CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-517/S025
20-517/S030
20-517/S032

Trade Name:	Lupron Depot, 3 Month 22.5 mg, 4 Month 30 mg, and 6 Month 45 mg
Generic Name:	leuprolide acetate for depot suspension
Sponsor:	Abbott Endocrine, Inc., a wholly owned subsidiary of Abbott Laboratories
Approval Date:	June 17, 2011
Indications:	S025: Addition of the phrase "Adult Use Only" to Section 2.4 Administration of Injection in the package insert; S030: New formulation for the palliative treatment of advanced prostatic cancer; and S032: Revisions to the package insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Complete Response Letter	**X**
Labeling	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S025

20-517/S030

20-517/S032

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020517/S-025
NDA 020517/S-030
NDA 020517/S-032

SUPPLEMENT APPROVAL

Abbott Endocrine Inc., a wholly owned subsidiary of Abbott Laboratories
Attention: Jean M. Conaway, R.Ph., RAC, M.B.A.
Associate Director, Regulatory Affairs
PPG200 Abbott Park Road, Dept. PA76/Bldg. AP30-1E
Abbott Park, IL 60064-6157

Dear Ms. Conaway:

Please refer to your Supplemental New Drug Applications (sNDAs) dated April 27, 2007, December 17, 2010, and January 12, 2011, received on April 30, 2007, December 11, 2009, December 17, 2010, and January 12, 2011, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron Depot® (leuprolide acetate for depot suspension), 3 Month 22.5 mg, 4 Month 30 mg and 6 Month 45 mg.

We acknowledge receipt of your amendments dated December 10, 2007; June 16, 2008; August 19, 2010; December 22, 2010; February 3, 2011; February 4, 2011; February 14, 2011; March 21, 2011; March 30, 2011; May 2, 2011; May 11, 2011; May 19, 2011.

The December 17, 2010 (S-030), submission constituted a complete response to our October 5, 2010, action letter.

The “Prior Approval” supplemental new drug application (S-030) provides for data to support a new formulation of Lupron Depot, for the palliative treatment of advanced prostatic cancer.

The “Prior Approval” supplemental new drug application (S-032) provides for revisions to the package insert.

The “Changes Being Effected” supplemental new drug application (S-025) provides for the addition of the phrase “Adult Use Only” to Section 2.4 Administration of Injection in the package insert.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 17, 2010, submission containing final printed carton and container labels.

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and the carton and immediate container labels submitted on December 17, 2010, as soon as they are available, but no more than 30 days after they are printed.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Kim J. Robertson, Regulatory Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Anthony J. Murgo, M.D., M.S., FACP
Acting Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and 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/

ANTHONY J MURGO
06/17/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

COMPLETE RESPONSE LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020517/S-030

COMPLETE RESPONSE

Abbott Endocrine Inc.,
Attention: Natalie Tolli,
Director, Dyslipidemia/Metabolism/Oncology
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-PA76/AP30-1NE
Abbott Park, IL 60064

Dear Ms. Tolli:

Please refer to your Supplemental New Drug Application (sNDA) dated December 11, 2009, received December 11, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupron Depot (leuprolide acetate for depot suspension) 3 Month, 22.5 mg; 4 Month, 30 mg; 6 Month, 45 mg.

We acknowledge receipt of your amendments dated January 28 and 29, February 4, 5 and 16, March 1, April 2, 9, and 27, May 7, 11, 17, and 26, June 3, July 16, August 11, and September 2, 7, and 14, 2010.

This Prior Approval efficacy supplemental new drug application proposes a new formulation of Lupron Depot 45 mg for Palliative Treatment of Advanced Prostatic Cancer.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

The Division of Scientific Investigations (DSI) conducted an audit of the Esoterix, Incorporated analytical laboratory located in Calabasas, California. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from your single phase 3 clinical study (Study L-PC-7-169). These deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of your drug product. Specifically, the samples in the failed runs identified in Item 3 of the Form FDA-483 come from 116 different subjects (77% of the total subject population) measured during the efficacy threshold window. Accuracy of all subject measurements during the threshold window must be established to evaluate if the primary endpoint was reached. In the absence of accurate data upon which an approval decision can be based, this NDA cannot be approved.

Information Needed to Address the Clinical Deficiency

Adequate and reliable data must be provided to assess the safety and efficacy of this drug product. Eliminating the subjects with failing samples from analysis provides too few subjects for proper evaluation. Therefore, the samples from the failed runs identified in the DSI audit should be re-analyzed. If these deficiencies cannot be adequately addressed, new Phase 3 data will be required.

PRODUCT QUALITY

The proposed in vitro release acceptance criteria do not control the shape of the release curve in (b) (4) therefore these criteria are not acceptable.

Information Needed to Address the Product Quality Deficiency

The following drug release acceptance criteria are recommended for Lupron Depot products using the proposed in vitro release methodology:

Acceptance criteria

(b) (4)

LABELING

1. Clam Shell Carton Labeling for all strengths

    a. Box the strength statement that is located below the proprietary name with the same color band that is used for each strength at the top of the clamshell labeling to increase visual differentiation between the 7.5 mg. 22.5 mg, 30 mg and 45 mg strengths.

    b. Present the route of administration, “For intramuscular injection” so that the labeling is in compliance with CFR 201.100(b)(3).

    c. Relocate all the strength and frequency of administration statements on all principle display panels so that the strength appears first and then is followed by the frequency in which it is administered.

Lupron Depot
(Leuprolide Acetate for Depot Suspension)
45 mg
For 6-month administration

d. Post-marketing surveillance indicates that errors occur between the various formulations and strengths of Lupron. Provide an area on the front of the clamshell dedicated for the placement of the pharmacy label to decrease the risk that information, such as frequency of administration and pictures, intended to be read by patients and practitioners is not covered by a pharmacy label. This free space for a pharmacy label could be created by removing the "front chamber" contents and "second chamber" contents information and placing this in the prescriber information.

If revising the clamshell carton labeling in this manner is not feasible, revise the interior of the clam shell so that it includes a warning or statement that alerts practitioners to the correct patient population and frequency of administration on the inside of the clam shell. If a pharmacy label covers the population recommendations provided by the pictures on the principal display panel, the practitioner that is administering the drug may see this information when the clam shell is opened.

2. Syringe Label (all strengths)

   a. Present the strength in the same color font as the color band used on the kit labeling. Alternatively, remove the color block currently used for the NDC number and product description and use it to present the strength.

   b. Present the route of administration, "For intramuscular injection" so that the label is in compliance with CFR 201.100(b)(3).

3. Submit draft labeling that incorporates revisions from the FDA labeling document dated August 26, 2010. We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call CDR Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

ANTHONY J MURGO

10/05/2010

Anthony J. Murgo, M.D. signing for:
Robert L. Justice, M.D., M.S.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lupron Depot safely and effectively. See full prescribing information for Lupron Depot.

Lupron Depot (leuprolide acetate for depot suspension)

Initial U.S. Approval: 1995

-------RECENT MAJOR CHANGES-------

Dosage and Administration (2.3, 2.4) 5/2011

Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5) 5/2011

-------INDICATIONS AND USAGE-------

LUPRON DEPOT is a gonadotropin releasing hormone (GnRH) agonist indicated for:

- palliative treatment of advanced prostatic cancer (1)

-------DOSAGE AND ADMINISTRATION-------

LUPRON DEPOT must be administered under the supervision of a physician. Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule. (2)

- LUPRON DEPOT 22.5 mg for 3–month administration, given as a single intramuscular injection every 12 weeks (2.1)
- LUPRON DEPOT 30 mg for 4–month administration, given as a single intramuscular injection every 16 weeks (2.2)
- LUPRON DEPOT 45 mg for 6–month administration, given as a single intramuscular injection every 24 weeks (2.3)

-------DOSAGE FORMS AND STRENGTHS-------

22.5 mg, 30 mg, and 45 mg injections in a kit with prefilled dual chamber syringe (3)

-------CONTRAINDICATIONS-------

- Hypersensitivity to GnRH, GnRH agonist or any of the excipients in LUPRON DEPOT (4.1)
- Pregnancy (4.2, 8.1)

-------WARNINGS AND PRECAUTIONS-------

- Increased serum testosterone (~ 50% above baseline) during first week of treatment; monitor serum testosterone and PSA (5.1, 5.5)
  - Isolated cases of transient worsening of symptoms, or additional signs and symptoms of prostate cancer during the first few weeks of treatment. (5.1)
  - A small number of patients may experience a temporary increase in bone pain which can be managed symptomatically. (5.1)
  - Isolated cases of ureteral obstruction and spinal cord compression have been reported with GnRH agonists, which may contribute to paralysis with or without fatal complications. (5.1)
- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice. (5.2)
- Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice. (5.3)
- Long-term androgen deprivation therapy prolongs the QT interval. Consider risks and benefits. (5.4)

-------ADVERSE REACTIONS-------

- LUPRON DEPOT 22.5 mg for 3–month administration: The most common related adverse reactions (>10%) were general pain, injection site reaction, hot flashes/sweats, GI disorders, joint disorders, testicular atrophy, urinary disorders. (6.1)
- LUPRON DEPOT 30 mg for 4–month administration: The most common adverse reactions (>10%) were asthenia, flu syndrome, general pain, headache, injection site reaction, hot flashes/sweats, GI disorders, edema, skin reaction, urinary disorders. (6.2)
- LUPRON DEPOT 45 mg for 6–month administration: The most common adverse reactions (>10%) were hot flush, injection site pain, upper respiratory infection, and fatigue. (6.3)

In postmarketing experience, mood swings, depression, rare reports of suicidal ideation and attempt, rare reports of pituitary apoplexy have been reported (6.4).

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

-------DRUG INTERACTIONS-------

- No interactions with LUPRON DEPOT are expected. (7)

-------USE IN SPECIFIC POPULATIONS-------

- Pediatric: These LUPRON DEPOT formulations are not indicated for use in children. See the LUPRON DEPOT PED® package insert for the use of leuprolide acetate in children with central precocious puberty.
- Geriatric: This label reflects clinical trials for LUPRON DEPOT in prostate cancer in which the majority of the subjects studied were at least 65 years of age.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2011

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 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration (leuprolide acetate) are indicated in the palliative treatment of advanced prostatic cancer.

LUPRON DEPOT is a gonadotropin releasing hormone (GnRH) agonist.

2 DOSAGE AND ADMINISTRATION

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

Table 1 LUPRON DEPOT Recommended Dosing

Dosage	22.5 mg for 3-Month Administration	30 mg for 4-Month Administration	45 mg for 6-Month Administration
Recommended dose	1 injection every 12 weeks	1 injection every 16 weeks	1 injection every 24 weeks

2.1 LUPRON DEPOT 22.5 mg for 3-Month Administration

The recommended dose of LUPRON DEPOT 22.5 mg for 3-month administration is one injection every 12 weeks. Due to different release characteristics, a fractional dose, or a combination of doses of this depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered every 12 weeks as a single intramuscular injection.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the instructions in Section 2.4.

2.2 LUPRON DEPOT 30 mg for 4-Month Administration

The recommended dose of LUPRON DEPOT 30 mg for 4-month administration is one injection every 16 weeks. Due to different release characteristics, a fractional dose, or a combination of doses of this depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered every 16 weeks as a single intramuscular injection.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the instructions in Section 2.4.

2.3 LUPRON DEPOT 45 mg for 6-Month Administration

The recommended dose of LUPRON DEPOT 45 mg for 6-month administration is one injection every 24 weeks. Due to different release characteristics, a fractional dose, or a combination of doses of this depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

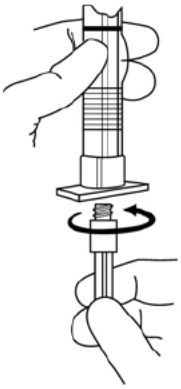
Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered every 24 weeks as a single intramuscular injection.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the instructions in Section 2.4.

2.4 Administration of Injection

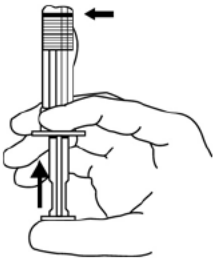
- The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection.
- Since LUPRON DEPOT does not contain a preservative, the suspension should be injected immediately or discarded if not used within two hours.
- As with other drugs administered by injection,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

1. The LUPRON DEPOT 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.

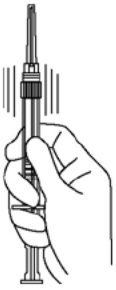


3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is <u>at the blue line</u> in the middle of the barrel.

blue line



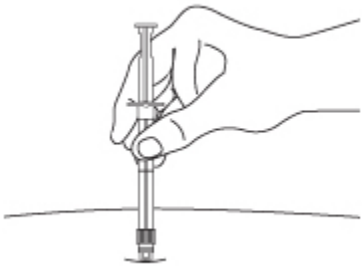
4. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into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



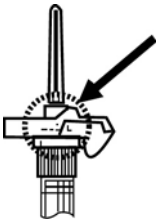
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.

6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.

