring the sponsors to add language to the PI regarding seizures (TSI 1404) and serious psychiatric adverse events (TSI 1405).

OPDP conducted a focused review of the proposed substantially complete versions of the labeling provided by DMEP project manager Elisabeth Hanan via e-mail on February 14 and March 3, 2017. OPDP has no comments on the attached versions of the substantially complete labeling.

The Division of Medical Policy Programs and OPDP will provide comments on the proposed MGs under separate cover in a joint review.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

107 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEENA RAMACHANDRA
03/06/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
019010Orig1s038

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM TO FILE

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

NDA/BLA #s: NDA 020263, NDA 19010, NDA 022058, NDA 019886
PRODUCTS: Lupron Depot-PED (leuprolide)
Lupron (leuprolide)
Supprelin LA (histrelin)
Synarel (nafarelin)
APPLICANTS: AbbVie Endocrine Inc. (Lupron Depot-PED and Lupron)
Endo Pharmaceuticals Solutions, Inc. (Supprelin LA)
G.D. Searle LLC. – a subsidiary of Pfizer, Inc. (Synarel)
FROM: Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety, Division of Metabolism and Endocrinology
DATE: May 19, 2017
TOPICS: Safety Labeling Changes, GnRH agonists and psychiatric events, ADDENDUM
TSI #: 1405

PURPOSE

This memorandum to file is an addendum to the memorandum filed on December 21, 2016, regarding the Division of Metabolism and Endocrinology Products' (DMEP) requirement for safety labeling changes (SLC) to address the safety issue of psychiatric adverse events with the GnRH agonists indicated for central precocious puberty (CPP). This safety issue has been captured by Tracked Safety Issue (TSI) #1405.

This addendum pertains to the approval of this class SLC regarding psychiatric adverse events. On this same day a second SLC for this class, pertaining to seizures (TSI #1404), will also be approved; please see the separate memorandum pertaining TSI #1404 dated May 19, 2017.

BACKGROUND

The GnRH agonists are indicated for the treatment of central precocious puberty (CPP), which is defined as early onset of secondary sexual characteristics (generally earlier than 8 years of age in girls and 9 years of age in boys) associated with pubertal pituitary gonadotropin activation. This can result in a significantly advanced bone age and ultimately diminished adult height.

The GnRH agonists act by inhibiting gonadotropin secretion. Following an initial stimulatory effect, chronic use results in downregulation of gonadotropins and suppression of ovarian or testicular steroidogenesis (reversible upon discontinuation of treatment). Reduction of gonadotropins and sex steroids allows for a return to age-appropriate growth and development.

GnRH agonists currently approved for the treatment of CPP are listed in Table 1. There are additional NDAs for products containing these active ingredients approved for other (non-CPP) indications; the non-CPP indications are beyond the scope of this review.

Table 1. Approved GnRH agonists

NDA	Trade name	Active ingredient	Dosage Form	Applicant	Year Approved	Division	Marketing Status
020263	Lupron Depot-PED	leuprolide	IM injection	AbbVie Endocrine	1993	DMEP	Marketed
019010	Lupron	Leuprolide	SC injection	AbbVie Endocrine	1985	DOP1	Not Marketed
022058	Supprelin LA	histrelin	SC implant	Endo Pharmaceuticals Solutions	2007	DMEP	Marketed
019886	Synarel	nafarelin	Nasal spray	G.D. Searle LLC., a subsidiary of Pfizer	1990	DBRUP	Marketed

Of note, NDA 019886, for Synarel (nafarelin), was approved in 1990 for the management of endometriosis; this application is managed by the Division of Bone, Reproductive, and Urologic Products (DBRUP). The application holder for Synarel submitted a separate application, NDA 020109, which proposed a new indication for the treatment of CPP. This application was reviewed and approved by DMEP in 1992. Per current CDER policy, NDA 020109 was administratively closed following approval, and no supplements are to be accepted under this NDA. The currently approved Synarel labeling for both indications is managed under NDA 019886. Regarding NDA 19010, for Lupron (leuprolide), this product is currently approved but not marketed; it has not been withdrawn. The product is indicated both for CPP as well as for prostate cancer, and the NDA is housed in the Division of Oncology Products 1 (DOP1).

SLC NOTIFICATION and ePV Request

On December 21, 2016, FDA issued SLC notification letters to application holders listed in Table 1 that since approval the Agency had become aware of the of the risk of psychiatric adverse events with the use GnRH agonists in patients treated for CPP. This information was considered to be “new safety information” as defined in section 505-1(b)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA).

The main changes to the prescribing information outlined in the SLC notification letters were as follows:

Section 5 (PLR) / Warnings (non-PLR)

Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists. Post-marketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with DRUG. *[See Adverse Reactions (6)]*

Section 6.X Postmarketing (PLR) / Adverse Reactions (non-PLR)

Psychiatric Disorders

Depression, including rare reports of suicidal ideation and attempt, have been reported for GnRH agonists. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities associated with an increased risk of depression.

Section 17 Patient Counseling (PLR) / Information for Patients (non-PLR)

Inform caregivers that symptoms of emotional lability, such as crying, irritability, impatience and anger, have been observed in patients receiving GnRH agonists. Alert caregivers to the possibility of development or worsening of psychiatric symptoms, including depression, during treatment with DRUG *[see Warnings and Precautions (5.X) or Warnings, Adverse Reactions (6)]*

In addition to the above changes, the SLC notification letter also specified that the new safety information should be included in a Medication Guide. Since none of the products currently have a Medication Guide, the application holders were also instructed to submit revised container or package labeling adding a prominent statement instructing dispensers to provide the Medication Guide to each patient, as per 21 CFR 208.24(d).

