CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020263Orig1s042

Trade Name: **Lupron Depot PED**

Generic Name: **leuprolide acetate**

Sponsor: **AbbVie Endocrine Inc.**

Approval Date: 5/19/2017

Indications: LUPRON DEPOT-PED is a gonadotropin releasing hormone (GnRH) agonist indicated in the treatment of children with central precocious puberty.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020263/S-042

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 November 17, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron Depot PED (leuprolide acetate) depot suspension/injection.

We also refer to our letters dated October 28 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 Depot PED, consistent with our October 28 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).

IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed immediate container labels submitted on April 21, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Container Labels for approved NDA 020263/S-042**." Approval of this submission by FDA is not required before the labeling is used.

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 Depot PED 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 Depot PED 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

ENCLOSURES:
Content of Labeling
Container 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT-PED safely and effectively. See full prescribing information for LUPRON DEPOT-PED.

LUPRON DEPOT-PED (leuprolide acetate for depot suspension)
Injection, Powder, Lyophilized, For Suspension
Initial U.S. Approval: 1993

RECENT MAJOR CHANGES

Warnings and Precautions (5.2)	5/2017
Warnings and Precautions (5.3)	5/2017

INDICATIONS AND USAGE

LUPRON DEPOT-PED is a gonadotropin releasing hormone (GnRH) agonist indicated in the treatment of children with central precocious puberty. (1)

DOSAGE AND ADMINISTRATION

- 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. (2)
- LUPRON DEPOT-PED is administered as a single intramuscular injection. The doses are either 11.25 mg or 30 mg for 3-month administration.(2)
- Hormonal and clinical parameters should be monitored during treatment to ensure adequate suppression. (2)
- The injection site should be varied periodically. (2)

DOSAGE FORMS AND STRENGTHS

LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration and LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration are provided in a prefilled dual chamber syringe for intramuscular injection. (3)

CONTRAINDICATIONS

- Hypersensitivity reactions. (4)
- Pregnancy. (4,8 1)

WARNINGS AND PRECAUTIONS

- An increase in clinical signs and symptoms of puberty may be observed during the first 2-4 weeks of therapy since gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug before being suppressed. (5.1)
- Psychiatric events have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms. (5.2)
- Convulsions have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions. (5.3)

ADVERSE REACTIONS

- Adverse events related to suppression of endogenous sex steroid secretion may occur with LUPRON DEPOT-PED 7 5 mg, 11.25 mg, or 15 mg for 1-month administration. (6.1, 6.3)
- In clinical studies for LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration, the most frequent (≥2 patients) adverse reactions were: injection site pain, weight increased, headache, mood altered, and injection site swelling. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

USE IN SPECIFIC POPULATIONS

- The use of LUPRON DEPOT-PED in children under 2 years is not recommended. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUPRON DEPOT-PED is indicated in the treatment of children with central precocious puberty (CPP).

CPP 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. It may show a significantly advanced bone age that can result in diminished adult height.

Prior to initiation of treatment a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of luteinizing hormone (LH) (basal or stimulated with a GnRH analog), sex steroids, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumors), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin secreting tumor), and adrenal steroid measurements to exclude congenital adrenal hyperplasia.

2 DOSAGE AND ADMINISTRATION

2.1 Dose and Principles of Dosing 7.5 mg, 11.25 mg, or 15 mg for 1-month administration

LUPRON DEPOT-PED must be administered under the supervision of a physician.

LUPRON DEPOT-PED is administered as a single intramuscular injection once a month. The starting dose will be dictated by the child's weight, as indicated in the table below.

Table 1. Dosing Recommendations Based on Body Weight for LUPRON DEPOT-PED 1-month Formulations

Body Weight	Recommended Dose
≤ 25 kg	7.5 mg
> 25-37.5 kg	11.25 mg
> 37.5 kg	15 mg

The dose of LUPRON DEPOT-PED must be individualized for each child. If adequate hormonal and clinical suppression is not achieved with the starting dose, it should be increased to the next available higher dose (e.g. 11.25 mg or 15 mg at the next monthly injection). Similarly, the dose may be adjusted with changes in body weight. The injection site should be varied periodically.

The goal of therapy is to suppress pituitary gonadotropins and peripheral sex steroids, and to arrest progression of secondary sexual characteristics. Hormonal and clinical parameters should be monitored after 1–2 months of initiating therapy and with each dose change to ensure adequate pituitary gonadotropin suppression. Once a dose that results in adequate hormonal suppression is found, it can often be maintained for the duration of therapy in most children. It is

recommended, however, that adequate hormonal suppression be verified in such patients as weight can increase significantly while on therapy.

Each LUPRON DEPOT-PED strength and formulation has different release characteristics. Do not use partial syringes or a combination of syringes to achieve a particular dose.

LUPRON DEPOT-PED should be discontinued at the appropriate age of onset of puberty at the discretion of the physician.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the instructions in Section 2.3.

2.2 Dose and Principles of Dosing 11.25 mg or 30 mg for 3-month administration

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration must be administered under the supervision of a physician.

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration should be administered once every three months (12 weeks) as a single intramuscular injection. Regardless of the dose chosen, the goal of therapy is to suppress pituitary gonadotropins and peripheral sex steroids, and to arrest progression of secondary sexual characteristics. Hormonal and clinical parameters should be monitored during treatment, for instance at month 2-3, month 6 and further as judged clinically appropriate, to ensure adequate suppression. In case of inadequate suppression, other available GnRH agonists indicated for the treatment of CPP should be considered.

Each LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration strength and formulation has different release characteristics. Do not use partial syringes or a combination of syringes to achieve a particular dose.

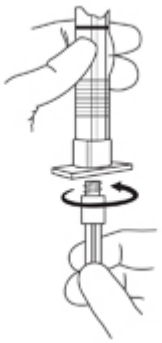
LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration treatment should be discontinued at the appropriate age of onset of puberty at the discretion of the physician.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the instructions in Section 2.3.

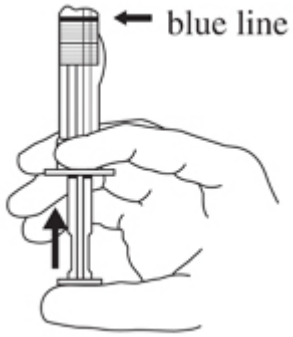
2.3 Reconstitution and Administration Instructions

- The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection.
- Since LUPRON DEPOT-PED does not contain a preservative, the suspension should be injected immediately or discarded if not used within two hours.
- As with other drugs administered by injection, the injection site should be varied periodically.