7. After cleaning the injection site with an alcohol swab, insert the needle completely at a 90 degree angle.



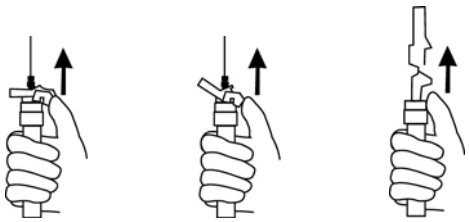
NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc® safety device. If blood is present remove the needle immediately. Do not inject the medication.



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

AFTER INJECTION

9. Withdraw the needle. Immediately activate the LuproLoc® safety device by pushing the arrow forward with the thumb or finger, as illustrated, until the device is fully extended and a CLICK is heard or felt.



ADDITIONAL INFORMATION

- Please see the handling information in the Reference Section 15.0.
- Dispose of the syringe according to local regulations/procedures.

3 DOSAGE FORMS AND STRENGTHS

LUPRON DEPOT 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration are each supplied as a kit with prefilled dual chamber syringe.

4 CONTRAINDICATIONS

4.1 HYPERSENSITIVITY

LUPRON DEPOT is contraindicated in individuals with known hypersensitivity to GnRH agonists or any of the excipients in LUPRON DEPOT. Reports of anaphylactic reactions to GnRH agonists have been reported in the medical literature.

4.2 PREGNANCY

LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Expected hormonal changes that occur with LUPRON DEPOT treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. LUPRON DEPOT is contraindicated in women who are or may become pregnant. If this drug is 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 Tumor Flare

Initially, LUPRON DEPOT, like other GnRH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first weeks of treatment. Isolated

cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. Transient worsening of symptoms may develop. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

5.2 Hyperglycemia and Diabetes

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

5.3 Cardiovascular Diseases

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

5.4 Effect on QT/QTc Interval

Long-term androgen deprivation therapy prolongs the QT interval. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

5.5 Laboratory Tests

Response to LUPRON DEPOT 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration should be monitored by measuring serum levels of testosterone. In the majority of patients, testosterone levels increased above baseline, declining thereafter to castrate levels (< 50 ng/dL) within four weeks. *[see Clinical Studies (14) and Adverse Reactions (6)]*.

6 ADVERSE REACTIONS

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.

6.1 LUPRON DEPOT 22.5 mg for 3-Month Administration

Clinical Trials

In two clinical trials of LUPRON DEPOT 22.5 mg for 3-month administration, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. **Often, causality is difficult to assess in patients with metastatic prostate cancer.** Reactions considered not drug-related are excluded.

Table 2. Adverse Reactions Reported in ≥ 5% of Patients

LUPRON DEPOT 22.5 mg for 3-Month Administration		
Body System/Reaction	**N=94**	**(%)**
Body As A Whole		
Asthenia	7	(7.4)
General Pain	25	(26.6)
Headache	6	(6.4)
Injection Site Reaction	13	(13.8)
Cardiovascular System		
Hot flashes/Sweats	55	(58.5)
Digestive System		
GI Disorders	15	(16.0)
Musculoskeletal System		
Joint Disorders	11	(11.7)
Central/Peripheral Nervous System		
Dizziness/Vertigo	6	(6.4)
Insomnia/Sleep Disorders	8	(8.5)
Neuromuscular Disorders	9	(9.6)
Respiratory System		
Respiratory Disorders	6	(6.4)
Skin and Appendages		
Skin Reaction	8	(8.5)
Urogenital System		
Testicular Atrophy	19	(20.2)
Urinary Disorders	14	(14.9)

In these same studies, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT 22.5 mg for 3-month administration.

Body As A Whole - Enlarged abdomen, Fever

Cardiovascular System - Arrhythmia, Bradycardia, Heart failure, Hypertension, Hypotension, Varicose vein

Digestive System - Anorexia, Duodenal ulcer, Increased appetite, Thirst/dry mouth

Hemic and Lymphatic System - Anemia, Lymphedema

Metabolic and Nutritional Disorders - Dehydration, Edema

Central/Peripheral Nervous System - Anxiety, Delusions, Depression, Hypesthesia, Libido decreased*, Nervousness, Paresthesia

Respiratory System - Epistaxis, Pharyngitis, Pleural effusion, Pneumonia

Special Senses - Abnormal vision, Amblyopia, Dry eyes, Tinnitus

Urogenital System - Gynecomastia, Impotence*, Penis disorders, Testis disorders.

* Physiologic effect of decreased testosterone.

Laboratory

Abnormalities of certain parameters were observed, but are difficult to assess in this population. The following were recorded in ≥5% of patients: Increased BUN, Hyperglycemia, Hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), Hyperphosphatemia, Abnormal liver function tests, Increased PT, Increased PTT. Additional laboratory abnormalities reported were: Decreased platelets, Decreased potassium and Increased WBC.

6.2 LUPRON DEPOT 30 mg for 4-Month Administration

Clinical Trials

The 4-month formulation of LUPRON DEPOT 30 mg was utilized in clinical trials that studied the drug in 49 nonorchiectomized prostate cancer patients for 32 weeks or longer and in 24 orchiectomized prostate cancer patients for 20 weeks.

In the above described clinical trials, the following adverse reactions were reported in ≥ 5% of the patients during the treatment period regardless of causality.

Table 3. Adverse Events Regardless of Causality Reported in ≥ 5% of Patients LUPRON DEPOT 30 mg for 4-Month Administration				
Body System/Events	**Nonorchiectomized**		**Orchiectomized**	
	Study 013		**Study 012**	
	N=49	**(%)**	**N=24**	**(%)**
Body As a Whole				
Asthenia	6	(12.2)	1	(4.2)
Flu Syndrome	6	(12.2)	0	(0.0)
General Pain	16	(32.7)	1	(4.2)
Headache	5	(10.2)	1	(4.2)
Injection Site Reaction	4	(8.2)	9	(37.5)
Cardiovascular System				
Hot flashes/Sweats	23	(46.9)	2	(8.3)
Digestive System				
GI Disorders	5	(10.2)	3	(12.5)
Metabolic and Nutritional Disorders				
Dehydration	4	(8.2)	0	(0.0)
Edema	4	(8.2)	5	(20.8)
Musculoskeletal System				
Joint Disorder	8	(16.3)	1	(4.2)
Myalgia	4	(8.2)	0	(0.0)
Nervous System				
Dizziness/Vertigo	3	(6.1)	2	(8.3)
Neuromuscular Disorders	3	(6.1)	1	(4.2)
Paresthesia	4	(8.2)	1	(4.2)
Respiratory System				
Respiratory Disorder	4	(8.2)	1	(4.2)
Skin and Appendages				
Skin Reaction	6	(12.2)	0	(0.0)
Urogenital System				
Urinary Disorders	5	(10.2)	4	(16.7)

In these same studies, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT 30 mg for 4-month administration.

Body As a Whole - Abscess, Accidental injury, Allergic reaction, Cyst, Fever, Generalized edema, Hernia, Neck pain, Neoplasm

Cardiovascular System - Atrial fibrillation, Deep thrombophlebitis, Hypertension

Digestive System - Anorexia, Eructation, Gastrointestinal hemorrhage, Gingivitis, Gum hemorrhage, Hepatomegaly, Increased appetite, Intestinal obstruction, Periodontal abscess

Hemic and Lymphatic System - Lymphadenopathy

Metabolic and Nutritional Disorders - Healing abnormal, Hypoxia, Weight loss

Musculoskeletal System - Leg cramps, Pathological fracture, Ptosis

Nervous System - Abnormal thinking, Amnesia, Confusion, Convulsion, Dementia, Depression, Insomnia/sleep disorders, Libido decreased*, Neuropathy, Paralysis

Respiratory System - Asthma, Bronchitis, Hiccup, Lung disorder, Sinusitis, Voice alteration

Skin and Appendages - Herpes zoster, Melanosis

Urogenital System - Bladder carcinoma, Epididymitis, Impotence*, Prostate disorder, Testicular atrophy*, Urinary incontinence, Urinary tract infection.

* Physiologic effect of decreased testosterone.

Laboratory

Abnormalities of certain parameters were observed, but their relationship to drug treatment is difficult to assess in this population. The following were recorded in ≥ 5% of patients: Decreased bicarbonate, Decreased hemoglobin/hematocrit/RBC, Hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), Decreased HDL-cholesterol, Eosinophilia, Increased glucose, Increased liver function tests (ALT, AST, GGTP, LDH), Increased phosphorus. Additional laboratory abnormalities were reported: Increased BUN and PT, Leukopenia, Thrombocytopenia, Uricaciduria.

6.3 LUPRON DEPOT 45 mg for 6-Month Administration

Clinical Trials

One open label, multicenter study was conducted with LUPRON DEPOT 45 mg for 6–month administration in 151 prostate cancer patients. Patients were treated for 48 weeks, with 139/151 receiving two injections 24 weeks apart.

In the above described clinical trial, the following adverse events were reported in ≥5% of the patients during the treatment period. The Table 4 includes all adverse events reported in ≥5% of patients as well as the incidences of these adverse events that were considered, by the treating physician, to have a definite or possible relationship to LUPRON.

Table 4. Adverse Events in ≥ 5% of Patients				
LUPRON DEPOT 45 mg for 6-Month Administration				
	Treatment Emergent		Treatment Related	
Adverse Event	**N=151**	**(%)**	**N = 151**	**(%)**
Hot Flush/Flushing	89	58.9	88	58.3
Injection Site Pain/Discomfort	29	19.2	16	10.6
Upper Respiratory Tract Infection/Influenza-like Illness[1]	32	21.2	0	0
Fatigue/Lethargy	20	13.2	18	11.9
Constipation	15	9.9	5	3.3
Arthralgia	14	9.3	2	1.3
Insomnia/Sleep Disorder	13	8.6	5	3.3
Headache/Sinus Headache	12	7.9	3	2.0
Musculoskeletal Pain/ Myalgia	12	7.9	3	2.0
Second Primary Neoplasm[2]	11	7.3	0	0
Cough	10	6.6	2	1.3
Hematuria/Hemorrhagic Cystitis	10	6.6	0	0
Hypertension/BP Increased	10	6.6	3	2.0
Rash	9	6.0	3	2.0
Dysuria	9	6.0	1	0.7
Urinary Tract Infection/Cystitis	9	6.0	0	0
Anemia/Hemoglobin Decreased	10	6.6	2	1.3
Back Pain	8	5.3	0	0
COPD	8	5.3	0	0
Dizziness	8	5.3	3	2.0
Dyspnea/Dyspnea on Exertion	8	5.3	2	1.3
Nocturia	8	5.3	2	1.3
Peripheral/Pitting Edema	8	5.3	2	1.3
Coronary Artery Disease/Angina	8	5.3	1	0.7

[1]Includes influenza, nasal congestion, nasopharyngitis, rhinorrhea, upper respiratory tract infection, and viral upper respiratory tract infection

[2]Includes basal cell carcinoma, bladder transitional cell carcinoma, lung neoplasm, malignant melanoma, non-Hodgkin's lymphoma, and squamous cell carcinoma

The following adverse events led to discontinuation; fatigue, hot flush, second primary neoplasm, asthenia, coronary artery disease, constipation, hyperkalemia, and sleep disorder. Serious adverse events in ≥2% of patients, regardless of causality, included chronic obstructive pulmonary disease, coronary artery disease/angina, cerebrovascular accident/transient ischemic attack, pneumonia, and second primary neoplasms.

Laboratory

At baseline, 13.9% of patients had a CTCAE v4.0 grade 1 or 2 decreased hemoglobin. During the study, 42.4% of subjects had grade 1 decreased hemoglobin (10 -<12-5 g/dL), 2.0% had grade 2 (8 - <10 g/dL) and 1.3% of subjects had grade 3 or 4 (<8 g/dL). Likewise, 28.5% of patients had a grade 1 or 2 increased cholesterol at baseline while 55.0% had grade 1 increased cholesterol (>199- 300 mg/dL), 3.3% had a grade 2 increase (>300-400 mg/dL), and 0.7% of subjects had grade 3 (>400 mg/dL) during the study.

6.4 Postmarketing

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

Like other drugs in this class, mood swings, including depression, have been reported. There have been very rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of development or worsening of depression during treatment with LUPRON.

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

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

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

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

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

Cardiovascular System – Hypotension, Myocardial infarction, Pulmonary embolism

Hemic and Lymphatic System - Decreased WBC

Central/Peripheral Nervous System - Convulsion, Peripheral neuropathy, Spinal fracture/paralysis

Endocrine System – Diabetes

Musculoskeletal System - Tenosynovitis-like symptoms

Urogenital System - Prostate pain

See other LUPRON DEPOT and LUPRON Injection package inserts for other reactions reported in women and pediatric populations.

7 DRUG INTERACTIONS

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

See Clinical Pharmacology (12.3).

7.1 Drug/Laboratory Test Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.2)]*.

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. Expected hormonal changes that occur with LUPRON DEPOT treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman. If

this drug is 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.