The December 21, 2016, letter also included a request for enhanced pharmacovigilance (ePV) as follows:

We request that for a period of 5 years, you submit all cases of suicidal ideation and behavior, self-injury, or depression reported with DRUG as 15-day alert reports, and that you provide detailed analyses of suicidal ideation and behavior, self-injury, or depression events reported from clinical study and post-marketing reports of suicidal ideation and behavior, self-injury, or depression events as adverse events of special interest in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of this letter as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of suicidal ideation and behavior, self-injury, or depression reported with DRUG should also be provided in the periodic safety report.

The intent of the requested ePV is to provide for a more systemic collection of postmarketing data that could serve to refine how suicidality is addressed in labeling.

RESPONSES TO SLC NOTIFICATION

Submissions made in response to the SLC notification are detailed in Table 2.

Table 2. Responses to December 21, 2016, SLC notification

NDA	Brand name	Active ingredient(s)	Response to SLC
<i>AbbVie Endocrine</i>			
020263	Lupron Depot-PED	leuprolide	1/20/2017 amendment to S-042
019010	Lupron	leuprolide	1/20/2017 amendment to S-038
<i>Endo Pharmaceuticals Solutions</i>			
022058	Supprelin LA	histrelin	S-015
<i>G.D. Searle LLC., a subsidiary of Pfizer</i>			
019886	Synarel	nafarelin	S-035

The application holders' responses are discussed below.

Lupron Depot-PED (leuprolide) and Lupron (leuprolide)

In response to the December 21, 2016, SLC notification letter, AbbVie Endocrine (AbbVie) submitted amendments to prior approval supplements S-042 and S-038, for Lupron Depot-PED and Lupron, respectively, on January 20, 2017. These amendments proposed a substantive change, specifically, the addition of the sentence highlighted in bold below:



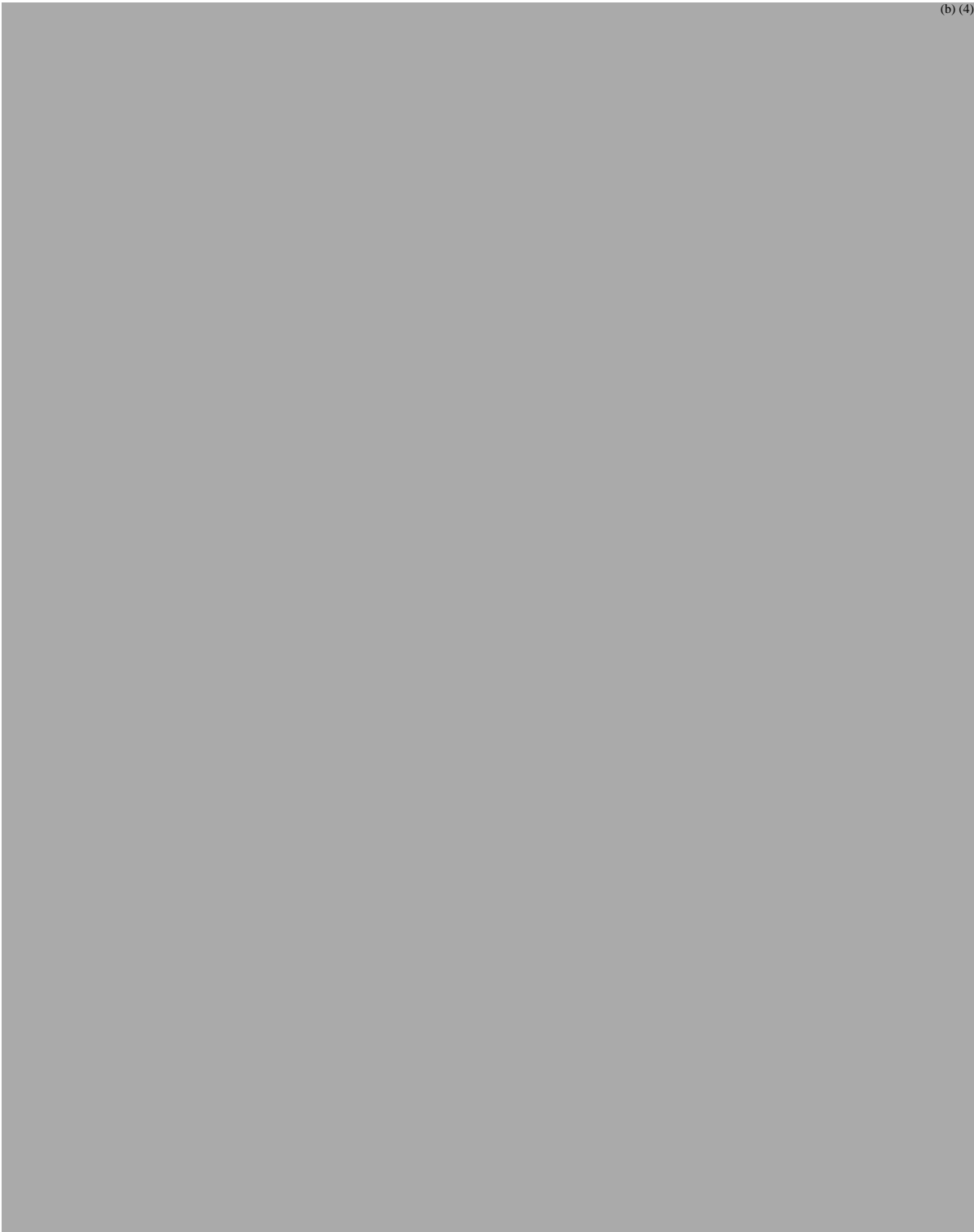
(b) (4)

DMEP did not agree with this additional language, as we found it to be [redacted] (b) (4)

[redacted] In response to our deletion of this text, AbbVie requested further discussion with the division. A teleconference with the company was held on February 22, 2017; the clinical team and Associated Director for Labeling were present. The application holder's main points, and DMEP's responses, were as follows:



(b) (4)



Supprelin LA (histrelin)

In response to the December 21, 2016, SLC notification letter, Endo Pharmaceuticals Solutions (Endo) submitted S-015 on January 16, 2017. The PAS accepted the language specified in the SLC notification letter, and added a few edits to Section 6.3, Postmarketing Experience: the

addition of text on emotional lability, and the addition of a phrase to the text on depression and suicidality (additions are underlined below):



These revisions were also found to be acceptable, and were applied across the class where relevant.