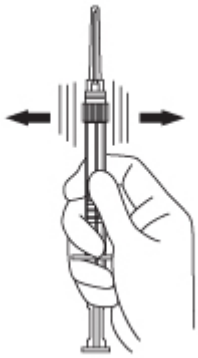
1. The LUPRON DEPOT-PED powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



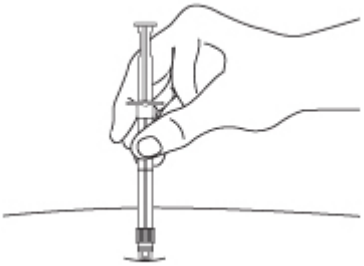
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.



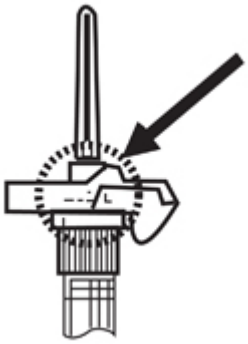
4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.



5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, the intramuscular injection should be performed by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or shoulder; injection sites should be alternated.



NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc® safety device. If blood is present remove the needle immediately. Do not inject the medication.



8. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT-PED should be mixed and used immediately.

AFTER INJECTION

9. Withdraw the needle. Once the syringe has been withdrawn, activate immediately the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device is fully extended over the needle and a CLICK is heard or felt.

ADDITIONAL INFORMATION

- Dispose of the syringe according to local regulations/procedures.

3 DOSAGE FORMS AND STRENGTHS

LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration and LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration is provided in a prefilled dual chamber syringe for intramuscular injection.

4 CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonists or any of the excipients in LUPRON DEPOT-PED. Reports of anaphylactic reactions to GnRH agonists have been reported in the medical literature.
- All formulations of LUPRON DEPOT may cause fetal harm if administered to a pregnant woman. When LUPRON DEPOT was administered subcutaneously to rabbits it produced a dose related increase in major fetal abnormalities, and fetal mortality. The possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. LUPRON DEPOT-PED is contraindicated in women who are or may become pregnant. If this drug is inadvertently used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Initial Rise of Gonadotropins and Sex Steroid Levels

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms of puberty may be observed *[see Clinical Pharmacology (12.3)]*.

5.2 Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists, including LUPRON DEPOT-PED. Postmarking 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 DEPOT-PED *[see Adverse Reactions (6.3)]*.

5.3 Convulsions

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. These 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.

5.4 Monitoring and Laboratory Tests

Response to LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration should be monitored with a GnRHa stimulation test, basal LH or serum concentration of sex steroid levels beginning 1-2 months following initiation of therapy, with changing doses, or potentially during therapy in order to confirm maintenance of efficacy. Measurement of bone age for advancement should be done every 6-12 months.

Response to LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration should be monitored with a GnRHa stimulation test, basal LH or serum concentration of sex steroid levels at months 2-3, month 6 and further as judged clinically appropriate, to ensure adequate suppression. Additionally, height (for calculation of growth rate) and bone age should be assessed every 6-12 months.

Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels. Gonadotropins and/or sex steroids may increase or rise above prepubertal levels if the dose is inadequate. Noncompliance with drug regimen or inadequate dosing may result in inadequate control of the pubertal process with gonadotropins and/or sex steroids increasing above prepubertal levels *[see Clinical Studies (14) and Adverse Reactions (6)]*.

6 ADVERSE REACTIONS

The most common adverse reactions with GnRH agonists including LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration and LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration are injection site reactions/pain including abscess, general pain, headache, emotional lability and hot flushes/sweating.

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug (hormonal flare effect). Therefore, an increase in clinical signs and symptoms of puberty may be observed *[see Warnings and Precautions (5.1)]*.

6.1 LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration - Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

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 which are not considered drug-related are excluded.

Table 2. Percentage of Patients with Treatment-Emergent Adverse Reactions Occurring in ≥2% of Pediatric Patients Receiving LUPRON DEPOT-PED 1-month	
	Number of Patients (N = 421)

	N	(%)
Body as a Whole		
Injection Site Reactions Including Abscess*	37	(9)
General Pain	12	(3)
Headache	11	(3)
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.		

Less Common Adverse Reactions

The following treatment-emergent adverse reactions were reported in less than 2% of the patients and are listed below by body system.

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.

6.2 LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration - Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Table 3. Percentage of Patients with Treatment-Emergent Adverse Reactions Occurring in ≥2 Pediatric Patients

Receiving LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration.						
	11.25 mg every 3 Months N=42		30 mg every 3 Months N=42		Overall N = 84	
	N	%	N	%	N	%
Injection site pain	8	(19)	9	(21)	17	(20)
Weight increased	3	(7)	3	(7)	6	(7)
Headache	1	(2)	3	(7)	4	(5)
Mood altered	2	(5)	2	(5)	4	(5)
Injection site swelling	1	(2)	1	(2)	2	(2)

Less Common Adverse Reactions

The following treatment-emergent adverse reactions were reported in one patient and are listed below by system organ class:

Gastrointestinal Disorders – abdominal pain, nausea; *General Disorders and Administration Site Conditions* – asthenia, gait disturbance, injection site abscess sterile, injection site hematoma, injection site induration, injection site warmth, irritability; *Metabolic and Nutritional Disorders* – decreased appetite, obesity; *Musculoskeletal and Connective Tissue Disorders* - musculoskeletal pain, pain in extremity; *Nervous System Disorders* – dizziness; *Psychiatric Disorders* – crying, tearfulness; *Respiratory, Thoracic and Mediastinal Disorders* – cough; *Skin and Subcutaneous Tissue Disorders* – hyperhidrosis; *Vascular Disorders* – pallor.

6.3 Postmarketing

The following adverse events have been observed with this or other formulations of leuprolide acetate injection. As leuprolide has multiple indications, and therefore patient populations, some of these adverse events may not be applicable to every patient.

Allergic reactions (anaphylactic, rash, urticaria, and photosensitivity reactions) have also been reported.

Gastrointestinal Disorders: nausea, abdominal pain, vomiting;

General Disorders and Administration Site Conditions: chest pain, injection site reactions including induration and abscess have been reported;

Investigations: decreased WBC, weight increased;

Metabolism and Nutrition Disorders: diabetes mellitus;

Musculoskeletal and Connective Tissue Disorders: tenosynovitis-like symptoms;

Psychiatric Disorders: Emotional lability, such as crying, irritability, impatience, anger, and aggression has been observed with GnRH agonists, including LUPRON DEPOT-PED *[see Warnings and Precautions (5.2)]*; Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists, including LUPRON DEPOT-PED, 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.