Major fetal abnormalities were observed in rabbits after a single administration of the monthly formulation of LUPRON DEPOT on day 6 of pregnancy at doses of 0.00024, 0.0024, and 0.024 mg/kg (approximately 1/1600 to 1/16 the human dose based on body surface area using an estimated daily dose in animals and humans). Since a depot formulation was utilized in the study, a sustained exposure to leuprolide was expected throughout the period of organogenesis and to the end of gestation. Similar studies in rats did not demonstrate an increase in fetal malformations, however, there was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.3 Nursing Mothers

LUPRON DEPOT is not indicated for women *[see Indications and Usage (1)]*. It is not known whether leuprolide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from LUPRON DEPOT, a decision should be made to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

8.5 Geriatric Use

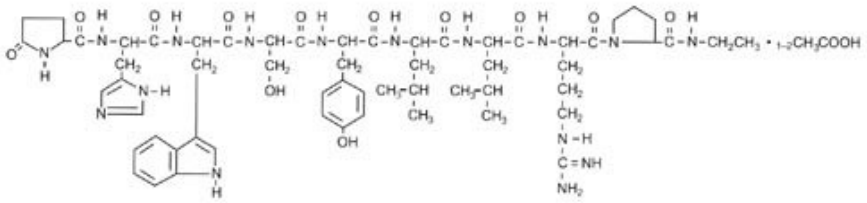
In the clinical trials for LUPRON DEPOT in prostate cancer, the majority (approximately 80%) of the subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON DEPOT in this population.

10 OVERDOSAGE

There is no experience of overdosage in clinical trials. In rats, a single subcutaneous dose of 100 mg/kg (approximately 4,000 times the estimated daily human dose based on body surface area), resulted in dyspnea, decreased activity, and excessive scratching. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

11 DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH). 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 22.5 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 12 WEEKS**.

The front chamber of LUPRON DEPOT 22.5 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate (22.5 mg), polylactic acid (198.6 mg) and D-mannitol (38.9 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.

LUPRON DEPOT 30 mg for 4-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 16 WEEKS**.

The front chamber of LUPRON DEPOT 30 mg for 4-month administration prefilled dual-chamber syringe contains leuprolide acetate (30 mg), polylactic acid (264.8 mg) and D-mannitol (51 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.

LUPRON DEPOT 45 mg for 6-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 24 WEEKS**.

The front chamber of LUPRON DEPOT 45 mg for 6-month administration prefilled dual-chamber syringe contains leuprolide acetate (45 mg), polyactic acid (169.9 mg), D-mannitol (39.7 mg), and stearic acid (10.1 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.

During the manufacture of LUPRON DEPOT 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration, acetic acid is lost, leaving the peptide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate, a GnRH agonist, acts as an inhibitor of gonadotropin secretion. Animal studies indicate that following an initial stimulation, continuous administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect was reversible upon discontinuation of drug therapy.

Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

12.2 Pharmacodynamics

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for more than five years.

Leuprolide acetate is not active when given orally.

12.3 Pharmacokinetics

Absorption

LUPRON DEPOT 22.5 mg for 3-Month Administration

Following a single injection of LUPRON DEPOT 22.5 mg for 3-month administration in patients, mean peak plasma leuprolide concentration of 48.9 ng/mL was observed at 4 hours and then declined to 0.67 ng/mL at 12 weeks. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing, providing steady

plasma concentrations through the 12-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Detectable levels of leuprolide were present at all measurement points in all patients. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

LUPRON DEPOT 30 mg for 4-Month Administration

Following a single injection of LUPRON DEPOT 30 mg for 4-month administration in sixteen orchiectomized prostate cancer patients, mean plasma leuprolide concentration of 59.3 ng/mL was observed at 4 hours and the mean concentration then declined to 0.30 ng/mL at 16 weeks. The mean plasma concentration of leuprolide from weeks 3.5 to 16 was 0.44 ± 0.20 ng/mL (range: 0.20-1.06). Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the fourth week after dosing, providing steady plasma concentrations throughout the 16-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations.

LUPRON DEPOT 45 mg for 6-Month Administration

Following a single injection of LUPRON DEPOT 45 mg for 6-month administration in 26 prostate cancer patients, mean peak plasma leuprolide concentration of 6.7 ng/mL was observed at 2 hours and the mean concentration then declined to 0.07 ng/mL at 24 weeks. Leuprolide appeared to be released continuously following the onset of steady-state levels during the third week after dosing providing steady plasma concentrations through the 24-week dosing interval. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations. In this study, mean leuprolide plasma concentration-time profiles were similar after the first and second dose.

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.

Special Populations

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Genotoxicity studies were conducted with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of mutagenic effects or chromosomal aberrations.

Leuprolide may reduce male and female fertility. Administration of leuprolide acetate to male and female rats at doses of 0.024, 0.24, and 2.4 mg/kg as monthly depot formulation for up to 3 months (approximately as low as 1/30 of the human dose based on body surface area using an estimated daily dose in animals and humans) caused atrophy of the reproductive organs, and suppression of reproductive function. These changes were reversible upon cessation of treatment. Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and

similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

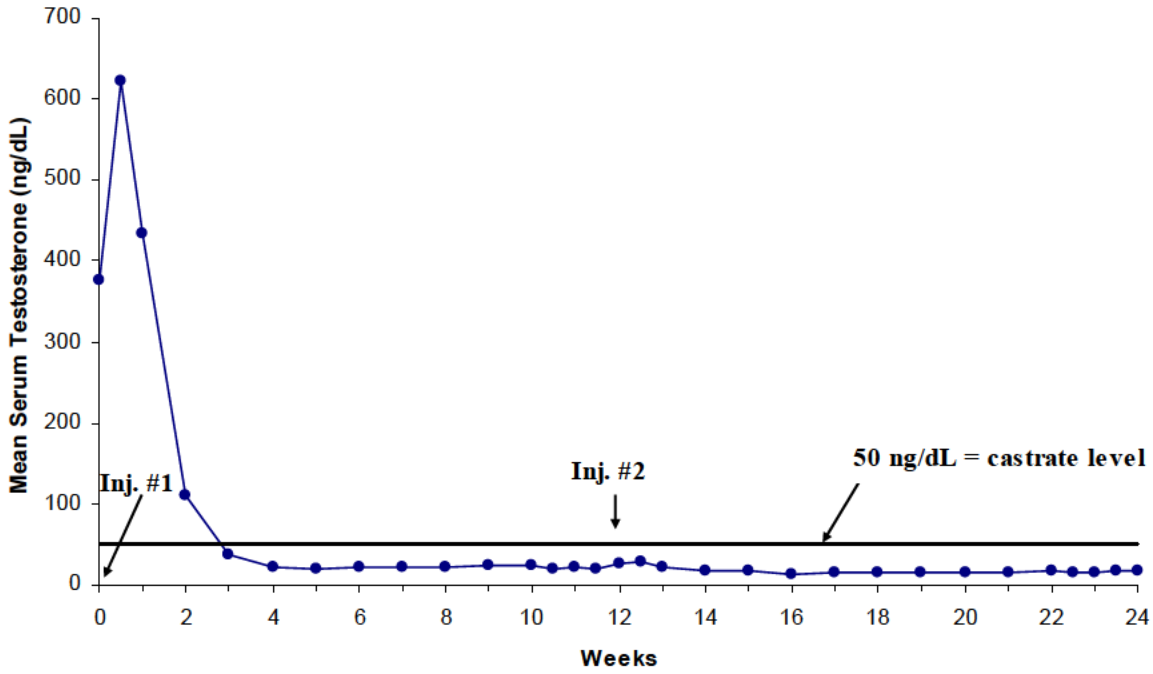
Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

14 CLINICAL STUDIES

14.1 LUPRON DEPOT 22.5 mg for 3-Month Administration

In clinical studies, serum testosterone was suppressed to castrate within 30 days in 87 of 92 (95%) patients and within an additional two weeks in three patients. Two patients did not suppress for 15 and 28 weeks, respectively. Suppression was maintained in all of these patients with the exception of transient minimal testosterone elevations in one of them, and in another an increase in serum testosterone to above the castrate range was recorded during the 12 hour observation period after a subsequent injection. This represents stimulation of gonadotropin secretion.

Figure 1. LUPRON DEPOT 22.5 mg for 3-Month Administration Mean Serum Testosterone Concentrations



Note: Measurements were taken in a subset of patients from one study at Weeks 10.5, 11.5, 12.5, 22.5 and 23.5.

An 85% rate of "no progression" was achieved during the initial 24 weeks of treatment. A decrease from baseline in serum PSA of ≥90% was reported in 71% of the patients and a change to within the normal range (≤3.99 ng/mL) in 63% of the patients.

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

14.2 LUPRON DEPOT 30 mg for 4-Month Administration

In an open-label, noncomparative, multicenter clinical study of LUPRON DEPOT 30 mg for 4-month administration, 49 patients with stage D2 prostatic adenocarcinoma (with no prior treatment) were enrolled. The objectives were to determine whether a 30 mg depot formulation of leuprolide injected once every 16 weeks would reduce and maintain serum testosterone levels at castrate levels (≤ 50 ng/dL), and to assess the safety of the formulation. The study was divided into an initial 32-week treatment phase and a long-term treatment phase. Serum testosterone levels were determined biweekly or weekly during the first 32 weeks of treatment. Once the patient completed the initial 32-week treatment period, treatment continued at the investigator's discretion with serum testosterone levels being done every 4 months prior to the injection.

In the majority of patients, testosterone levels increased 50% or more above the baseline during the first week of treatment. Mean serum testosterone subsequently suppressed to castrate levels within 30 days of the first injection in 94% of patients and within 43 days in all 49 patients during the initial 32-week treatment period. The median dosing interval between injections was 112 days. One escape from suppression (two consecutive testosterone values greater than 50 ng/dL after castrate levels achieved) was noted at Week 16. In this patient, serum testosterone increased to above the castrate range following the second depot injection (Week 16) but returned to the castrate level by Week 18. No adverse reactions were associated with this rise in serum testosterone. A second patient had a rise in testosterone at Week 17, then returned to the castrate level by Week 18 and remained there through Week 32. In the long-term treatment phase two patients experienced testosterone elevations, both at Week 48. Testosterone for one patient returned to the castrate range at Week 52, and one patient discontinued the study at Week 48 due to disease progression.

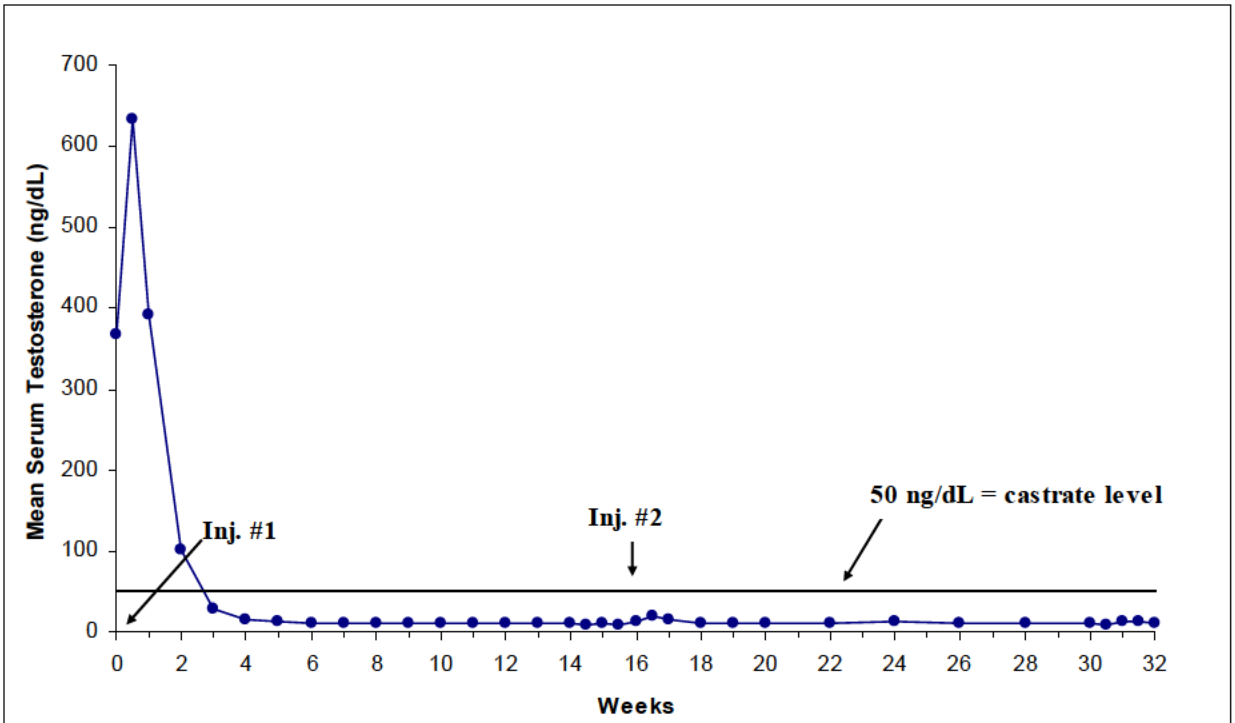
Secondary efficacy endpoints evaluated in the study were the objective tumor response as assessed by clinical evaluations of tumor burden (complete response, partial response, objectively stable and progression) and evaluations of changes in prostatic involvement and prostate-specific antigen (PSA). These evaluations were performed at Weeks 16 and 32 of the

treatment phase. The long-term treatment phase monitored PSA at each visit (every 16 weeks). The objective tumor response analysis showed "no progression" (i.e. complete or partial response, or stable disease) in 86% (37/43) of patients at Week 16, and in 77% (37/48) of patients at Week 32. Local disease improved or remained stable in all patients evaluated at Week 16 and/or 32. For patients with elevated baseline PSA, 50% (23/46) had a normal PSA (less than 4.0 ng/mL) at Week 16, and 51% (19/37) had a normal PSA at Week 32.