Synarel (nafarelin)

In response to the December 21, 2016, SLC notification letter, G.D. Searle LLC., a subsidiary of Pfizer (G.D. Searle) submitted S-035 on January 20, 2017. The PAS accepted the language in specified in the SLC notification letter.

Additional Revisions to Prescribing Information

Additional revisions to the Prescribing Information were made during the discussion period, based on feedback from the application holders (mainly the Supprelin LA application holder). They were applied across the class where relevant. For final labeling, please see the associated labeling review and approval letters.

Medication Guides, Instructions for Use, and Carton and Container labeling

All applicants submitted new Medication Guides, as instructed in the SLC notification letter. The discussion period for this SLC was extended, mainly in order to provide sufficient time to reach agreement on the new Medication Guides.

The Medication Guides were reviewed by the Division of Medical Policy Programs (DMPP) and DMEP, and after revision, were found to be acceptable. In addition, revisions were made to the products with Instructions for Use (IFU), namely, Lupron and Synarel, based on recommendations from a collaborative review between DMPP and the Division of Medication Error and Prevention Analysis (DMEPA). For Lupron, DMPP and DMEPA requested changes to update the IFU to current patient labeling standards; these comments were provided to the applicant as requested changes, which were not required under section 505(o)(4) of the FDCA. For Synarel, DMPP and DMEPA removed some information that was redundant with the new MG; therefore these were considered required changes under section 505(o)(4) of the FDCA. It should be noted that the new MG for Supprelin LA will replace the currently-approved patient package insert (PPI).

The application holders also submitted carton and container labeling updated with a statement alerting the dispenser to provide the Medication Guide, as required by 21 CFR 208.24(d). This labeling was reviewed by DMEPA and found to be acceptable.

CONCLUSION

DMEP has reached agreement with the application holders for GnRH agonists indicated for CPP regarding revised labeling responding to new safety information regarding the risk of psychiatric adverse events. Supplements 020263/S-042, 019010/S-038, 022058/S-015, and 019886/S-035 are ready for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER R PIPPINS
05/19/2017

MEMORANDUM TO FILE

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

NDA/BLA #s: NDA 020263, NDA 19010, NDA 022058, NDA 019886
PRODUCTS: Lupron Depot-PED (leuprolide)
Lupron (leuprolide)
Supprelin LA (histrelin)
Synarel (nafarelin)
APPLICANTS: AbbVie Endocrine Inc. (Lupron Depot-PED and Lupron)
Endo Pharmaceuticals Solutions, Inc. (Supprelin LA)
G.D. Searle LLC. – a subsidiary of Pfizer, Inc. (Synarel)
FROM: Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety, Division of Metabolism and Endocrinology
DATE: May 19, 2017
TOPICS: Safety Labeling Changes, GnRH agonists and seizure, ADDENDUM
TSI #: 1404

PURPOSE

This memorandum to file is an addendum to the memorandum filed on October 28, 2016, regarding the Division of Metabolism and Endocrinology Products' (DMEP) requirement for safety labeling changes (SLC) to address the safety issue of seizures with the GnRH agonists indicated for central precocious puberty (CPP). This safety issue has been captured by Tracked Safety Issue (TSI) #1404.

This addendum pertains to the approval of this class SLC regarding seizures. On this same day a second SLC for this class, pertaining to psychiatric adverse events (TSI #1405), will also be approved; please see the separate memorandum pertaining TSI #1405 dated May 19, 2017.

BACKGROUND

The GnRH agonists are indicated for the treatment of central precocious puberty (CPP), which is defined as early onset of secondary sexual characteristics (generally earlier than 8 years of age in girls and 9 years of age in boys) associated with pubertal pituitary gonadotropin activation. This can result in a significantly advanced bone age and ultimately diminished adult height.

The GnRH agonists act by inhibiting gonadotropin secretion. Following an initial stimulatory effect, chronic use results in downregulation of gonadotropins and suppression of ovarian or testicular steroidogenesis (reversible upon discontinuation of treatment). Reduction of gonadotropins and sex steroids allows for a return to age-appropriate growth and development.

GnRH agonists currently approved for the treatment of CPP are listed in Table 1. There are additional NDAs for products containing these active ingredients approved for other (non-CPP) indications; the non-CPP indications are beyond the scope of this review.

Table 1. Approved GnRH agonists

NDA	Trade name	Active ingredient	Dosage Form	Applicant	Year Approved	Division	Marketing Status
020263	Lupron Depot-PED	leuprolide	IM injection	AbbVie Endocrine	1993	DMEP	Marketed
019010	Lupron	Leuprolide	SC injection	AbbVie Endocrine	1985	DOP1	Not Marketed
022058	Supprelin LA	histrelin	SC implant	Endo Pharmaceuticals Solutions	2007	DMEP	Marketed
019886	Synarel	nafarelin	Nasal spray	G.D. Searle LLC., a subsidiary of Pfizer	1990	DBRUP	Marketed

Of note, NDA 019886, for Synarel (nafarelin), was approved in 1990 for the management of endometriosis; this application is managed by the Division of Bone, Reproductive, and Urologic Products (DBRUP). The application holder for Synarel submitted a separate application, NDA 020109, which proposed a new indication for the treatment of CPP. This application was reviewed and approved by DMEP in 1992. Per current CDER policy, NDA 020109 was administratively closed following approval, and no supplements are to be accepted under this NDA. The currently approved Synarel labeling for both indications is managed under NDA 019886. Regarding NDA 19010, for Lupron (leuprolide), this product is currently approved but not marketed; it has not been withdrawn. The product is indicated both for CPP as well as for prostate cancer, and the NDA is housed in the Division of Oncology Products 1 (DOP1).