Nervous System Disorders: neuropathy peripheral, convulsion *[see Warnings and Precautions (5.3)]*, spinal fracture/paralysis;

Skin and Subcutaneous Tissue Disorders: hot flush, flushing, hyperhidrosis;

Reproductive System and Breast Disorders: prostate pain;

Vascular Disorders: hypertension, hypotension.

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 different patient populations.

7 DRUG INTERACTIONS

No pharmacokinetic-based drug-drug interaction studies have been conducted; however, drug interactions are not expected to occur *[see Clinical Pharmacology (12.3)]*.

7.1 Drug/Laboratory Test Interactions

Administration of LUPRON DEPOT-PED in therapeutic doses results in suppression of the pituitary-gonadal system. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to six months after discontinuation of LUPRON DEPOT-PED may be affected. Normal pituitary-gonadal function is usually restored within six months after treatment with LUPRON DEPOT-PED is discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

LUPRON DEPOT-PED is contraindicated in women who are or may become pregnant while receiving the drug *[see Contraindications (4)]*.

Safe use of leuprolide acetate in pregnancy has not been established in clinical studies. Before starting and during treatment with leuprolide acetate, it is advisable to establish whether the patient is pregnant. Leuprolide acetate is not a contraceptive. If contraception is required, a non-hormonal method of contraception should be used.

When LUPRON DEPOT was administered subcutaneously to groups of rabbits as one time dosing on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/1900 to 1/19 of the human pediatric dose) it 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 DEPOT in rabbits and with the highest dose in rats. No fetal malformations but increase in fetal resorptions and mortality were observed in rat and rabbit when the daily injection formulation of leuprolide acetate was dosed subcutaneously once daily at lower doses (0.1-1 mcg/kg/day in rabbit; 10 mcg/kg/day in rat) during the period of organogenesis. The effects on fetal mortality are logical 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.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. The use of LUPRON DEPOT-PED in children under 2 years is not recommended.

8.5 Geriatric Use

LUPRON DEPOT 1-month 7.5 mg and 4-month 30 mg are indicated for the palliative treatment of advanced prostate cancer. For LUPRON DEPOT-PED 11.25 mg or 15 mg for 1-month administration and LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration, no clinical information is available for persons aged 65 and over.

10 OVERDOSAGE

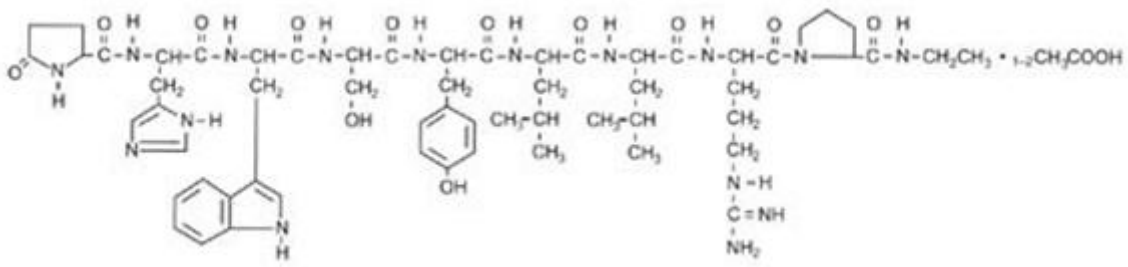
In early clinical trials using leuprolide acetate in adult patients, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

In rats, subcutaneous administration of leuprolide acetate as a single dose 225 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 cases of overdosage, standard of care monitoring and management principles should be followed.

11 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 DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration

LUPRON DEPOT-PED is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a single intramuscular injection.

The front chamber of LUPRON DEPOT-PED 7.5 mg, 11.25 mg, and 15 mg prefilled dual-chamber syringe contains leuprolide acetate (7.5/11.25/15 mg), purified gelatin (1.3/1.95/2.6 mg), DL-lactic and glycolic acids copolymer (66.2/99.3/132.4 mg), and D-mannitol (13.2/19.8/26.4 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection to be given **ONCE EVERY THREE MONTHS**.

The front chamber of LUPRON DEPOT-PED 11.25 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

The front chamber of LUPRON DEPOT-PED 30 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate (30 mg), polylactic acid (264.8 mg) and D-mannitol (51.9 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Human studies indicate that following an initial stimulation of gonadotropins, chronic stimulation with leuprolide acetate results in suppression

or "downregulation" of these hormones and consequent suppression of ovarian and testicular steroidogenesis. These effects are reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

12.3 Pharmacokinetics

Absorption

LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration

Following a single LUPRON DEPOT-PED 7.5 mg for 1-month administration to adult patients, mean peak leuprolide plasma concentration was almost 20 ng/mL at 4 hours and then declined to 0.36 ng/mL at 4 weeks. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT-PED 7.5 mg administration, but testosterone levels appear to be maintained at castrate levels.

In a study of 55 children with central precocious puberty, doses of 7.5 mg, 11.25 mg and 15.0 mg of LUPRON DEPOT-PED were given every 4 weeks and in a subset of 22 children, trough leuprolide plasma levels were determined according to weight categories as summarized below:

Patient Weight Range (kg)	Group Weight Average (kg)	Dose (mg)	Trough Plasma Leuprolide Level Mean ±SD (ng/mL)*
20.2 - 27.0	22.7	7.5	0.77±0.033
28.4 - 36.8	32.5	11.25	1.25±1.06
39.3 - 57.5	44.2	15.0	1.59±0.65
* Group average values determined at Week 4 immediately prior to leuprolide injection. Drug levels at 12 and 24 weeks were similar to respective 4 week levels.			

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration

Following a single LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration to children with CPP, leuprolide concentrations increased with increasing dose with mean peak leuprolide plasma concentration of 19.1 and 52.5 ng/mL at 1 hour for the 11.25 and 30 mg dose levels, respectively. The concentrations then declined to 0.08 and 0.25 ng/mL at 2 weeks after dosing for the 11.25 and 30 mg dose levels. Mean leuprolide plasma concentration remained constant from month 1 to month 3 for both 11.25 and 30 mg doses. The mean leuprolide concentrations 3 months after the first and second injections were similar indicating no accumulation of leuprolide from repeated 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 ^{14}C-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.

Specific Populations

The pharmacokinetics of LUPRON DEPOT-PED has not been determined in patients with hepatic or renal impairment.

Drug-Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT-PED. 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 are not expected to occur.

13 NONCLINICAL TOXICOLOGY

13.1 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 (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 leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. 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.