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

Using historical comparisons, the safety and efficacy of LUPRON DEPOT 30 mg for 4-month administration appear similar to the other LUPRON DEPOT formulations.

Figure 2. LUPRON DEPOT 30 mg for 4-Month Administration Mean Serum Testosterone Concentrations



Note: Measurements were taken in a subset of patients from one study at Weeks 14.5, 15.5, 16.5, 30.5, 31 and 31.5.

14.3 LUPRON DEPOT 45 mg for 6-Month Administration

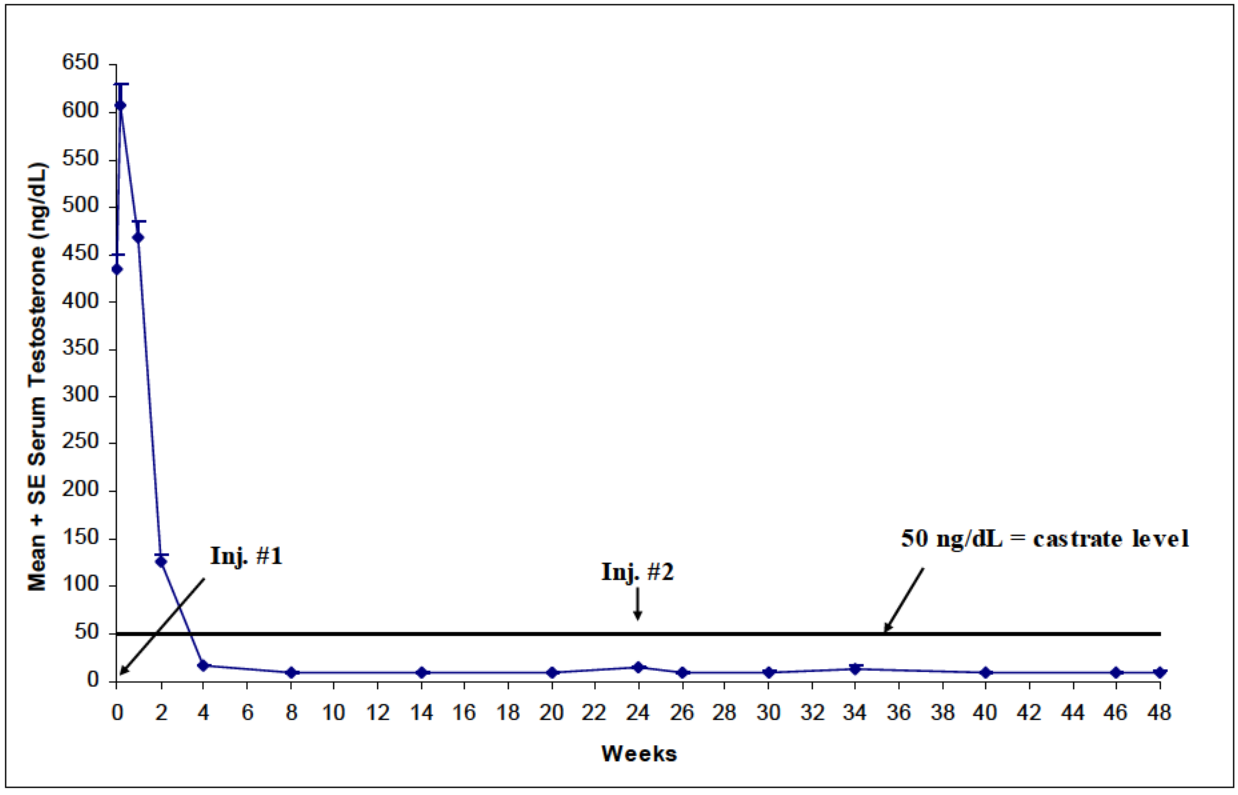
An open-label, non-comparative, multicenter clinical study of LUPRON DEPOT 45 mg for 6-month administration enrolled 151 patients with prostate cancer. The study drug was administered as two intramuscular injections of LUPRON DEPOT 45 mg at 24 week intervals (139/151 received 2 injections), and patients were followed for a total of 48 weeks.

Among 148 patients who had testosterone value at Week 4, serum testosterone was suppressed to castrate levels (< 50 ng/dL) from Week 4 through Week 48 in an estimated 93.4% (two-sided 95% CI: 89.2%, 97.6%) of patients. One patient failed to achieve testosterone suppression by Week 4, and eight patients had escapes from suppression (any testosterone value > 50 ng/dL after castrate levels were achieved). Mean testosterone levels increased to 608 ng/dL from a baseline of 435 ng/dL during the first week of treatment. By Week 4, the mean testosterone concentration had decreased to below castrate levels (16 ng/dL).

Periodic monitoring of serum testosterone levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. Testosterone determinations are dependent on assay methodology and it is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Figure 3 below shows the mean testosterone concentration at various time points.

Figure 3. LUPRON DEPOT 45 mg for 6-Month Administration Serum Testosterone Concentrations (Mean + SE)



15 REFERENCES

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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.

4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd Ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each LUPRON DEPOT 22.5 mg for 3-month administration (NDC 0074-3346-03), 30 mg for 4-month administration (NDC 0074-3683-03), 45 mg for 6-month administration (NDC 0074-3473-03) contains:

- one prefilled dual-chamber syringe containing needle with LuproLoc® safety device
- one plunger
- two alcohol swabs
- a complete prescribing information enclosure

The prefilled dual-chamber syringe contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid polymer.

When mixed with 1.5 mL of accompanying diluent, LUPRON DEPOT 22.5 mg for 3-month administration is administered as a single intramuscular injection **EVERY 12 WEEKS.**

When mixed with 1.5 mL of accompanying diluent, LUPRON DEPOT 30 mg for 4-month administration is administered as a single intramuscular injection **EVERY 16 WEEKS.**

When mixed with 1.5 mL of accompanying diluent, LUPRON DEPOT 45 mg for 6-month administration is administered as a single intramuscular injection **EVERY 24 WEEKS**.

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 Patients

Patients should be informed that:

- If they experience an allergic reaction to other drugs like LUPRON DEPOT, they should not use this drug.
- The most common side effects associated with LUPRON DEPOT are hot flashes, pain (especially joint pain and back pain), injection site pain and fatigue.
- LUPRON DEPOT may cause impotence.
- The increase in testosterone that occurs during the first weeks of therapy can cause an increase in urinary symptoms or pain.
- If they have metastatic cancer to the spine or urinary tract, they need close medical attention during the first weeks of therapy.
- They should notify their doctor if they develop new or worsened symptoms after beginning LUPRON DEPOT treatment.

Manufactured for

Abbott Laboratories

North Chicago, IL 60064

by Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

Rev. 05/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	13-JUN-2-11
From	Anthony J. Murgo, M.D., M.S.
Subject	Acting Deputy Division Director Summary Review
NDA # **Supplement #**	20517 S-030
Applicant Name	Abbott
Date of Submission	17-DEC-2010 (cycle 2 resubmission)
PDUFA Goal Date	17-JUN-2011
Proprietary Name / **Established (USAN) Name**	Lupron Depot/ Leuprolide Acetate
Dosage Forms / Strength	Depot suspension for injection/ 45 mg, 6-Month Administration
Proposed Indication(s)	For the palliative treatment of advanced prostate cancer
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	X
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X (Product Quality)
Clinical Pharmacology Review	X (including ONDQA Biopharmaceutics
DDMAC	X
DSI	X
CDTL Review	X
OSE/DMEPA	X
OSE/DDRE	
OSE/DRISK	
Other - Consults	Division of Reproductive and Urologic Products

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This supplemental NDA (20517/S-030) for Lupron Depot® (leuprolide acetate for depot suspension), which was originally submitted on 11-DEC-2009, provides safety and efficacy information to support a new 45 mg, 6-month formulation for the palliative treatment of advanced prostate cancer. The application was supported by a single arm efficacy study, L-PC07-169-A, with additional safety data provided by LPC07- 169-B and C02-008. The FDA issued a complete response letter on October 5, 2010 because of deficiencies in *in vitro* release specifications and sterility assurance and because a DSI audit revealed that there were violations in stability, precision, accuracy, and calibration curve of the analytical method in measuring total testosterone. The applicant addressed these deficiencies in a resubmission dated December 17, 2010. This summary review pertains for the most part to this cycle 2 resubmission. See the DDD Summary Review signed 04-OCT-2010 for more details pertaining to the review of the original submission.

2. Background

The purpose of this supplemental NDA is to provide data to support a new formulation of Lupron Depot for the palliative treatment of advanced prostate cancer. The proposed new formulation provides for the administration of an injection of Lupron Depot containing 45 mg of leuprolide acetate, at six-monthly intervals. This formulation provides an alternative dosing regimen which results in fewer injections per year, compared to the currently-approved 3-month (22.5 mg) and 4-month (30 mg) Lupron Depot formulations.

Lupron is a synthetic nonapeptide agonist analog of naturally occurring gonadotropin releasing hormone, GnRH or LH-RH. It acts as an inhibitor of gonadotropin secretion (after an initial stimulation) with continuous exposure. The drug has the potential to retard the growth of hormone dependent tumors. In males, testosterone levels can be reduced to that of castration.

The applicant submitted one pivotal study in support of this supplemental NDA: Protocol LPC07-169 (*A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety and Pharmacokinetics of Two 6 Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma*). This was an open label trial of Lupron 45 mg administered intramuscularly six months apart. Enrolled were 151 subjects at 30 sites. Only one of the formulations (Formulation A) met its efficacy endpoint while the other (Formulation B) did not. Efficacy and safety data has been submitted from patients who received Formulation A. Only safety data has been submitted from patients who received Formulation B. The sponsor reported that testosterone suppression was rapid and sustained throughout the 12 month testing period and that the suppression rate for testosterone levels (to less than or equal to 50 ng/dL after study Week 4) was 93.7%.

During the first cycle, the Division of Scientific Investigation (DSI) identified that the bioanalytical site, Esoterix, Inc. (Calabasas Hills, CA), violated stability, precision, accuracy, and calibration curve of the analytical method in measuring total testosterone. Following DSI's inspection of Esoterix, Inc. on 17-AUG-2010, Form FDA-483 was issued and DSI's

evaluation was sent to DDOP on 09-SEPT-2010. These deficiencies raised serious questions regarding the validity of the data needed to determine the efficacy and safety of the new formulation. DSI received responses to the inspection on 08-SEPT-2010 from Esoterix and Abbott. DSI evaluated these responses, and found them to be inadequate (21-SEPT-2010 addendum to the DSI GLP and Bioequivalence Branch review).

In the Complete Response Letter, the Agency recommended that samples from the failed runs identified in the DSI audit of Esoterix should be reanalyzed such that efficacy and safety can be assessed based on adequate and reliable data.

Frozen back-up samples from the failed testosterone runs identified in the DSI audit of Esoterix were shipped from Esoterix to Abbott for reanalysis. Abbott Bioanalysis (Abbott Park, Illinois) measured testosterone concentration in 369 Formulation A back-up samples for reanalysis using a validated high performance liquid chromatography (HPLC) method with tandem mass spectrometric detection (MS/MS). The method validation and in-study assay appear generally acceptable. The method comparison for testosterone between Abbott Drug Analysis and Esoterix Endocrine Sciences suggests that methods at both sites produce data that is both reproducible and provide similar results between the two analytical sites.

3. CMC/ONDQA Biopharmaceutics

The initial CMC review was signed on August 26, 2010. That review recommended for Not Approval due to deficiencies in *in-vitro* release specifications (noted in the original ONDQA Biopharmaceutics review signed August 12, 2010) and sterility assurance (noted in the original Microbiology Product Quality review signed July 2, 2010). A revised CMC review was signed by the primary reviewer and the Branch Chief on September 14 and September 15, 2010, respectively, noting that the sterility deficiencies were adequately addressed (see revised Microbiology Product review signed on August 19, 2010). I concur with the conclusions reached by these reviewers that there are no outstanding CMC or Microbiology Product Quality deficiencies. Please see Section 5, below, regarding ONDQA Biopharmaceutics deficiencies.