SLC NOTIFICATION

On October 28, 2016, FDA issued SLC notification letters to application holders for the GnRH agonists (Lupron Depot-PED, Supprelin LA, and Synarel) that since approval the Agency had become aware of the of postmarketing cases of seizures in central precocious puberty patients receiving GnRH agonists. Notification for the Lupron product followed on November 14, 2016. This information was considered to be “new safety information” as defined in section 505-1(b)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA). The notification letters outlined changes that provided for harmonization of labeling for seizures across the class.

For both Supprelin LA (histrelin), Synarel (nafarelin), and Lupron (leuprolide) the changes include addition of a new statement to align with the current Warning and Precaution statement

for Lupron Depot-PED (leuprolide). Since Supprelin is in PLR format, the new language was added to Section 5, Warnings and Precautions. For Synarel and Lupron, which are not in PLR format, the new language was added to Warnings. For all three products, text is also added regarding the information health care providers should provide to patients. One point of distinction between the Supprelin LA (histrelin) and Synarel (nafarelin) labels is that the phrase “including Supprelin LA” is included in the sentence “postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, **including Supprelin LA**” (emphasis added). This statement is not included in the Synarel (nafarelin), as there were no cases identified for Synarel.

Supprelin LA (histrelin)

5 WARNINGS AND PRECAUTIONS

5.3 Convulsions

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including SUPPRELIN LA. Reports with GnRH agonists have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

17 PATIENT COUNSELING INFORMATION

Inform patients that reports of convulsions have been observed in patients receiving SUPPRELIN LA. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications have been associated with convulsions may be at increased risk [*see Warnings and Precautions (5.3)*].

Synarel (nafarelin)

WARNINGS

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists. Reports with GnRH agonists have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

Information for Patients, Patients’ Parents or Guardians

Inform patients that reports of convulsions have been observed in patients receiving GnRH agonists. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications have been associated with convulsions may be at increased risk [*see Warnings*].

Lupron (leuprolide)

WARNINGS

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. Reports with GnRH agonists have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

Information for Parents

Inform parents that reports of convulsions have been observed in patients receiving leuprolide acetate. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications have been associated with convulsions may be at increased risk [*see Warnings*].

For Lupron Depot-PED, which already had a Warnings and Precautions statement pertaining to seizures, the only change was a revision (indicated below in tracked changes) to indicate that events have been seen in more than one GnRH agonists product. The currently approved label includes the active ingredient name, rather than the trade name, and this was retained. In addition, the introductory phrase “Reports with GnRH agonists” at the start of the warning’s second sentence in the Supprelin LA (histrelin) and Synarel (nafarelin) labels was omitted, as the description of cases originates from the leuprolide experience.

Lupron Depot-PED (leuprolide)

5 WARNINGS AND PRECAUTIONS

5.2 Convulsions

Postmarketing reports of convulsions have been observed in patients receiving **GnRH agonists, including** leuprolide acetate **therapy**. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

A subsection also added to Section 17 of the Lupron Depot-PED (leuprolide) label, as the currently approved label does not address seizure in Section 17.

17 PATIENT COUNSELING INFORMATION

Inform patients that reports of convulsions have been observed in patients receiving leuprolide acetate. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications have been associated with convulsions may be at increased risk [*see Warnings and Precautions (5.2)*].

The SLC notification also specified revisions to the patient labeling for Supprelin LA (histrelin) and Synarel (nafarelin), which were based on recommendations from the Division of Medical

Policy Programs (DMPP). No corresponding revisions were issued to Lupron Depot-PED or Lupron, as those products had no associated patient labeling at that time. Subsequent to the issuance of the October 28, 2016, SLC notification for seizures, DMEP issued a second SLC notification pertaining to the risk of psychiatric adverse events with the GnRH agonists indicated for central precocious puberty (CPP). This second SLC notification, dated December 21, 2016, specified that the applicants develop a new Medication Guide (MG). These MGs included information describing both the risk of psychiatric adverse events and seizures, and were reviewed by the Division of Medical Policy Programs (DMPP). For further details, see the memorandum pertaining to TSI #1405 dated May 19, 2017.

RESPONSES TO SLC NOTIFICATION

Application holders for Lupron Depot-PED (leuprolide), Lupron (leuprolide), and Supprelin LA (histrelin) submitted prior approval supplements (PAS) in response to the SLC notification,

[Redacted] (b) (4)

Table 1. Responses to October 28, 2016, SLC notification

NDA	Brand name	Active ingredient(s)	Response to SLC
<i>AbbVie Endocrine</i>			
020263	Lupron Depot-PED	leuprolide	S-042
019010	Lupron	leuprolide	S-038
<i>Endo Pharmaceuticals Solutions</i>			
022058	Supprelin LA	histrelin	S-014

The application holders’ responses to the SLC notification are discussed below.

Lupron Depot-PED (leuprolide)

In response to the October 28, 2016, SLC notification letter, AbbVie Endocrine (AbbVie) submitted a prior approval supplement (PAS) on November 17, 2016, for Lupron Depot-PED (leuprolide), accepting the language specified in the SLC notification letter.