Following subcutaneous administration of LUPRON DEPOT to male and female rats before mating there was atrophy of the reproductive organs and suppression of reproductive performance.

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 has been evaluated using LUPRON DEPOT formulation to groups of rats as one-time subcutaneous dose of 0.024 mg/kg (1/19 of the pediatric dose) on Day 15 of gestation or dosing on parturition day at doses up to 8 mg/kg (18 fold of the pediatric dose). There was no effect on growth, morphological development and reproductive performance of F1 generation.

14 CLINICAL STUDIES

14.1 LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration

In children with central precocious puberty (CPP), therapeutic doses of LUPRON DEPOT-PED reduce stimulated and basal gonadotropins to prepubertal levels. Testosterone and estradiol are also reduced to prepubertal levels in males and females respectively. Reduction of gonadotropins and sex steroids allow a return to age-appropriate physical and psychological growth and development. The following effects have been noted with the chronic administration of leuprolide: cessation of menses (in girls), normalization and stabilization of linear growth and bone age advancement, stabilization of clinical signs and symptoms of puberty.

55 CPP subjects (49 females and 6 males, naïve to previous GnRHa treatment), were treated with LUPRON DEPOT-PED 1-month formulations until age appropriate for entry into puberty (see treatment period data below) and a subset of 40 subjects were then followed post-treatment (see follow-up period data below).

Treatment Period Data:

During the treatment period, LUPRON DEPOT-PED suppressed gonadotropins and sex steroids to prepubertal levels. Suppression of peak stimulated LH concentrations to < 1.75 mIU/mL was achieved in 96% of subjects by month 1. Five subjects required increased doses of study drug to achieve or retain LH suppression. The number and percentage of subjects with suppression of peak stimulated LH < 1.75 mIU/mL and mean ± SD peak stimulated LH over time is shown in Table 4. The mean ± SD age at the start of treatment was 7 ± 2 years and the duration of treatment was 4 ± 2 years. Six months after the treatment period was finished, the mean peak stimulated LH was 20.6 ± SD 13.7 mIU/mL (n=30).

Table 4. The number and percentage of patients with peak stimulated LH < 1.75 mIU/mL and Mean (SD) peak LH at each clinic visit

	n with peak stimulated LH < 1.75 mIU/mL/ N with a LH measurement for that week		
Weeks on Study	**n/N**	**%**	**Mean (SD) peak LH**

Baseline	0/55	0%	35.0 (21.32)
Week 4	53/55	96.4%	0.8 (0.57)
Week 12	48/54	88.9%	1.1 (1.77)
Week 24	48/53	90.6%	0.8 (0.79)
Week 36	51/54	94.4%	0.6 (0.43)
Week 48	51/54	94.4%	0.6 (0.47)
Week 72	52/52	100%	0.5 (0.30)
Week 96	46/46	100%	0.4 (0.33)
Week 120	40/40	100%	0.4 (0.27)
Week 144	36/36	100%	0.4 (0.24)
Week 168	27/28	96.4%	1.2 (4.58)
Week 216	18/19	94.7%	0.5 (0.90)
Week 240	16/17	94.1%	0.4 (0.62)
Week 264	14/15	95.3%	0.4 (0.41)
Week 288	11/11	100%	0.3 (0.22)
Week 312	9/9	100%	0.4 (0.20)
Week 336	6/6	100%	0.3 (0.10)
Week 360	6/6	100%	0.3 (0.13)
Week 384	5/5	100%	0.2 (0.10)
Week 408	3/3	100%	0.2 (0.09)
Week 432	2/2	100%	0.3 (0.04)
Week 456	2/2	100%	0.2 (0.04)
Week 480	1/1	100%	0.2 (NA)
Week 504	1/1	100%	0.2 (NA)

Suppression (defined as regression or no change) of the clinical/physical signs of puberty was achieved in most patients. In females, suppression of breast development ranged from 66.7 to 90.6% of subjects during the first 5 years of treatment. The mean stimulated estradiol was 15.1 pg/mL at baseline, decreased to the lower level of detection (5.0 pg/mL) by Week 4 and was maintained there during the first 5 years of treatment. In males, suppression of genitalia development ranged from 60% to 100% of subjects during the first 5 years of treatment. The mean stimulated testosterone was 347.7 ng/dL at baseline and was maintained at levels no greater than 25.3 ng/dL during the first 5 years of treatment.

A “flare effect” of transient bleeding or spotting during the first 4 weeks of treatment was observed in 19.4% (7/36) females who had not reached menarche at baseline. After the first 4 weeks and for the remainder of the treatment period, no subject reported menstrual-like bleeding, and only rare spotting was noted.

In many subjects, growth rate decreased on treatment, as did bone age: chronological age ratio. Through year 5, the mean growth rate ranged between 3.4 and 5.6 cm/yr. The mean ratio of bone age to chronological age decreased from 1.5 at baseline to 1.1 by end of treatment. The mean

height standard deviation score changed from 1.6 at baseline to 0.7 at the end of the treatment phase.

Follow-up Period Data:

35 females and 5 males participated in a post-treatment follow-up period to assess reproductive function (in females) and final height. At 6 months post-treatment, most subjects reverted to pubertal levels of LH (87.9%) and clinical signs of resumption of pubertal progression were evident with increase in breast development in girls (66.7%) and increase in genitalia development in boys (80%).

Of the 40 patients evaluated in the follow-up, 33 were observed until they reached final or near-final adult height. These patients had a mean increase in final adult height compared to baseline predicted adult height. The mean final adult height standard deviation score was -0.2.

After stopping treatment, regular menses were reported for all female subjects who reached 12 years of age during follow-up; mean time to menses was approximately 1.5 years; mean age of onset of menstruation after stopping treatment was 12.9 years. Data to assess reproductive function was collected in a post-study survey of 20 girls who reached adulthood (ages 18-26): menstrual cycles were reported to be normal in 80% of women; 12 pregnancies were reported for a total of 7 of the 20 subjects, including multiple pregnancies for 4 subjects.

14.2 LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration

In a randomized, open-label clinical study of LUPRON DEPOT-PED 3-Month formulations, 84 subjects (76 female, 8 male) between 1 and 11 years of age received the LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration formulation. Each dose group had an equal number of treatment-naïve patients who had pubertal LH levels and patients previously treated with GnRHa therapies who had prepubertal LH levels at the time of study entry. The percentage of subjects with suppression of peak-stimulated LH to < 4.0 mIU/mL, as determined by assessments at months 2, 3 and 6 is 78.6% in the 11.25 mg dose and 95.2% in the 30 mg dose as shown in Table 5.