In the complete response letter, FDA stated that the in vitro release acceptance criteria in the 11-DEC-2009 submission had not adequately control the shape of the release curve during (b) (4) and recommended criteria to the applicant. In this resubmission, the applicant has used the FDA recommended criteria for their in vitro release specifications, as noted in the ONDQA Biopharmaceutics review signed 12-JAN-2011.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding deficiencies in the non-clinical pharmacology/toxicology data. The pharmacology/toxicology review this cycle primary involves review of the product labeling (for more information see review signed 23-MAY-2011).

5. Clinical Pharmacology

The Clinical Pharmacology review during this cycle primarily involves the review of the product labeling (see review signed 25-APR-2011 and 28-APR-2011 by the primary and secondary reviewers, respectively).

See Section 3 regarding the Biopharmaceutics information.

6. Clinical Microbiology

Not applicable to this application.

7. Clinical/Statistical-Efficacy

For comprehensive details of the clinical data, please refer to review of the original submission of this application signed by the DDOP Clinical Team on 01-OCT-2010 and those of the statisticians and consultants from the Division of Reproductive and Urologic Products (DRUP) signed on 02-SEPT-2010 and 30-SEPT-2010, respectively,. Briefly, the primary endpoint of the protocol (L-PC07-169) was the percentage of subjects with suppression of serum testosterone (T) to "medically castrate" levels (≤ 50 ng/dL) from week 4 through week 48. Success for this endpoint for an individual subject required:

- Onset of T suppression (≤ 50 ng/dL) by week 4 (day 32),
- No escapes (T > 50 ng/dL) at any visit, and
- Continued suppression at week 48.

Success for the entire study population was defined as the lower bound of 2-sided 90% confidence interval no less than 87%, reflecting a point estimate success rate of approximately 91%.

Based on the submitted efficacy data from Study L-PC07-169, the estimated percentage of the patients who had suppression of serum testosterone (≤ 50 ng/dL) (suppression rate) from Week 4 through Week 48 was 93.7 % (95% CI: 89.7; 97.7). The result of the suppression rate met the pre-specified criterion of being successful for a new formula of Lupron Depot® that the lower bound of the 95% confidence interval (CI) of the suppression rate should be greater than 87%. The Statistical team deferred to the clinical review team as to whether the suppression rate demonstrated in Study L-PC07-169 is clinically meaningful and whether there is a favorable benefit-risk profile for the use of the new formulation of Lupron Depot® (leuprolide acetate) for the palliative treatment of advanced prostate cancer.

For reasons stated in Section 2, above, the clinical team recommended that that samples from the failed runs identified in the DSI audit of Esoterix should be reanalyzed such that efficacy and safety can be assessed based on adequate and reliable data. The deficiencies raised serious questions regarding the validity of the data needed to determine the efficacy and safety of the drug product being considered for approval. DRUP reviewers raised similar concerns in their 30-SEPT-2010 review.

Frozen back-up samples from the failed testosterone runs identified in the DSI audit of Esoterix were shipped from Esoterix to Abbott for reanalysis. Abbott Bioanalysis (Abbott Park, Illinois) measured testosterone concentration in 369 Formulation A back-up samples for reanalysis using a validated high performance liquid chromatography (HPLC) method with tandem mass spectrometric detection (MS/MS). The method validation and in-study assay appear generally acceptable. The method comparison for testosterone between Abbott Drug Analysis and Esoterix Endocrine Sciences suggests that methods at both sites produce data that is both reproducible and provide similar results between the two analytical sites. With the re-analyzed samples, the applicant was able to demonstrate that testosterone levels remained below 50 ng/mL in 93.4% of patients. This is similar to the efficacy findings seen in the prior dosing formulations.

Additional comments regarding conclusions drawn from other clinical data are as follows:

- Due to concerns about the reliability of the central laboratory, no conclusions can be drawn about secondary endpoints involving measurement of prostate specific antigen and luteinizing hormone.
- Due to design flaws, the study was not able to demonstrate an improvement in bone pain, pain on urination, or difficulty with urination.

I concur with the conclusions of the clinical review of the cycle 2 resubmission signed by the primary reviewer and team leader on 17-May-2011 and 18-May-2011, respectively, that the application is now approvable.

8. Safety

The safety profile of the proposed formulation is consistent with the previously approved formulations and that there are no new safety signals.

9. Advisory Committee Meeting

An advisory committee meeting was not held.

10. Pediatrics

A pediatric waiver was granted.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

A multidisciplinary team reviewed the labeling in negotiation with the applicant. The deficiencies in the product labeling noted in the previous cycle are resolved. The final agreed upon labeling will be attached to the action letter.

13. Decision/Action/Risk Benefit Assessment

I concur with the conclusion in the review of the CDTL (signed 20-MAY-2011) that the application is now approvable.

Regulatory Action: **Approval**

APPEARS THIS WAY ON ORIGINAL

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

/s/

ANTHONY J MURGO
06/13/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 02517/S-030

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Julie Bullock
Katherine Delorenzo
Adam George
Xiaoping (Janet) Jiang
Young-Jin Moon
Anthony Murgo
Hasmukh B. Patel
Kimberly Ringgold
Kim J. Robertson
Haleh Saber
Sarah Simon
Shenghui Tang
Anne Tobenkin
Stuart Zimmerman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 12, 2011
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	20-517 SE2-030
Applicant	Abbott Laboratories
Date of Submissions	December 11, 2009 and December 17, 2010
PDUFA Goal Date	June 17, 2011
Proprietary Name / **Established (USAN) names**	Lupron Depot-6 month (45 mg) Leuprolide acetate for depot suspension
Dosage forms / Strength	IM/45 mg
Proposed Indication(s)	Palliative treatment of advanced prostate cancer
Recommended:	Approval

1. Introduction

On December 11, 2009, Abbott Laboratories submitted a new drug application for Lupron Depot-6 Month for the palliative treatment of advanced prostate cancer. This application was supported by a single arm study, L-PC07-169-A with additional safety data provided by L-PC07-169-B and C02-008. A complete response letter was issued on October 5, 2010. The applicant responded on December 17, 2010. This review contains information from both submissions.

2. Background

GnRH (gonadotropin releasing hormone) agonists cause a transient surge in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. This surge down regulates the LH and FSH receptors and is followed by a sustained decrease in testosterone to levels that are comparable to orchiectomy. When GnRH agonists (as a class) are compared to orchiectomy, the hazard ratio for overall survival is 1.262 (95% CI 0.915, 1.386) in favor of orchiectomy. Given this overlap in confidence intervals and the increased patient acceptability of GnRH agonists/antagonists, these products have become the standard of care for the first line treatment of metastatic prostate cancer.

Because GnRH agonists/antagonists act by causing a decrease in serum testosterone, the ability to induce castrate testosterone levels has been used as a surrogate endpoint for full approval of these products. Product approvals have relied upon the point estimate (and 95% confidence interval) of the number of patients achieving castrate testosterone levels over the treatment period. Here, values in which the lower bound of the 95% confidence interval is greater than 90% have led to approval. This point estimate is influenced by the number of testosterone assessments and the reproducibility and sensitivity of the testosterone assay. Typically, liquid chromatography/mass spectroscopy (LC-MS) is needed to reproducibly

detect hypogonadal testosterone levels. Using this approach, multiple depot formulations of leuprolide, as well as other GnRH agonists and antagonists, have received FDA approval.

Table 1: Available Treatments

Class	Product Name	Formulations
GnRH Agonist	Leuprolide (Lupron)	Every 3 months Every 4 months
	Leuprolide (Eligard)	Every month Every 3 months Every 6 months
	Leuprolide (Viadur)	Every 12 months
	Goserelin	Every 28 days Every 12 weeks
	Histrelin	Every 12 months
	Triptorelin	Every 4 weeks Every 12 weeks Every 24 weeks
GnRH Antagonist	Degarelix	Every 28 days
	Abarelix	Not marketed in the US

The efficacy and safety data in the current application focuses on a 6 month depot formulation of leuprolide acetate that will be referred to as Formulation A. In addition, the applicant provided safety data from two other 6 month leuprolide acetate formulations that did not meet their efficacy criteria.

Regulatory History

In December 2009, the applicant submitted a new drug application for Lupron Depot-6 month. The primary endpoint of the pivotal study examined the ability of this formulation to achieve castrate serum testosterone levels. Testosterone levels were analyzed by a central laboratory, Esoterix, Inc. Inspection of Esoterix by the Division of Scientific Integrity identified deficiencies in their quality control measures and some of the testosterone levels measured by this laboratory were considered unreliable. A complete response letter was issued on October 5, 2010. Abbott Laboratories was able to obtain frozen back up samples from this study and to analyze the level of testosterone in the samples from runs which had failed quality control at Esoterix. With this data, Abbott has submitted a complete response to FDA's October 5, 2010 letter. The testosterone levels provided in the resubmission were obtained from both Esoterix (assays with acceptable quality control) and Abbott Laboratories (analysis of frozen back up samples from assays with unacceptable quality control at Esoterix. This data, along with safety data from the December 2009 submission, is reviewed in this report.

3. CMC/Device

Lyophilized leuprolide acetate microspheres and vehicle for suspension are separately filled in a dual chambered syringe. These are mixed by forcing the contents of the vehicle chamber into the lyophilized powder, forming a uniform suspension for intramuscular administration.

The table below shows the compositions of Formulation A, Formulation B, and the formulation used in study C02-0008. Formulation A is the to-be-marketed product. The other 2

formulations did not meet their efficacy endpoints. Given the similarities in these products, safety data from all 3 formulations will be used to increase the size of the safety database.

Table 2: Leuprolide Acetate 6 Month Depot Formulations			
Component	**Formulation A**	Formulation B	Formulation C02-0008
Microsphere Powder			
Leuprolide Acetate	45.0 mg	(b) (4)	
Polylactic Acid	169.9 mg[1]		
Mannitol	39.7 mg		
Stearic Acid	(b) (4) mg		
Vehicle			
Mannitol	75.0 mg		
Carboxymethylcellulose Sodium	7.5 mg		
Polysorbate 80	1.5 mg		
Glacial Acetic Acid	qs		
Water for Injection	(b) (4) mL		

(b) (4)

In the complete response letter, FDA stated that the in vitro release acceptance criteria in the December 2009 submission did not adequately control the shape of the release curve during (b) (4) and recommended criteria to the applicant. In this resubmission, the applicant has used the FDA recommended criteria for their in vitro release specifications.

4. Nonclinical Pharmacology/Toxicology

Pharmacokinetic studies showed that after a single subcutaneous (rat) and intramuscular (dog) dose, leuprolide acetate levels were sustained for at least 24 weeks. Pharmacodynamic studies showed that testosterone levels were suppressed during the 24 week period post dosing. Local tolerance studies in rabbits did not show local irritation.

A re-analysis of the animal-to-human extrapolation of the amount of leuprolide given to pregnant rabbits and rats (overdose study) was conducted and product labeling was updated.

5. Clinical Pharmacology/Biopharmaceutics

The pharmacokinetics of leuprolide acetate 45 mg was determined in 26 patients in study L-PC07-169. Each patient received an intramuscular injection on Day 1 and Day 169. After dosing, an initial rapid increase of plasma leuprolide concentration was observed, followed by a rapid decline over the first 7 days post dose. The maximum leuprolide concentration, C_{max} 6.7 ng/mL, occurred at approximately 2 hours after injection. Leuprolide appeared to be released continuously by the third week after dosing with steady plasma concentrations through the 24 week dosing interval, mean AUC 1282 $\pm$ 551 ng·hr/mL. Mean leuprolide plasma concentration-time profiles were similar after the first and second dose.

6. Clinical Microbiology

Please see CMC Review.

7. Clinical/Statistical- Efficacy

The studies submitted to support the approval of Formulation A include:

1. Efficacy data from the 151 patients who received Formulation A in L-PC07-169; and

2. Safety data from
    a. L-PC07-169 Formulation A: N = 151
    b. L-PC07-169 Formulation B: N = 159
    c. C02-008: N = 164.

L-PC07-169A

L-PC07-169A was a single arm, open label, multicenter study designed to evaluate the efficacy and safety of Formulation A. Key entry criteria are listed below.

- Histologically confirmed clinical $T_{1b-4}N_{any}M_{any}$ prostate cancer
- Patients may have had a rising PSA with no other evidence of disease. A rising PSA following radical prostatectomy was defined as an increase of 0.2 ng/dL on 2 consecutive assessments or a rising PSA following prostate irradiation. Patients who met the Phoenix definition: a rise of ≥ 2.0 ng/dL above their nadir were also eligible.
- Baseline testosterone > 150 ng/dL

The first 150 patients enrolled were to receive Formulation A for both injections (actual N = 151). The next 150 patients were to receive Formulation B for both injections (actual N = 159). Study drug was given on Days 1 and 169 and patients were followed until Week 52. Study drug was to be discontinued in patients who did not achieve medical castration and in those who required another drug that interfered with the evaluation of study product.

- Testosterone levels, the primary endpoint, were obtained at baseline and at frequent intervals in the 2 weeks following the Day 1 and 169 injections. Additional levels were obtained at Weeks 4, 8, 14, 20, 30, 34, 40, 46, and 48.
- Routine safety laboratories, complete blood count, urinalysis, and chemistry panel, were obtained at baseline and weeks 1, 8, 14, 24, 25, 34, 40, and 48.