Lupron (leuprolide)

In response to the November 14, 2016, SLC notification letter, AbbVie submitted a PAS on December 8, 2016, for Lupron (leuprolide), accepting the language specified in the SLC notification letter.

Supprelin LA (histrelin)

In response to the October 28, 2016, SLC notification letter, Endo Pharmaceuticals Solutions (Endo) submitted a PAS on November 29, 2016, for Supprelin LA (histrelin). The PAS accepted the language specified in the SLC notification letter, with one edit to Section 17 that was found to be acceptable and was incorporated, where applicable, to other products in the class.

Synarel (nafarelin)

(b) (4)



(b) (4) to submit proposed labeling, which they did in the form of a Changes Being Effected (CBE) supplement (NDA 019886/S-033) on December 16, 2016. This CBE supplement accepted all of the labeling revisions outlined in the October 28, 2016, SLC notification letter.

The discussion period for this SLC was extended to allow for coordination with approval of the SLC for TSI #1405. For final labeling, please see the associated labeling review and approval letters.

(b) (4)



CONCLUSION

DMEP has reached agreement with the application holders for GnRH agonists indicated for CPP regarding revised labeling responding to new safety information regarding the risk of seizures. Supplements 020263/S-042, 019010/S-038, 022058/S-014, and 019886/S-033 are ready for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER R PIPPINS
05/19/2017

From: [Johnson, Jennifer](#)
To: "Neall, Patti"
Bcc: [Johnson, Jennifer](#)
Subject: NDAs 19010/S-038 (Lupron) and 20263/S-042 (Lupron Depot-Ped) - REVISED FDA PI, MEDICATION GUIDE, INSTRUCTIONS FOR USE
Date: Wednesday, April 12, 2017 6:56:33 PM
Attachments: [Lupron Depot-PED PI-MG 07Apr2017-FDA comments.doc](#)
[Lupron PI-IFU-MG 07Apr2017-FDA comment.doc](#)

Hi Patti,

Please find attached our final edits for the Lupron and Lupron Depot-Ped content of labeling.

We respectfully request a response by Tuesday, April 18th.

A response via email is acceptable; once we clear the final label we will request that you submit the final labeling through the Gateway.

Also, we are requesting formal submission of the carton labeling (updated with the Medication Guide statements) as well as formal submission of the container labeling that you sent via email, no later than Friday, April 21st.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Neall, Patti [mailto:patti.neall@Abbvie.com]
Sent: Friday, April 07, 2017 6:38 PM
To: Johnson, Jennifer
Subject: RE: AbbVie Inc. - NDAs 19010/S-038 (Lupron) and 20263/S-042 (Lupron Depot-Ped) - REVISED MEDICATION GUIDE, INSTRUCTIONS FOR USE, DRAFT CONTAINER LABELING

Hi Jennifer,

Thank you for confirming receipt of the draft labeling.

Have a nice weekend!

Kind regards,
Patti Neall

(847) 937-0680

Patti Neall
Director, Regulatory Affairs
Global Regulatory Strategy

abbvie

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AP30-1, Dept. PA72
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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Friday, April 07, 2017 5:30 PM
To: Neall, Patti
Subject: RE: AbbVie Inc. - NDAs 19010/S-038 (Lupron) and 20263/S-042 (Lupron Depot-Ped) - REVISED MEDICATION GUIDE, INSTRUCTIONS FOR USE, DRAFT CONTAINER LABELING

Hi Patti,

I am confirming receipt of your email. Thank you very much—we will let you know if we have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Phone: (301) 796-2194
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jennifer.johnson@fda.hhs.gov

From: Neall, Patti [<mailto:patti.neall@Abbvie.com>]
Sent: Friday, April 07, 2017 2:53 PM
To: Johnson, Jennifer

Subject: AbbVie Inc. - NDAs 19010/S-038 (Lupron) and 20263/S-042 (Lupron Depot-Ped) - REVISED MEDICATION GUIDE, INSTRUCTIONS FOR USE, DRAFT CONTAINER LABELING

Importance: High

Hi Jennifer,

As requested, we are sending via email the remaining draft container labeling for the Lupron Depot-PED 11.25 mg 1-month, 15 mg 1-month, 11.25 mg 3-month, and 30 mg 3-month dosage strengths with the statement, "Dispense the accompanying Medication Guide to each patient."

Also attached is the revised Lupron Injection (NDA 019010) and Lupron Depot-PED (NDA 020263) Medication Guides and revised Instructions for Use labeling. A tracked changes version and clean version of the labeling are attached.

If you have any questions, please let me know.

Kind regards,
Patti Neall
Director, Regulatory Affairs
AbbVie Inc.
(847) 937-0680

Patti Neall
Director, Regulatory Affairs
Global Regulatory Strategy

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EMAIL: patti.neall@abbvie.com

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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]

Sent: Thursday, March 23, 2017 3:26 PM

To: Neall, Patti

Subject: NDAs 19010/S-038 (Lupron) and 20263/S-042 (Lupron Depot-Ped): Latest FDA labeling comments (MG, IFU, carton/container)

Dear Patti,

Please find attached our edits and comments on the Lupron and Lupron Depot Medication Guides and Instructions for Use and carton/container labeling.

We kindly request a response by **COB Thursday, April 6th**.

NDA 019010/S-038 – Lupron

- Medication Guide – Note that we have made extensive edits to your proposed MG for consistency across the class and per current patient labeling practices. Given the extensive edits, we are providing both clean and tracked changes versions of the document.
- Instructions for Use – Note that the marked changes are being requested per current patient labeling standards and are not required as a part of the FDAAA SLC.