Table 5. Suppression of Peak-Stimulated LH from Month 2 Through Month 6

	LUPRON DEPOT-PED 11.25 mg every 3 Months			**LUPRON DEPOT-PED 30 mg every 3 Months**		
Parameter	**Naïve N = 21**	**Prev Trt[a] N = 21**	**Total N = 42**	**Naïve N = 21**	**Prev Trt[a] N = 21**	**Total N = 42**
Percent with Suppression	76.2	81.0	78.6	90.5	100	95.2
2-sided 95% CI	52.8, 91.8	58.1, 94.6	63.2, 89.7	69.6, 98.8	83.9, 100	83.8, 99.4

a. Previously treated with GnRHa for at least 6 months prior to enrollment in pivotal Study L-CP07-167.

The mean peak stimulated LH levels for all visits are shown by dose and subgroup (naïve vs. previously treated subjects) in Figures 1 and 2.

Figure 1. Mean Peak Stimulated LH for LUPRON DEPOT-PED 11.25 mg for 3-month administration

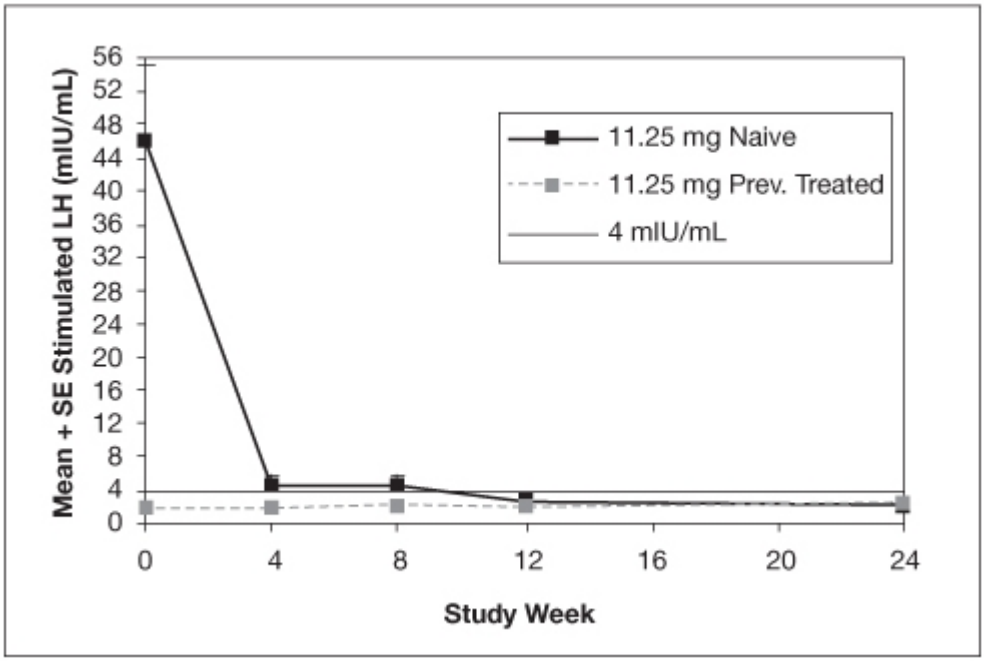
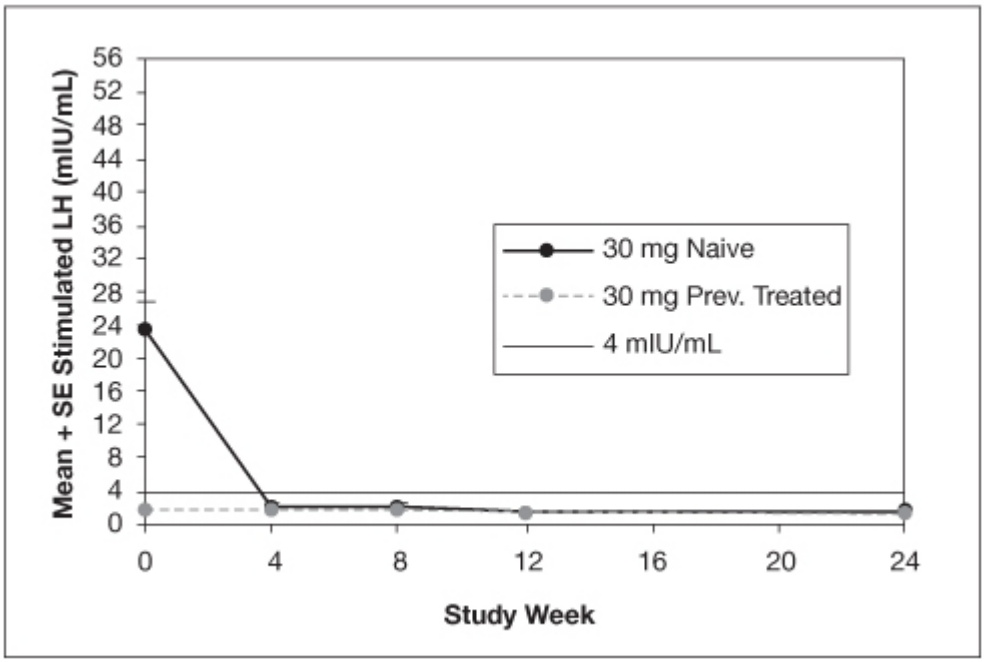


Figure 2. Mean Peak Stimulated LH for LUPRON DEPOT-PED 30 mg for 3-month administration



For the LUPRON DEPOT-PED 11.25 mg dose for 3-month administration, 93% (39/42) of subjects and for LUPRON DEPOT-PED 30 mg dose for 3-month administration 100% (42/42) of subjects had sex steroid (estradiol or testosterone) suppressed to prepubertal levels at all visits. Clinical suppression of puberty in female patients was observed in 29 of 32 (90.6%) and 28 of 34 (82.4%) of patients in the 11.25 mg and 30 mg groups, respectively, at month 6. Clinical

suppression of puberty in males was observed in 1 of 2 (50.0%) and 2 of 5 (40.0%) patients in the 11.25 mg and 30 mg groups, respectively, at month 6. In subjects with complete data for bone age, 29 of 33 (87.9 %) in the 11.25 mg group and 30 of 40 in the 30 mg group (75.0%) had a decrease in the ratio of bone age to chronological age at month 6 compared to screening.