Statistical Plan

The primary endpoint was suppression of testosterone levels (≤ 50 ng/dL) from Week 4 to 48. The percentage of patients who achieved medical castration and the 1-sided 95% confidence interval were estimated using the Kaplan-Meier method. The statistical plan stated that the formulation must achieve a 1-sided 95% confidence interval ≥ 87%.

The primary analysis population was defined as patients who:
1. Received study drug;
2. Had at least 1 post baseline testosterone;
3. Did not use treatments that lower/block testosterone days 1-32;
4. Did not discontinue prior to Day 19 with a testosterone level > 50 ng/dL; and
5. Had a Week 4 testosterone (day 20-32).

Patients who prematurely discontinued with castrate testosterone levels were censored at the time of discontinuation. Secondary endpoints included: change from baseline in PSA at each visit, mean testosterone concentration at each visit, and acute on chronic changes in testosterone and LH in the 2 weeks following the 2nd injection.

During the study period, there was ongoing review of testosterone levels with a plan to discontinue the study if ≥15 patients were not suppressed by Day 32 or escaped suppression. No alpha was spent in these evaluations.

Patient Disposition

Day 1 of Formulation A was administered to 151 patients and Day 169 to 139 patients. The study was completed by 134 patients. Among the 12 patients who discontinued after the 1st injection, 7 discontinued due to an adverse event and 5 withdrew consent. Among the 5 patients who discontinued after the 2nd injection, 1 discontinued due to a protocol violation (prohibited medication), 2 due to treatment failure/disease progression, and 2 due to unrelated causes. While only 1 patient discontinued due to the use of a prohibited medication (bicalutamide), 8 additional patients received prohibited medications (bicalutamide (4), megestrol acetate (4)). Please see protocol violations.

Baseline Characteristics

The median age of the 151 patients who received Formulation A was 76 years. The patient population was 84.2% White and 19.9% Black. At entry, only 14.0% of patients had Stage IV disease. The median PSA at entry was 9.8 ng/mL (range; 0.2-1517.3) and 55/151 patients entered due to a rising PSA. This includes 26 patients with an increase in PSA ≥ 0.2 ng/dL and 29 with a rise in PSA ≥ 2 ng/dL above their nadir.

Protocol Violations

Protocol violations were found in 41.7% of patients. Major violations included:

- Patients 118, 171, 187, and 281 received megestrol acetate. These patients were included in the FDA's primary analysis, but were censored at the initiation of megestrol acetate.

- Patients 132, 155, 160, and 282 received bicalutamide. Patient 132 was discontinued by the applicant due to this protocol violation and was censored in the primary analysis at the time of discontinuation. Patient 155 was not censored in the primary analysis. Since bicalutamide may raise rather than lower testosterone levels, this patient was not excluded from the primary analysis (Br J Urol 1995 75:335). Patients 160 and 282 both had non-castrate testosterone levels prior to use of bicalutamide and were included in the analysis as patients who did have a castrate testosterone level.

- On Week 14, patient 200 had a single elevated testosterone level at Esoterix. The back up samples were run x 2 and these had castrate levels. Further, all other testosterone levels for patient 200 were < 50 ng/dL. It was thought that an error had been made in sample

labeling. When Abbott re-analyzed the frozen back-up samples, this patient did not have sufficient sample at Week 14 to permit analysis. In the FDA's primary analysis, the patient was censored at this time point.

- Patient 145 did not have a testosterone level drawn at Week 4 and was not included in the primary analysis. Two additional patients (148, 248) did not have frozen back up samples available at Week 4 and were not included in the primary analysis.

Primary Endpoint

The primary endpoint was suppression of testosterone levels (≤ 50 ng/dL) from Week 4 to 48. The results of this analysis (patient handling as per protocol violations) are included below.

Table 3: Primary Analysis	
Primary Analysis	Formulation A N = 148
Percentage of Patients Maintaining Castrate Testosterone Levels Week 4-48 (2-sided 95% CI)	93.4% (89.2, 97.6)

Non-castrate testosterone levels were seen in 10 patients. These are listed in the table below.

Table 4: Non-Castrate Testosterone Levels			
Patient Number	Visit of First Failure	Testosterone Value	Maximum Testosterone Value
153	2 h after 2nd injection	51 ng/dL	51 ng/dL
159	Prior to 2nd injection	60	86
160	Week 30	227	555
167	Prior to 2nd injection	105	105
190	Week 48	58	58
192	2 d after 2nd injection	57	57
200	Week 14	337, 17, 12	337-remainder castrate
255	Week 4	69	69
282	Prior to 2nd injection	67	98
318	4 h after 2nd injection	61	74

Among the 148 patients in the primary analysis, frozen back up samples were not available for 20 patients at 26 time points. These are shown in the table below.

Table 5: Missing Back Up Samples			
Patient Number	Visit Day of Missing Sample		
104	Unscheduled		
107	Week 14 Day 99	Week 25 Day 176	Week 26 Day 183
108	Week 14 Day 99	Week 26 Day 183	
109	Week 14 Day 99		
111	Week 14 Day 99	Week 25 Day 176	
124	Week 26 Day 183		
128	Week 26 Day 183		
133	Week 14 Day 99	Week 25 Day 171	
145	Week 34 Day 239		
173	Week 34 Day 239		
182	Week 8 Day 57	Week 20 Day 141	
183	Week 14 Day 99		
199	Week 14 Day 99		
200	Unscheduled		
220	Week 8 Day 57		
240	Week 8 Day 57		
266	Week 26 Day 183		
273	Week 8 Day 57		
295	Week 48 Day 337		
304	Week 14 Day 99		

In addition to the patients in the table below, missing testosterone values were identified in the original December 2009 submission. The number of patients with samples at each time point can be found in the table of mean testosterone values in the primary clinical review.

Sensitivity Analyses

If the 2 patients are removed from the study population due to inadequate back up samples at Week 4 are included as treatment failures, 92.3% (95% CI; 88.7%, 96.0) of patients maintained castrate testosterone levels from Week 4 to 48.

In a second sensitivity analysis, testosterone levels for missing back up samples were imputed from the testosterone levels immediately preceding and following the missing value. Here, 93.7% (95% CI; 90.3, 97.0) maintained castrate testosterone levels from Week 4 to 48.

Secondary Endpoints

See primary review for information concerning secondary and exploratory endpoints.

6. Safety

Overview of Adverse Events

The table below provides an overview of adverse events seen in patients receiving Formulation A. The adverse event profile of patients receiving Formulation B and patients who received study drug on C02-008 is similar.

In general, the adverse event profile of patients who received Formulation A was similar to that on patients on approved Lupron formulations. Adverse events/abnormal laboratory values common to all of these products include hot flushes, injection site pain/discomfort, decreased hemoglobin, hyperlipidemia, and increased glucose. Prolongation of the QT interval was not examined with Formulation A. Reports of testicular atrophy were much lower in patients receiving Formulation A than in those receiving other Lupron formulations. It is unclear if this is due to an under reporting of known consequences of testosterone deprivation. Further, the incidence of injection site reactions with Formulation A (all injection site reactions 23.2%) was higher than that reported with other formulations. Finally, second primary neoplasms were reported in 7.3% (4 were non-skin cancers) of patients receiving Formulation A. It is unclear if this incidence (secondary neoplasms as a group as opposed to individual types of cancer) is higher than that with other Lupron formulations.

Table 6: Safety Summary (Formulation A)	
Deaths	
All Causes of Death	Aspiration Pneumonia (1)
Discontinuations	
Overall	4.6%
All Causes of Discontinuation	Fatigue, Hot Flush, Second Primary Neoplasm, Asthenia, Constipation, Coronary Artery Disease, Hyperkalemia, Sleep Disorder
Serious Adverse Events	
Overall Treatment Emergent	20.5%
Treatment Emergent Serious Adverse Events in $\geq$ 2% of Patients	COPD, Coronary Artery Disease, CVA/TIA, Pneumonia, Heart Failure, Second Primary Neoplasm
Severe Adverse Events	
Overall Treatment Emergent	20.5%
Treatment Emergent Severe Adverse Events in $\geq$ 2% of Patients	Hot Flush, Atrial Fibrillation/Flutter, COPD, Heart Failure
Adverse Events	
Overall Treatment Emergent	94.7%
Treatment Emergent Adverse Events in $\geq$ 10% of Patients	Hot Flush, Upper Respiratory Infection, Injection Site Pain/Discomfort, Fatigue/Lethargy
Overall Treatment Related	72.8%
Treatment Related Adverse Events in $\geq$ 5% of Patients	Hot Flush, Fatigue/Lethargy, Injection Site Pain/Discomfort
Laboratory Abnormalities	
CTCAE v 4 Grade 3-4 in $\geq$ 5% of Patients	None
CTCAE v 4 Grade 1-2 Abnormalities in $\geq$ 10% of patients	Grade 1-2 abnormalities in which the incidence increased by $\geq$ 10% when compared to baseline include increased glucose, increased triglyceride, increased cholesterol, decreased hemoglobin, increased creatinine, and increased ALT.

7. Advisory Committee Meeting

An advisory committee meeting was not held.

8. Pediatrics

A pediatric waiver was granted.

9. Other Relevant Regulatory Issues

Please see Regulatory History in Section 2.0.

Two clinical sites were inspected and both were found to be compliant with Good Clinical Practice. The applicant showed due diligence in obtaining financial disclosures from all principal investigators. No reportable financial arrangements were disclosed among principal investigators entering patients in the pivotal study.

The Office of Compliance was concerned about excessive manual manipulations of sterile, lyophilized powder prior to filling the final dual chamber syringe. A regulatory meeting was held with Takeda (manufacturer) on March 7, 2011. Takeda has committed to the use of an automated rather than a manual process in the future. The establishment inspections have been considered acceptable for approval of Lupron Depot-6 months.

10. Labeling

Please see final product labeling.

11. Recommendations/Risk Benefit Assessment

- Approval

- Risk Benefit Assessment

  - Risk
    - Due to the risk of initial tumor flare, GnRH agonists should not be used in patients with impending spinal cord compression or urinary tract obstruction. Pituitary apoplexy has been reported with GnRH agonists.
    - Treatment emergent adverse events seen in $\geq$ 10% of patients include hot flush, upper respiratory infection, injection site pain/discomfort, and fatigue/lethargy. Treatment related adverse event seen in $\geq$ 10% of patients include hot flush, fatigue/lethargy, and injection site pain/discomfort.
    - Grade 1-2 laboratory abnormalities in $\geq$ 10% of patients compared to baseline include increased glucose, increased triglyceride, increased cholesterol, decreased hemoglobin, increased creatinine, and increased ALT.
  - Benefit
    - Lupron Depot 45 mg 6-month maintained castrate testosterone levels in 93.4% (95% CI; 89.2, 97.6) of patient from Weeks 4 to 48.
    - Due to design flaws, the study was not able to demonstrate an improvement in bone pain, pain on urination, or difficulty with urination.

- Recommendation for Postmarketing Risk Management Activities
  None

- Recommendation for other Postmarketing Study Commitments

No post-marketing commitments or requirements are recommended.

- Recommended Comments to Applicant
  None

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/s/

VIRGINIA E MAHER
05/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Commercial
Application Number(s)	20-517
Priority or Standard	Complete Response Resubmission
Submit Date(s)	December 17, 2010
Received Date(s)	December 17, 2010
PDUFA Goal Date	June 17, 2011
Reviewer Name(s)	Katherine DeLorenzo, MD
Team Leader	V. Ellen Maher, MD
Review Completion Date	May 17, 2011
Established Name	Leuprolide Acetate Injection, Powder, Lyophilized for Suspension
(Proposed) Trade Name	Lupron® Depot
Therapeutic Class	Gonadotropin Releasing Hormone Agonist
Applicant	Abbott Laboratories
Formulation(s)	Injection
Dosing Regimen	45 mg IM every 6 months
Indication(s)	Palliative Treatment of Advanced Prostate Cancer
Intended Population(s)	Patient with Advanced Prostate Cancer

Table of Contents

Table of Tables

Table of Figures

APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval

1.2 Risk Benefit Assessment

Risk

Risks associated with leuprolide acetate 45 mg include:

- Leuprolide acetate 45 mg and other gonadotropin releasing hormone agonists should not be used in patients with impending spinal cord compression or urinary tract obstruction.
- Treatment emergent adverse events seen in ≥ 10% of patients include hot flush, injection site pain/discomfort, upper respiratory infection, and fatigue/lethargy.
- Treatment related adverse events seen in ≥ 5% of patients include hot flush, fatigue/lethargy, and injection site pain/discomfort.
- Grade 1-2 laboratory abnormalities in which the incidence increased by ≥ 10% when compared to baseline includes hyperglycemia, hypertriglyceridemia, hypercholesterolemia, anemia, increased creatinine, and elevated ALT.
- No anaphylactic or anaphylactoid reactions were seen. Pituitary apoplexy was not seen.