NDA 020263/S-042 – Lupron Depot-Ped

- Medication Guide – As for Lupron, note that we have made extensive edits to your proposed MG for consistency across the class and per current patient labeling practices. Given the extensive edits, we are providing both clean and tracked changes versions of the document.
- The revised container labeling submitted on March 14, 2017, for the 7.5 mg 1 month dose strength is acceptable. Please proceed with submitting the remaining revised carton/container labeling as outlined in our March 21, 2017, letter.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
04/12/2017

From: [Johnson, Jennifer](#)
To: "Neall, Patti"
Bcc: [Johnson, Jennifer](#)
Subject: NDAs 19010/S-038 (Lupron) and 20263/S-042 (Lupron Depot-Ped): Latest FDA labeling comments (MG, IFU, carton/container)
Date: Thursday, March 23, 2017 4:26:30 PM
Attachments: [Lupron Depot PED MG-clean.doc](#)
[Lupron Depot PED MG-marked.doc](#)
[Lupron IFU-clean.doc](#)
[Lupron IFU-marked.doc](#)
[Lupron MG-clean.doc](#)
[Lupron MG-marked.doc](#)

Dear Patti,

Please find attached our edits and comments on the Lupron and Lupron Depot Medication Guides and Instructions for Use and carton/container labeling.

We kindly request a response by **COB Thursday, April 6th**.

NDA 019010/S-038 – Lupron

- Medication Guide – Note that we have made extensive edits to your proposed MG for consistency across the class and per current patient labeling practices. Given the extensive edits, we are providing both clean and tracked changes versions of the document.
- Instructions for Use – Note that the marked changes are being requested per current patient labeling standards and are not required as a part of the FDAAA SLC.

NDA 020263/S-042 – Lupron Depot-Ped

- Medication Guide – As for Lupron, note that we have made extensive edits to your proposed MG for consistency across the class and per current patient labeling practices. Given the extensive edits, we are providing both clean and tracked changes versions of the document.
- The revised container labeling submitted on March 14, 2017, for the 7.5 mg 1 month dose strength is acceptable. Please proceed with submitting the remaining revised carton/container labeling as outlined in our March 21, 2017, letter.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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/s/

JENNIFER L JOHNSON
03/23/2017



NDA 019010/S-038

LABELING DISCUSSION EXTENSION

AbbVie Endocrine Inc.
Attention: Patti Neall
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Neall:

Please refer to your December 8, 2016, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron (leuprolide acetate) injection.

On November 14, 2016, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Lupron to address the risk of seizures in central precocious puberty patients, with the use of GnRH agonists, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On December 8, 2016, we received your prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

We refer to our letter dated December 21, 2016, informing you that we determined that an extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling.

Also on December 21, 2016, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Lupron to address the risk of serious psychiatric adverse events in central precocious puberty patients, with the use of GnRH agonists, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, including development of a new Medication Guide and corresponding revisions to the carton and container labeling, or notify FDA that you

do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

In response to our December 21, 2016, Safety Labeling Change Notification letter, we received your amendment to S-038 dated January 20, 2017, containing your proposed safety related labeling changes for the prescribing information. We also refer to your amendment dated March 1, 2017, containing a proposed new Medication Guide. We note that Lupron is currently not marketed, and therefore revised carton and container labeling were not submitted. If you resume marketing of this product, you will need to submit a prior approval supplement with revised carton and container labeling as described in our December 21, 2016, Safety Labeling Change Notification letter.

Per our letters issued on December 21, 2016, the discussion period for this supplement was to end on March 21, 2017.

This letter is to inform you that we have determined that another extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on May 5, 2017.

If you have any questions, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER R PIPPINS
03/21/2017

From: [Johnson, Jennifer](#)
To: "Neall, Patti"
Bcc: [Johnson, Jennifer](#)
Subject: RE: AbbVie Inc. - NDAs 019010/S-038 (Lupron) and 020263/S-042 (Lupron Depot Ped): Labeling Discussion Comments - Revised Draft Prior Approval Supplements-Labeling and Medication Guide - submitted on March 1, 2017
Date: Tuesday, March 07, 2017 5:26:59 PM
Attachments: [Lupron Depot PI-FDA comments_06Mar2017.doc](#)
[Lupron PI-FDA comments_06Mar2017.doc](#)

Hi Patti,

Thank you for confirming. Have you and your team decided on a submission timeline for the revised carton/container labeling?

Also, please find attached the revised Lupron PIs; we consider these to be our final edits to the PIs. We will provide comments for the Medication Guides within the next 1-2 weeks. Please provide us with your response PIs within 1 week and the revised carton/container labeling as soon as possible (within 1 week at the latest).

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Neall, Patti [mailto:patti.neall@Abbvie.com]
Sent: Thursday, March 02, 2017 2:54 PM
To: Johnson, Jennifer
Cc: Wheeler, Charlene
Subject: RE: AbbVie Inc. - NDAs 019010/S-038 (Lupron) and 020263/S-042 (Lupron Depot Ped): Labeling Discussion Comments - Revised Draft Prior Approval Supplements-Labeling and Medication Guide - submitted on March 1, 2017
Importance: High

Hi Jennifer,

Thank you for confirming receipt of the labeling submissions.

We are aware of the requirement for revising the carton/container labeling with a statement to dispense the accompanying Medication Guide to each patient. We are proposing to include the following text, "Dispense the accompanying Medication Guide to each patient."

I'll follow up with our team regarding the timing for the submission. I'm aware that the FDA discussion period for the Safety Labeling Change Notification is by March 21, 2017.

If you have any questions, please let me know.