16 HOW SUPPLIED/STORAGE AND HANDLING

LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration is packaged as follows:		
1-month Kit with prefilled dual-chamber syringe	7.5 mg	NDC 0074-2108-03
1-month Kit with prefilled dual-chamber syringe	11.25 mg	NDC 0074-2282-03
1-month Kit with prefilled dual-chamber syringe	15 mg	NDC 0074-2440-03
LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration is packaged as follows:		
3-month Kit with prefilled dual-chamber syringe	11.25 mg	NDC 0074-3779-03
3-month Kit with prefilled dual-chamber syringe	30 mg	NDC 0074-9694-03

LUPRON DEPOT-PED prefilled syringe for 1-month administration contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid/glycolic acid copolymer.

LUPRON DEPOT-PED prefilled syringe for 3-month administration contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid polymer.

When mixed with 1 milliliter of accompanying diluent, LUPRON DEPOT-PED for 1-month administration is administered as a single intramuscular injection. When mixed with 1.5 milliliter of accompanying diluent, LUPRON DEPOT-PED for 3-month administration is administered as a single intramuscular injection.

Each kit contains:

- one prefilled dual-chamber syringe containing 1½ inch needle with LuproLoc® safety device
- one plunger
- two alcohol swabs
- population, dose and frequency confirmation insert
- a complete prescribing information enclosure

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Information for Caregivers

Prior to starting therapy with LUPRON DEPOT-PED, patients should be informed that:

- All formulations are contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential risk to the fetus.
- Continuous therapy is important and that adherence to the recommended drug administration schedule (monthly for LUPRON DEPOT-PED for 1-month administration and every three months for LUPRON DEPOT-PED for 3-month administration) must be accepted if therapy is to be successful. If the injection schedule is not followed, pubertal development may begin again.
- During the first weeks of treatment, signs of puberty, e.g., vaginal bleeding, may occur. This is a common initial effect of the drug. If these symptoms continue beyond the second month of treatment, the physician should be notified.
- Inform caregivers that symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression, have been observed in patients receiving GnRH agonists, including LUPRON DEPOT-PED. Alert caregivers to the possibility of development or worsening of psychiatric symptoms, including depression, during treatment with LUPRON DEPOT-PED *[see Warnings and Precautions (5.2), Adverse Reactions (6.3)]*.
- 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 and Precautions (5.3)]*.
- The most common side effects related to treatment with LUPRON DEPOT-PED for 1-month or 3-month administration in clinical studies are: pain, acne/seborrhea, injection site reactions including pain, swelling and abscess, rash including erythema multiforme, vaginitis/bleeding/discharge, increased weight, headache, and altered mood.
- After injection, some pain and irritation is expected; however if more severe symptoms occur, the physician should be contacted. Any unusual signs or symptoms should be reported to the physician.
- The caregivers should notify the physician if new or worsened symptoms develop after beginning treatment.

Manufactured for
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North Chicago, IL 60064
by Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

03-B510 May, 2017

MEDICATION GUIDE

LUPRON DEPOT-PED® (loo-pron depo peed)
(leuprolide acetate for depot suspension)

What is the most important information I should know about LUPRON DEPOT-PED?

- During the first 2 to 4 weeks of treatment, LUPRON DEPOT-PED can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including vaginal bleeding. **Call your doctor if these signs continue after the second month of treatment with LUPRON DEPOT-PED.**
- Some people taking gonadotropin releasing hormone (GnRH) agonists like LUPRON DEPOT-PED 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 DEPOT-PED.

- Some people taking GnRH agonists like LUPRON DEPOT-PED 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 DEPOT-PED**.

What is LUPRON DEPOT-PED?

- LUPRON DEPOT-PED is an injectable prescription gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).
- It is not known if LUPRON DEPOT-PED is safe and effective in children under 2 years of age.

LUPRON DEPOT-PED should not be taken if your child is:

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

Before your child receives LUPRON DEPOT-PED, tell their 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 plans to breastfeed. It is not known if LUPRON DEPOT-PED passes into the 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 DEPOT-PED?

- Your child's doctor should do tests to make sure your child has CPP before treating them with LUPRON DEPOT-PED.
- LUPRON DEPOT-PED is injected into your child's muscle each month or every 3 months by a doctor or trained nurse. Your doctor will decide how often your child will receive the injection.
- Keep all scheduled visits to the doctor. If a scheduled dose is 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 DEPOT-PED?

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

The most common side effects of LUPRON DEPOT-PED received 1 time each month include:

- injection site reactions such as pain, swelling, and abscess
- weight gain
- 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

The most common side effects of LUPRON DEPOT-PED received every 3 months include:

- injection site pain
- weight gain
- headache
- mood changes
- injection site swelling

These are not all the possible side effects of LUPRON DEPOT-PED. **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 DEPOT-PED INJECTION?

- Store LUPRON DEPOT-PED INJECTION at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep LUPRON DEPOT-PED INJECTION and all medicines out of the reach of children.**

General information about the safe and effective use of LUPRON DEPOT-PED.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LUPRON DEPOT-PED for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about LUPRON DEPOT-PED. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about LUPRON DEPOT-PED that is written for doctors or trained nurses.

What are the ingredients in LUPRON DEPOT-PED?

LUPRON DEPOT-PED 7.5 mg, 11.25 mg or 15 mg for 1-month administration:
Active Ingredients: leuprolide acetate for depot suspension
Inactive Ingredients: purified gelatin, DL-lactic and glycolic acids copolymer, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP to control pH.

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration:
Active Ingredients: leuprolide acetate for depot suspension
Inactive Ingredients: polylactic acid, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP to control pH.

Manufactured for:
AbbVie Inc.
North Chicago, IL 60064

By Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

For more information, go to www.lupronped.com or call 1-800-633-9110.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May, 2017

03-B510

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020263Orig1s042

OTHER REVIEW(S)

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

Application: NDA 020263/S-042

Name of Drug: Lupron Depot PED (leuprolide acetate) depot suspension/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 letter. (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 NDA 022058/S-015	Supprelin LA (histrelin acetate) subcutaneous implant
G.D. Searle LLC., a subsidiary of Pfizer Inc.	NDA 019886/S-033 NDA 019886/S-035	Synarel (nafarelin acetate) nasal solution

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 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 Depot PED (leuprolide acetate) depot suspension/injection:

Labeling Reviewed	Final Proposed Labeling Submission Date	Currently Approved (supplement and date)
Prescribing Information	May 3, 2017	NDA 020263/S-039 May 14, 2013

Review

The prescribing information was compared to the currently approved version, 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 October 28 and December 21, 2016, SLC Notification letters and the labeling comments issued on February 14, March 7, and April 12, 2017.