Benefit

- The key efficacy analyses were based upon the ability of leuprolide acetate 45 mg to achieve castrate (≤ 50 ng/dL) serum testosterone levels. Upon inspection of the central laboratory conducting the testosterone assays for the applicant's December 22, 2009 submission, the results of these assays were found to be unreliable. As a result a complete response letter was issued on October 5, 2010. The applicant re-analyzed existing testosterone samples and provided a complete response to our letter on December 17, 2010. With the re-analyzed samples, the applicant was able to demonstrate that testosterone levels remained below 50 ng/mL in 93.4% of patients. This is similar to the efficacy findings seen in the prior dosing formulations.
- Due to concerns about the reliability of the central laboratory, no conclusions can be drawn about secondary endpoints involving measurement of prostate specific antigen and luteinizing hormone.
- Due to design flaws, the study was not able to demonstrate an improvement in bone pain, pain on urination, or difficulty with urination.

1.3 Recommendations for Postmarket Risk Management Activities

None

1.4 Recommendations for Postmarket Studies/Clinical Trials

None

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Leuprolide Acetate Injection, Powder, Lyophilized for Suspension

Proprietary Name: Lupron Depot®

Applicant: Abbott Endocrine, Inc.
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064

Pharmacological Class: Gonadotropin Releasing Hormone Agonist

Chemical Class: Peptide

Proposed Indication: The proposed indication is for the palliative treatment of advanced prostate cancer.

Proposed Dosage and Administration: Leuprolide acetate 45 mg will be administered every 24 weeks as a single intramuscular injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatment options for patients with hormone responsive advanced prostate cancer include gonadotropin releasing hormone agonists (GnRH), gonadotropin releasing hormone antagonists, and orchiectomy. Anti-androgen therapies such as bicalutamide, flutamide, and nilutamide are sometimes added to these agents. Although the adverse event profile is similar, GnRH agonists and antagonists are typically preferred to orchiectomy. The table below lists the GnRH agonists and antagonists that are available for the treatment of patients with advanced prostate cancer.

Table 1: Available Treatments		
Class	**Product Name**	**Formulations**
GnRH Agonist	Leuprolide (Lupron)	Every 3 months Every 4 months
	Leuprolide (Eligard)	Every month Every 3 months Every 6 months
	Leuprolide (Viadur)	Every 12 months
	Goserelin	Every 28 days Every 12 weeks
	Histrelin	Every 12 months
	Triptorelin	Every 4 weeks Every 12 weeks Every 24 weeks
GnRH Antagonist	Degarelix	Every 28 days
	Abarelix	Not marketed in the US

2.3 Availability of Proposed Active Ingredient in the United States

Several formulations of leuprolide, including those marketed by the applicant, are available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Gonadotropin releasing hormone agonists cause a transient surge in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. This surge desensitizes the LH and FSH receptors and is followed by a sustained decrease in testosterone to levels comparable to those following orchiectomy. Gonadotropin releasing hormone antagonists act by directly interfering with the binding of endogenous GnRH to its receptor and cause a sustained decrease in testosterone. Because GnRH antagonists do not cause an initial testosterone surge, they may be safely used in patients with impending spinal cord compression or urinary tract obstruction. Following the initial surge in testosterone seen with GnRH agonists, the adverse event profiles of these products are very similar and are primarily related to the consequences of androgen deprivation. The direct effects of testosterone deprivation include hot flushes, loss of libido, fatigue, gynecomastia, testicular atrophy, anemia, and osteoporosis.

Androgen deprivation therapy also produces a decrease in muscle mass and an increase in subcutaneous fat. This may results in obesity, insulin resistance, and an unfavorable alteration in the lipid profile (J Urol 2009 181(5):1998). Changes in these risk factors have, in turn, been linked, by some investigators, to an increased incidence of cardiovascular disease (Circulation 2010 121:833) and new onset diabetes (J Clin Oncol 2006 24:4448).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The clinical development of the 24 week formulation of leuprolide acetate was initiated in July 2002 with the submission of protocol C02-008, “Pharmacokinetics, Safety, and Efficacy Study

of a 6-Month Depot Formulation of Leuprolide in Subjects with Advanced Prostatic Adenocarcinoma" for Special Protocol Assessment. A non-agreement letter was issued in August 2002. This study failed to meet its efficacy endpoint and has been included in this efficacy supplement as part of the safety database.

In November 2007, an end of Phase 2 meeting was held to discuss the study design of L-PC07-169, "A Phase 3, Multicenter, Open-label Trial to Evaluate the Efficacy, Safety, and PK of Two 6-Month Leuprolide Formulations, in Subjects with Prostatic Adenocarcinoma." This study enrolled 151 patients to Formulation A followed by the enrollment of 159 patients to Formulation B. This protocol was initiated in February of 2008 and the last study visit for patients treated with Formulation A occurred in June 2009. Formulation A met its efficacy endpoint while Formulation B did not. Efficacy and safety data has been submitted from patients who received Formulation A. Safety data has been submitted from patients who received Formulation B.

Pre-NDA questions were submitted to the Agency and were addressed in a communication to the applicant in June 2009. The NDA was submitted in December 2010.

On August 17, 2010, DSI conducted an inspection of Esoterix, Inc. analytical laboratory in Calabasas, CA and issued a Form FDA-483. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from the single Phase 3 clinical study (Study L-PC-7-169). The deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of the drug product being considered for approval.

The deficiency of critical importance was that many analytical runs had > 33.3% of the total quality controls (QCs) and/or > 50% of the QCs at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations. The firm used the Westgard rules to accept or reject analytical runs, rather than the acceptance criteria listed in the 'FDA Guidance for Industry- Bioanalytical Method Validation'. During inspection, the firm was requested to recalculate the QC results in each run using criteria listed in the FDA guidance (i.e. reject a run when > 33.3 % of total # of QCs and/or > 50% of QCs at the same concentration with deviations > 15% (for MS based assays) or 20% (for ligand based assays). Many runs failed the acceptance criteria used in this FDA guidance.

On September 7, 2010, Abbott Endocrine, Inc. provided a response to the Esoterix Form FDA-483 observations. The response addressed only the validation of the testosterone assay. The response did not address the extensive in-study failures of the testosterone calibration curve and QC accuracy. Abbott's response has been discussed with the NDA review team. The FDA advised Abbott that adequate and reliable data must be provided to assess the safety and efficacy of this drug product.

A complete response letter was sent to the applicant in October 2010 due to the Division of Scientific Integrity's (DSI) inspection of Esoterix, the central laboratory used to assay the serum testosterone levels. Testosterone levels were the primary endpoint in the key study in the

application, and DSI's inspection found that 59 analytical runs had quality control deviations of >15-20%. Additionally, the central laboratory did not reject 15 analytical runs in which 25% of their calibration standards did not meet the criteria for assay precision described in "Guidance for Industry, Bioanalytical Method Validation."

The applicant had all available back-up samples from these analytical runs assayed at an alternative laboratory (Abbott), and re-submitted their application on December 17, 2010.

2.6 Other Relevant Background Information

The full regulatory approval of GnRH agonists and antagonists has been based on the achievement and maintenance of castrate testosterone levels (≤ 50 ng/dL). These studies calculate the percentage of patients who achieve castrate testosterone levels and the confidence intervals around this point. The lower bound of the 95% confidence interval is expected to be > 90%. Other marketed Lupron formulations have achieved castrate testosterone levels in the following percentages of patients.

Table 2: Achieving Castrate Testosterone Levels with Other Lupron Formulations

	Lupron Depot 1 Month 7.5 mg	Lupron Depot 3 Months 22.5 mg	Lupron Depot 4 Months 30 mg
Castration Rate by Day 30	94%	95%	94%

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant certified that the studies in this submission were conducted in accordance with Good Clinical Practice (GCP) as described in the ICH E6 Guideline for Good Clinical Practice and in accordance with CFR Parts 50, 56, 312, and 314.

3.2 Compliance with Good Clinical Practices

Compliance with GCP was assessed by inspection of the following sites by the Division of Scientific Integrity.

Table 3: Inspection Sites

Site #	Protocol #	Number Randomized	Comments
#50042 David Lipsitz, MD 1084 Vinehaven Drive Concord, NC 28025	L-PC07-169	11	5 subjects with SAEs 20 protocol violations
#11706 Daniel Saltzstein, MD Urology San Antonio Research, PA 7909 Fredericksburg Road, Ste 115 San Antonio, TX 78229	L-PC07-169	14	6 subjects with SAEs 10 protocol violations

Both sites were found to be GCP compliant and no inspection findings were issued.

Please see Regulatory History for information on the testosterone assays conducted by the central laboratory.

Establishment inspections were carried out at facilities which manufacture several different dosing formulations of Lupron, including the 6 month formulation that is the subject of this review. The Office of Compliance's review of the inspection reports found issues with the excessive manual manipulations of sterile, lyophilized powder prior to filling the final dual chamber syringes for the Lupron products. Excessive manual manipulations pose a potential risk to the sterility of the product. The Office of Compliance held a regulatory meeting on March 7, 2011 with Takeda to discuss all concerns. Takeda has committed to the use of an automated rather than a manual process in the future, similar to the one used in one in use at it's other manufacturing site. The Establishment Inspections have, therefore, been considered acceptable for approval of the 6 mo Lupron Depot formulation.

3.3 Financial Disclosures

Two studies were submitted with this application, C02-008 and L-PC07-169. C02-008 was conducted by TAP Pharmaceuticals and TAP obtained financial disclosure information from all investigators. L-PC07-169 was initiated by TAP Pharmaceuticals and completed by Abbott Laboratories. TAP Pharmaceuticals obtained financial disclosure information from all investigators participating in L-PC07-169 and Abbott attempted to again obtain financial disclosure information from all investigators participating in L-PC07-169. Abbott did not obtain financial disclosure information from 3 principal investigators who did not enroll any patients on L-PC07-169. Abbott states that they exerted due diligence in attempting to contact these investigators. Abbott Laboratories certified that none of the investigators contacted disclosed reportable financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Leuprolide acetate 45 mg is given as an IM injection. Just prior to injection a lyophilized microsphere powder which contains leuprolide acetate, polylactic acid, steric acid, and mannitol is mixed with the aqueous vehicle containing water for injection, mannitol, carboxymethylcellulose sodium, polysorbate 80, and glacial acetic acid. During formulation, (b) (4)

On review, the proposed specifications for the product dissolution curve ([(b) (4)] were not acceptable and this deficiency was conveyed to the applicant. The applicant modified their [(b) (4)] in vitro specifications to be consistent with the FDA proposal in their complete response letter and they are now considered acceptable.

The table below presents information on the composition of each of the 24 week formulations of leuprolide acetate that have been studied by the applicant, Abbott Laboratories, or their commercial partners. These formulations differ [(b) (4)]. Both Formulation B and the formulation used in study C02-0008 failed to meet their efficacy endpoint and Formulation A is the to-be-marketed product. Despite this, the formulations and the adverse event profiles of the 3 formulations are very similar and data from all 3 formulations are included in the safety database.

Table 4: Leuprolide Acetate Formulations Used in this Submission

Component	**Formulation A**	Formulation B	C02-0008
Microsphere Powder			
Leuprolide Acetate	45.0 mg	[(b) (4)]	
Polylactic Acid	169.9 mg[1]		
Mannitol	39.7 mg		
Stearic Acid	[(b) (4)] mg		
Vehicle			
Mannitol	75.0 mg		
Carboxymethylcellulose Sodium	7.5 mg		
Polysorbate 80	1.5 mg		
Glacial Acetic Acid	qs		
Water for Injection	[(b) (4)] mL		

[(b) (4)]

4.2 Clinical Microbiology

The Microbiology division has reviewed sterilization information in the DP manufacturing process and recommended approval.

4.3 Preclinical Pharmacology/Toxicology

This submission included pharmacodynamic and local tolerance studies. In vivo pharmacodynamic studies were completed in the rat and dog. Pharmacokinetic studies showed that after a single subcutaneous (rat) and intramuscular (dog) dose, leuprolide acetate levels were sustained for at least 24 weeks. An additional in vivo study observed no release differences between the pilot lot and the clinical lot. Pharmacodynamic studies showed that testosterone levels were suppressed during the 24 week period post dosing. Local tolerance studies in rabbits did not show local irritation.

Pharmacology and toxicology data have been submitted and reviewed for Lupron (NDA 19010) and Lupron Depot (NDAs 19732 & 19943). These include studies of mutagenicity, carcinogenicity, and fetal effects. Mutagenicity studies in mammalian and bacterial systems have provided no evidence of mutagenic potential. Carcinogenicity studies in rats demonstrated

benign pituitary hyperplasia and pituitary adenomas. An increase in pancreatic islet cell adenomas and testicular interstitial cell adenomas was also seen. Carcinogenicity studies in mice demonstrated no pituitary abnormalities or other benign or malignant tumors. Major fetal abnormalities were observed in rabbits but not in rats after administration of an extended release formulation of leuprolide acetate. However, increased fetal mortality and decreased fetal weights were seen in both rats and rabbits at higher doses.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See Section 2.4.