Kind regards,
Patti Neall
Director, Regulatory Affairs
AbbVie Inc.
(847) 937-0680

Patti Neall
Director, Regulatory Affairs
Global Regulatory Strategy

abbvie

AbbVie, Inc.
AP30-1, Dept. PA72
1 North Waukegan Road
North Chicago, IL 60064
Office: 1-847-937-0680
Mobile: (b) (6)
EMAIL: patti.neall@abbvie.com

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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Thursday, March 02, 2017 12:01 PM
To: Neall, Patti
Cc: Wheeler, Charlene
Subject: RE: AbbVie Inc. - NDAs 019010/S-038 (Lupron) and 020263/S-042 (Lupron Depot Ped): Labeling Discussion Comments - Revised Draft Prior Approval Supplements-Labeling and Medication Guide - submitted on March 1, 2017

Dear Patti,

Thank you for the update; we have received the submissions.

We see that the submissions did not contain the revised carton and container labeling. Per the letters we issued on December 21, 2016, there is a requirement to submit revised carton/container labeling that includes a prominent and conspicuous instruction to authorized dispensers to provide a

Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. We wanted to remind you of this requirement and wanted to know when you will be submitting this revised labeling (ideally as soon as possible, due to our existing timelines).

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Neall, Patti [<mailto:patti.neall@Abbvie.com>]
Sent: Thursday, March 02, 2017 9:28 AM
To: Johnson, Jennifer
Cc: Wheeler, Charlene
Subject: AbbVie Inc. - NDAs 019010/S-038 (Lupron) and 020263/S-042 (Lupron Depot Ped): Labeling Discussion Comments - Revised Draft Prior Approval Supplements-Labeling and Medication Guide - submitted on March 1, 2017
Importance: High

Hi Jennifer,

This is to inform you that we have submitted via the Electronic Submissions Gateway on March 1, 2017, the revised draft Prior Approval Supplement (PAS)-Labeling, which incorporates the comments received by the FDA on February 14, 2017 to NDA 020263/S-042 and NDA 019010/S-038.

In addition, AbbVie provided, as required, a new proposed draft Medication Guide within the USPI labeling. An extension for the submission of the Medication Guide on March 1, 2017 was granted on January 19, 2017.

I've also copied Charlene Wheeler, MSHS, Senior Regulatory Health Project Manager, as the submission was also made to NDA 019010; Lupron Injection within the Division of Oncology Products I.

If you have any questions, please let me know.

Kind regards,
Patti Neall
Director, Regulatory Affairs
AbbVie Inc.
(847) 937-0680

Patti Neall
Director, Regulatory Affairs
Global Regulatory Strategy

abbvie

AbbVie, Inc.
AP30-1, Dept. PA72
1 North Waukegan Road
North Chicago, IL 60064
Office: 1-847-937-0680
Mobile: (b) (6)
EMAIL: patti.neall@abbvie.com

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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Tuesday, February 14, 2017 4:17 PM
To: Neall, Patti
Subject: NDAs 019010/S-038 (Lupron) and 020263/S-042 (Lupron Depot Ped): Labeling Discussion Comments
Importance: High

Dear Patti,

We have reviewed the package inserts submitted to your NDAs 019010/S-038 (Lupron injection) and 020263/S-042 (Lupron Depot Ped).

Please see the attached draft PIs containing our edits and comments and let me know if you have any questions.

Note that our comments on your proposed Medication Guides will be forthcoming.

We respectfully request a response in 1 week (i.e., by February 21, 2017).

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712

jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
03/07/2017

From: [Johnson, Jennifer](#)
To: "Neall, Patti"
Bcc: [Johnson, Jennifer](#)
Subject: NDAs 019010/S-038 (Lupron) and 020263/S-042 (Lupron Depot Ped): Labeling Discussion Comments
Date: Tuesday, February 14, 2017 5:17:13 PM
Attachments: [Lupron PI-FDA comments 14Feb2017.doc](#)
[Lupron Depot PI-FDA comments 14Feb2017.doc](#)
Importance: High

Dear Patti,

We have reviewed the package inserts submitted to your NDAs 019010/S-038 (Lupron injection) and 020263/S-042 (Lupron Depot Ped).

Please see the attached draft PIs containing our edits and comments and let me know if you have any questions.

Note that our comments on your proposed Medication Guides will be forthcoming.

We respectfully request a response in 1 week (i.e., by February 21, 2017).

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
02/14/2017

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE / DMEPA (attn.: Deveonne Hamilton-Stokes)

FROM: OND/ODE II/DMEP
Elisabeth Hanan (SRPM), Jennifer Pippins (DDS)

DATE February 1, 2017	IND NO.	NDA NO. Multiple (see below)	TYPE OF DOCUMENT Revised carton/container labeling	DATE OF DOCUMENT
NAME OF DRUG Multiple (see below)	PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG GnRH agonists	DESIRED COMPLETION DATE March 15, 2017	

NAME OF FIRM: Multiple (see below)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | | <input type="checkbox"/> MEDICATION ERRORS |
| <input type="checkbox"/> MEETING PLANNED BY | | <input type="checkbox"/> OTHER (SPECIFY BELOW): |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

On October 28 and December 21, 2016, DMEP issued SLC Notification letters for all GnRH agonists currently approved to treat central precocious puberty. These SLCs required that the NDA holders add language to the prescribing information (PI) regarding seizures (TSI 1404) and serious psychiatric adverse events (TSI 1405). The letters issued on December 21, 2016, also required that the NDA holders develop a Medication Guide (MG) for each of the approved products to include this new safety information. Supprelin LA and Synarel currently have approved patient labeling, which will be converted to MGs; Lupron does not currently have approved patient labeling. Because none of these products previously had a requirement for a MG, the letters also included instructions that the label of each container or package must now include a prominent and conspicuous instruction to authorized dispensers to provide a MG to each patient to whom the drug is dispensed, and state how the MG is provided.