Revisions have been made to the Highlights of Prescribing Information (Recent Major Changes, Warnings and Precautions, addition of Medication Guide) and Full Prescribing Information: Contents. These sections of the prescribing information have been revised: Warnings and Precautions, Adverse Reactions, and Patient Counseling Information. Other minor revisions (formatting, font, manufacturer name change, revision date) have been made throughout the labeling. All of these changes are acceptable.

Recommendations

The prescribing information 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.

The revised container labeling was reviewed by DMEPA, as documented in reviews dated March 20 and May 3, 2017. The container labels listed below were found to be acceptable and should be attached to the final approval letter. Per their April 21, 2017, submission, AbbVie noted that there is no carton labeling associated with these presentations.

- 7.5 mg 1 month container – submitted April 21, 2017
- 11.25 mg 1 month container – submitted April 21, 2017
- 15 mg 1 month container – submitted April 21, 2017

- 11.25 mg 3 month container – submitted April 21, 2017
- 30 mg 3 month container – submitted April 21, 2017

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

Reviewed by: Jennifer Johnson, Regulatory Health Project Manager
(see appended signature page)

Concurrency by: Pamela Lucarelli, Chief, Project Management Staff

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/s/

JENNIFER L JOHNSON
05/17/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	April 28, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products
Application Type and Number:	NDA 020263/S-042
Product Name and Strength:	Lupron Depot PED (leuprolide acetate) depot injection
Applicant/Sponsor Name:	Abbvie Inc. (b) (4)
Submission Date:	April 25, 2017
OSE RCM #:	2017-206-02
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products requested that we review the revised container label for Lupron Depot PED injection (Appendix A) to determine if they are acceptable from a medication error perspective. Initially the draft container label was only submitted for one of the strengths and subsequent strengths container labels would be submitted at a later time.[a] Thus, Abbvie is now submitting the container labels for all the strengths of Lupron Depot PED injection.

2 CONCLUSION

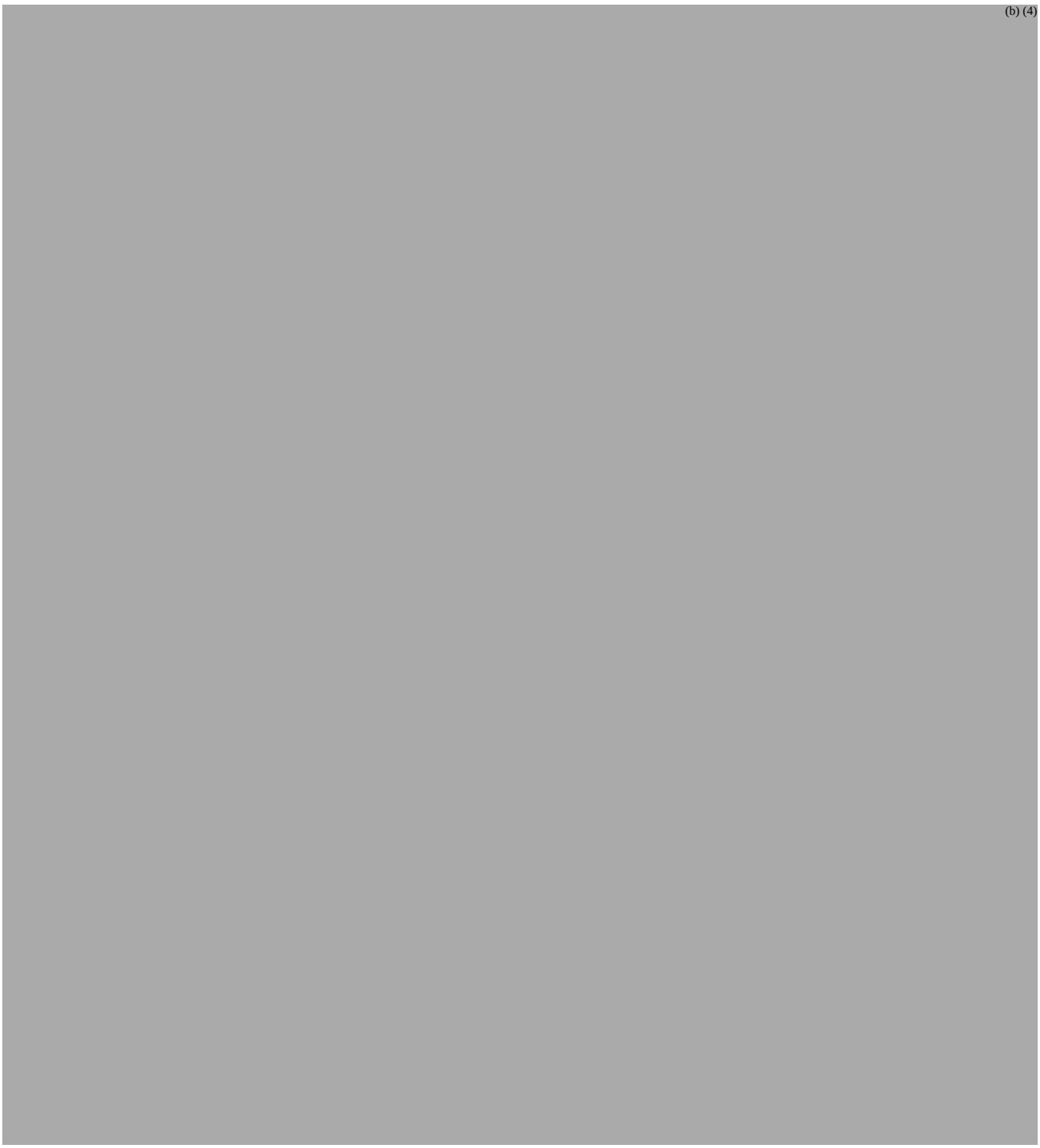
The revised container labels for Lupron Depot PED are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rychlik, I. Label and Labeling Review for Lupron (leuprolide) Lupron Dept and Supprelin LA (NDA 019010/S-038, NDA 020263/S-042). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 17. RCM No.: 2017-206.

APPENDIX A. LABEL AND LABELING SUBMITTED ON APRIL 25, 2017

Container labels

(b) (4)



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/s/

IDALIA E RYCHLIK
05/02/2017

HINA S MEHTA
05/03/2017

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. (b) (4)

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 *not* 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	• 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.

	• 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:

(b) (4)

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:

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

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\\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 Metobolic 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.

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

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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.