DMEP has received supplements for all of the products as listed in the table below. These supplements include proposed revisions to the PIs to incorporate the new safety information. Several of the applicants are still working to prepare the new MGs and revised carton/container (C/C) labeling. We expect to have all of the MGs and C/C labeling submitted by 03/01/2017.

NDA 019010/S-038	Lupron (leuprolide acetate) injection	AbbVie Endocrine Inc.
NDA 020263/S-042	Lupron Depot PED (leuprolide acetate) depot suspension/injection	AbbVie Endocrine Inc.
NDA 022058/S-014, S-015	Supprelin LA (histrelin acetate) subcutaneous implant	Endo Pharmaceuticals Solutions, Inc.
NDA 019886/S-033, S-035	Synarel (nafarelin acetate) nasal solution	G.D. Searle LLC., a subsidiary of Pfizer Inc.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ELISABETH A HANAN
02/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION	
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) OND/ODE II/DMEP Elisabeth Hanan (SRPM), Jennifer Pippins (DDS)	
REQUEST DATE: February 1, 2017	NDA/BLA NO.: Multiple (see below)	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)	
NAME OF DRUG: Multiple (see below)	PRIORITY CONSIDERATION: standard	CLASSIFICATION OF DRUG: GnRH agonists	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) March 15, 2017
SPONSOR: Multiple (see below)		PDUFA Date: April 5, 2017	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA/ANDA <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission: proposed Medication Guides are pending receipt			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: On October 28 and December 21, 2016, DMEP issued SLC Notification letters for all GnRH agonists currently approved to treat central precocious puberty. These SLCs required that the NDA holders add language to the prescribing information (PI) regarding seizures (TSI 1404) and serious psychiatric adverse events (TSI 1405). The letters issued on December 21, 2016, also required that the NDA holders develop a Medication Guide (MG) for each of the approved products to include this new safety information. Supprelin LA and Synarel currently have approved patient labeling, which will be converted to MGs; Lupron does not currently have approved patient labeling. Because none of these products previously had a requirement for a MG, the letters also included instructions that the label of each container or package must now include a prominent and conspicuous instruction to authorized dispensers to provide a MG to each patient to whom the drug is dispensed, and state how the MG is provided. DMEP has received supplements for all of the products as listed in the table below. These supplements include proposed revisions to the PIs to incorporate the new safety information. Several of the applicants are still working to prepare the new MGs and revised carton/container (C/C) labeling. We expect to have all of the MGs and C/C labeling submitted by 03/01/2017.			
NDA 019010/S-038	Lupron (leuprolide acetate) injection	AbbVie Endocrine Inc.	
NDA 020263/S-042	Lupron Depot PED (leuprolide acetate) depot suspension/injection	AbbVie Endocrine Inc.	
NDA 022058/S-014, S-015	Supprelin LA (histrelin acetate) subcutaneous implant	Endo Pharmaceuticals Solutions, Inc.	
NDA 019886/S-033, S-035	Synarel (nafarelin acetate) nasal solution	G.D. Searle LLC., a subsidiary of Pfizer Inc.	
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER			

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/s/

ELISABETH A HANAN
02/01/2017

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) OND/ODE II/DMEP Elisabeth Hanan (SRPM), Jennifer Pippins (DDS)	
REQUEST DATE: February 1, 2017	IND NO.	NDA/BLA NO. Multiple (see below)	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG: Multiple (see below)	PRIORITY CONSIDERATION: standard	CLASSIFICATION OF DRUG GnRH agonists	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) March 15, 2017
NAME OF FIRM: Multiple (see below)		PDUFA Date: April 5, 2017	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
---	--	--

EDR link to submission: proposed Medication Guides are pending receipt

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

On October 28 and December 21, 2016, DMEP issued SLC Notification letters for all GnRH agonists currently approved to treat central precocious puberty. These SLCs required that the NDA holders add language to the prescribing information (PI) regarding seizures (TSI 1404) and serious psychiatric adverse events (TSI 1405). The letters issued on December 21, 2016, also required that the NDA holders develop a Medication Guide (MG) for each of the approved products to include this new safety information. Supprelin LA and Synarel currently have approved patient labeling, which will be converted to MGs; Lupron does not currently have approved patient labeling. Because none of these products previously had a requirement for a MG, the letters also included instructions that the label of each container or package must now include a prominent and conspicuous instruction to authorized dispensers to provide a MG to each patient to whom the drug is dispensed, and state how the MG is provided.

DMEP has received supplements for all of the products as listed in the table below. These supplements include proposed revisions to the PIs to incorporate the new safety information. Several of the applicants are still working to prepare the new MGs and revised carton/container (C/C) labeling. We expect to have all of the MGs and C/C labeling submitted by 03/01/2017.

NDA 019010/S-038	Lupron (leuprolide acetate) injection	AbbVie Endocrine Inc.
NDA 020263/S-042	Lupron Depot PED (leuprolide acetate) depot suspension/injection	AbbVie Endocrine Inc.
NDA 022058/S-014, S-015	Supprelin LA (histrelin acetate) subcutaneous implant	Endo Pharmaceuticals Solutions, Inc.
NDA 019886/S-033, S-035	Synarel (nafarelin acetate) nasal solution	G.D. Searle LLC., a subsidiary of Pfizer Inc.
SIGNATURE OF REQUESTER		
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/s/

ELISABETH A HANAN
02/01/2017



NDA 019010/S-038

LABELING DISCUSSION EXTENSION

AbbVie Endocrine Inc.
Attention: Patti Neall
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Neall:

Please refer to your December 8, 2016, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron (leuprolide acetate) injection.

On November 14, 2016, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Lupron to address the risk of seizures in central precocious puberty patients, with the use of GnRH agonists, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On December 8, 2016, we received your prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that an extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on March 21, 2017.

If you have any questions, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER R PIPPINS
12/21/2016