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/s/

MEENA RAMACHANDRA
03/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020263Orig1s042

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 steroidgenesis (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 Pharma-ceuticals 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
AbbVie Endocrine			
020263	Lupron Depot-PED	leuprolide	1/20/2017 amendment to S-042
019010	Lupron	leuprolide	1/20/2017 amendment to S-038
Endo Pharmaceuticals Solutions			
022058	Supprelin LA	histrelin	S-015
G.D. Searle LLC., a subsidiary of Pfizer			
019886	Synarel	nafarelin	S-035

The application holders' responses are discussed below.

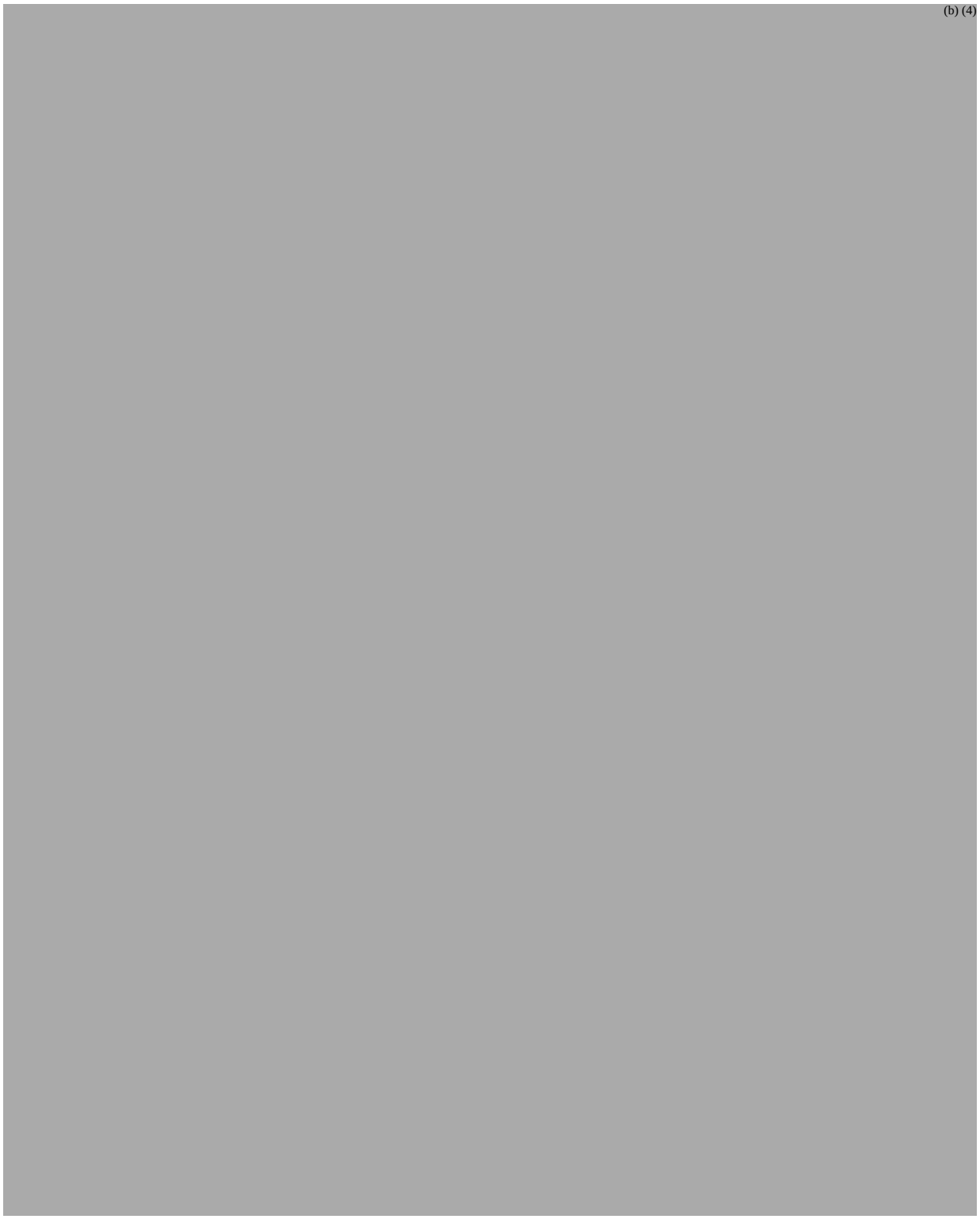
Lupron Depot-PED (leuprolide) and Lupron (leuprolide)

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 (b) (4) 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.

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/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 steroidgenesis (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 Pharma-ceuticals 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, (b) (4)

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

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

(b) (4)

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.

(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

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

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
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 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

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

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

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

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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

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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

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/s/

JENNIFER L JOHNSON
03/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020263/S-042

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 November 17, 2016, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron Depot PED (leuprolide acetate) depot suspension/injection.

On October 28, 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 Depot PED 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 November 17, 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 letters dated December 16, 2016, and January 9, 2017, informing you that we determined that extensions of the discussion period were warranted to allow us to complete our review and reach agreement on the content of the labeling.

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 Depot PED 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-042 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, and to your amendment dated March 14, 2017, containing revised draft container labeling for the 7.5 mg 1 month dose strength. We note that submission of the revised container labeling for the remaining dose strengths (11.25 mg 1 month, 15 mg 1 month, 11.25 mg 3 month, and 30 mg 3 month), and revised carton labeling for all dose strengths, is pending.

Per our letters issued on December 21, 2016, and January 9, 2017, 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

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

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
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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
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/s/

JENNIFER L JOHNSON
02/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

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	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 1, 2017		Multiple (see below)	Revised carton/container labeling	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Multiple (see below)	standard	GnRH agonists	March 15, 2017

NAME OF FIRM: Multiple (see below)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ 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) ☐ MAIL ☐ DARRTS ☐ 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 ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

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:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
February 1, 2017		Multiple (see below)	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Multiple (see below)	standard	GnRH agonists	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)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☒ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ 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) ☐ eMAIL ☐ HAND

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/s/

ELISABETH A HANAN
02/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

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)

- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ☐ ORIGINAL NDA/BLA/ANDA
- ☐ EFFICACY SUPPLEMENT
- ☒ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT

- ☒ INITIAL PROPOSED LABELING
- ☐ 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

Version: 06/06/2016

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/s/

ELISABETH A HANAN
02/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020263/S-042

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 November 17, 2016, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron Depot PED (leuprolide acetate) depot suspension/injection.

On October 28, 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 Depot PED 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 November 17, 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 16, 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.

This letter is to inform you that we have determined that a second 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
01/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020263/S-042

LABELING DISCUSSION EXTENSION

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Associate Director, Regulatory Affairs
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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 January 16, 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
12/16/2016