4.4.2 Pharmacodynamics

A pharmacodynamic assessment was performed using serum testosterone concentrations. Serum testosterone was initially assayed by Esoterix, Inc. Difficulties with these assays resulted in a complete response letter, issued in October 2010 (see Section 2.5). Most of these assays have been repeated, on frozen samples, by Abbott Laboratories.

The Esoterix assays showed an increase of leuprolide concentration that was associated with a rapid increase in testosterone serum concentration. Mean testosterone concentration (assays conducted by Esoterix and Abbott) was found to increase from a mean baseline value of 434.6 ng/dL to a mean peak of 608.2 ng/dL on Day 2 after dosing. Once continuous plasma leuprolide exposure was sustained, the high mean testosterone serum concentration decreased to a very low plateau (15.9 ng/dL by Week 4 after the first injection) that was maintained through the end of the study.

4.4.3 Pharmacokinetics

The pharmacokinetics (PK) of leuprolide acetate 45 mg was determined in a subset of patients (N=26) in study L-PC07-169. Each patient received two intramuscular injections, Day 1 and Day 169. Pharmacokinetic parameters, including the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), the concentration at the end of the dosing period (C_{trough}) and the area under the plasma concentration-time curve (AUC), were determined using noncompartmental methods. Leuprolide plasma concentrations were determined by a liquid chromatography/tandem mass spectrometry (LC/MS/MS). This method is applicable to the quantitation of leuprolide within a range of 0.0250 to 25.0 ng/mL. Intra or interassay precision (%CV) was less than 15%, and intra or interaccuracy (%bias) was within ±15%.

The PK profiles exhibited two phases. After dosing, an initial rapid increase of plasma leuprolide concentration was observed, followed by a rapid decline over the first 7 days post dose. The maximum leuprolide concentration occurred at approximately 2 hours after injection. The mean C_{max} value was 6.7 ng/mL after first dose. Leuprolide appeared to be released continuously by

the third week after dosing with steady plasma concentrations through the 24 week dosing interval. The mean AUC was 1282 ± 551 ng·hr/mL and the mean leuprolide concentration declined to 0.07 ng/mL at 24 weeks. Mean leuprolide plasma concentration-time profiles were similar after the first and second dose.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5: Leuprolide Acetate 45 mg Clinical Studies

Study	Design and Population	Dose and Regimen	Patients Evaluated	Duration
L-PC07-169	Single arm, multicenter study in men with prostate cancer or rising PSA post-radical prostatectomy	Formulation A 45 mg IM q 24 weeks x 2 Formulation B 45 mg IM q 24 week x 2	Formulation A: 151 Formulation B: 159	48 weeks
C02-008	Single arm, multicenter study in men with prostate cancer whose disease warrants therapy with a GnRH agonist	45 mg IM q 26 weeks x 2	164	52 weeks

All safety and efficacy data were submitted for both studies and the following data will be used in the review of this application:

- Efficacy data from Formulation A (to-be-marketed product); and
- Safety data from Formulation A, Formulation B, and C02-008.

5.2 Review Strategy

The Division of Scientific Integrity verified the source data collected at 2 clinical sites in the US and compared this data with that included in the case report forms. Adverse event (AE) and serious adverse event (SAE) reports in a portion of the case report forms included with the NDA were reviewed and compared with the supplied datasets. The primary efficacy endpoint was unable to be verified by inspection of Esoterix Laboratories and this data was not relied upon to form conclusions about the efficacy of leuprolide acetate 45 mg (see Section 2.5). Instead, testosterone assays were performed on available frozen samples from the failed runs by Abbott Laboratories. These results (both Esoterix results from runs with adequate QC and the Abbott reanalysis of frozen samples from failed runs) will be used in the analysis of the primary endpoint and in the analysis of the secondary endpoint, mean serum testosterone.

5.3 Discussion of Individual Studies/Clinical Trials

L-PC07-169, the key study, was conducted at 58 sites in the US from February 2008 until September 2009.

Study Title

A Phase 3, Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Two 6-Month Leuprolide Formulations, in Subjects with Prostatic Adenocarcinoma

Study Milestones

The table below provides the study milestones. The administrative letter referred to in the table changed the study sponsor to Abbott Laboratories.

Table 6: Study Milestones

Milestone	Date	Formulation A Patients Enrolled
Original Protocol 1	December 7, 2007	43
Amendment #1	March 31, 2008	108
Administrative Letter	July 31, 2008	0
Amendment #2	October 31, 2008	0
Final Statistical Analysis Plan	July 17, 2009	0
First Visit for 1st Subject	February 25, 2008 (Formulation A) April 28, 2008 (Formulation B)	-
Last Visit for Any Subject	June 19, 2009 (Formulation A) September 18, 2009 (Formulation B)	-

Amendment 1: The following substantive changes were made in Amendment 1.

- Defined a rising PSA following radical prostatectomy or prostate irradiation.
- Entry criterion for serum creatinine was changed to ≤ 1.9 mg/dL.
- Cryotherapy was excluded within 8 weeks of Screening.
- Use of 1-year GnRH implants was excluded within 60 weeks of Screening.
- Defined different washout periods for finasteride and dutasteride.
- Ketoconazole was added as an excluded medication.

Amendment #2: No substantive changes were included in Amendment 2.

Study Objectives

1) To assess the efficacy and safety of two new leuprolide acetate 45 mg formulations over 48 weeks. Each formulation will be delivered as 2 single injections 24 weeks apart, in patients with prostate cancer.
2) To establish a PK profile of serum leuprolide for the two new 45 mg formulations in a subset of subjects with prostate cancer.

Inclusion Criteria

1) Prior to any study specific procedures being performed, the subject voluntarily signed the IRB approved informed consent form and any required privacy statement/authorization form (i.e., Health Information Portability and Accountability Act) after having its content fully explained and all questions answered.
2) Subject was male, ≥ 18 years of age, with a pre-study serum testosterone > 150 ng/dL.

3) Subject had a histologically-confirmed prostatic adenocarcinoma in any of the following clinical stages (clinical staging should have been based on information available to the clinical investigator at the time of screening, and not necessarily at the time of diagnosis):

Jewett:	A_2, B, C, D
TNM:	cT_{1b}-$4N_{any}M_{any}$

Subjects with a rising PSA following radical prostatectomy were defined as patients with an increase of 0.2 ng/dL from the previous test on 2 consecutive assessments or rising PSA following prostate irradiation. Patients who met the Phoenix definition: a rise of ≥ 2.0 ng/dL above the nadir (lowest PSA achieved following radiation therapy) were also eligible.

4) In the opinion of the clinical investigator, prostate cancer status and general clinical status was sufficient to warrant at least 48 weeks of continuous androgen deprivation treatment, without concomitant anti-androgen treatment.
5) Subject had ECOG performance status grade 0-2.
6) Subject's life expectancy was at least 18 months.
7) Subject had serum creatinine ≤ 1.9 mg/dL, bilirubin ≤ 2.0 mg/dL (unless Gilbert's syndrome) and AST and ALT ≤ 2.5 times the ULN.
8) Subject was willing to complete all phases and all procedures of the study.

Exclusion Criteria

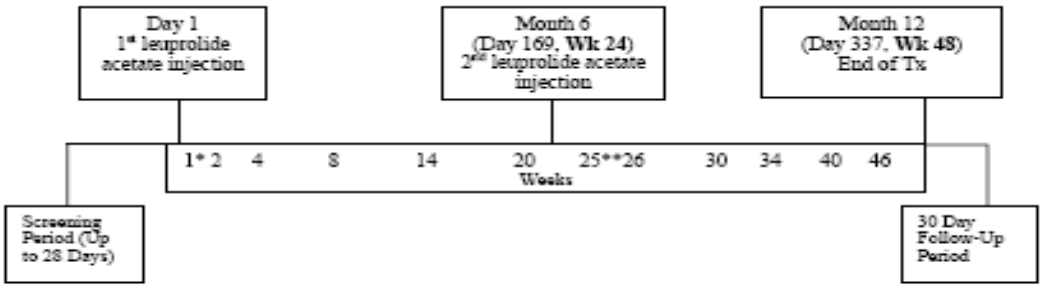
1) The clinical investigator anticipated the subject's need for radical prostatectomy or radiotherapy (including conventional electron beam radiation therapy, 3-D conformal radiation therapy, intensity modulated radiation therapy, proton beam radiation therapy or brachytherapy) or cryotherapy of local disease within the 48 week study period following the initial administration of the investigational leuprolide acetate 45 mg formulation.
2) Subject had historical, clinical, or radiographic evidence of central nervous system metastases, including spinal cord metastases.
3) Subject had clinical evidence of urinary tract obstruction, which, in the judgment of the clinical investigator, would have put the subject at significant risk, should disease flare have occurred.
4) Subject had a history of bilateral orchiectomy, adrenalectomy, or hypophysectomy.
5) History of clinical hypogonadism (testosterone < 150 ng/dL).
6) Subject had a current malignancy or history of malignancy within 5 years prior to screening with the exception of the following: prostate cancer or treated basal or squamous cell carcinoma of the skin.
7) Subject had clinical laboratory evidence of any severe underlying disease state (excluding prostate cancer) that would have placed subjects in additional jeopardy by participating in this study.
8) Subject had hypersensitivity to leuprolide, polylactic acid, or any excipient of the drug.
9) Subject had not completely recovered from the effects of any major surgery.
10) Subject had history of administration of the following prostate cancer therapies within 8 weeks prior to Screening Visit: chemotherapy, immunotherapy, anti-androgen, radiation therapy or brachytherapy), cryotherapy, strontium, or biological response modifiers.

11) Subject had a history of prostatic surgery (includes transurethral resection of the prostate and radical prostatectomy) within 4 weeks prior to the Screening Visit.
12) Subject had history of administration of hormonal therapy, including GnRH analogs (≤ 6 month depot formulation), estrogen, Megace and phytotherapy, within 32 weeks prior to the Screening Visit and through the treatment period or GnRH analog 1 year implants within 60 weeks prior to the Screening visit and through the treatment period.
13) Subject had a history of use of alternative medical therapies which have an estrogenic, androgenic, or anti-androgenic effect within 12 weeks prior to the Screening Visit and through the treatment period.
14) Subject had exposure to finasteride or ketoconazole within 1 week prior to the Screening Visit and through the treatment period; dutasteride within 25 weeks prior to the Screening Visit and through the treatment period.
15) Subject had exposure to experimental/investigational medication, device, or biologic within 5 half-lives of its pharmacologic effect or 3 months, whichever is longer, prior to the initial depot injection.
16) Subject required the chronic use of systemic corticosteroids or anticonvulsants that may have affected bone loss such as carbamazepine, phenobarbital, phenytoin, valproic acid, or primidone.
17) Subject had anticipated need for anti-androgen, immunotherapy, or surgical therapy for prostate cancer during the study.
18) Subject consumed >14 alcoholic beverages per week or had a history of alcoholism or illicit drug use within the 12 months prior to screening.
19) Employees and family members of the investigator, subinvestigator, or study coordinator were ineligible to participate. Employees or students of the institution/research facility who under the supervision of, or in a hierarchical subordinate role to, the investigator were also ineligible.

Treatment Plan

The first 150 patients enrolled were to receive Formulation A for both injections (injections are given 24 weeks apart). The next 150 patients were to receive Formulation B for both injections.

The trial included a Screening Period (up to 4 weeks), the 12 month Treatment Period (two 24 week treatment cycles) and a Follow-Up Period (30 days). During the first half of the treatment period, trial visits occurred on Days 1, 2, 8, and at the end of Weeks 2, 4, 8, 14, 20, and 24. During the second half of the treatment period, trial visits occurred at Weeks 24, 25 (on Days 170, 171, and 176) and at the end of Weeks 26, 30, 34, 40, 46, and 48, followed by a 30 day Post Treatment Follow up Visit. Figure 1 depicts the Trial Schematic.



* During Weeks 1, visits to take place on Days 1, 2, and 8.
** During Week 25, visits to take place on Days 170, 171, and 176.

Figure 1 Trial Schematic

The magnitude of the initial burst effect and the steady state leuprolide acetate systemic concentration was examined in a subset of patients following the 1st injection. Testosterone suppression was measured in all patients. The second IM injection of the same formulation (A or B) allowed assessment of possible elevations in testosterone concentrations and LH due to an acute-on-chronic effect on the hypothalamus-pituitary-gonadal axis. The second injection also permitted further observation of the duration of testosterone suppression.

Trial Procedures/Schedule of Visits

After signing the informed consent, patients underwent a Screening Period of up to 4 weeks. Blood draws (including pharmacokinetics), physical exam, and adverse events were assessed at pre-specified time points and are depicted in the Study Calendar shown below. Pharmacokinetic studies were conducted in 48 patients (24 Formulation A, 24 Formulation B).

Table 7: Schedule of Activities

		Screening Visit[1]	Treatment Period									Unscheduled Visit[11]
	Week	-4	1			2	4	8	14	20	24[10]	
Trial Time	Day	-28	1[2]	2	8	15	29	57	99	141	169	
Medical, Surgical and Social History		X										
Prostate Cancer History		X										
Admission Criteria		X										
Symptom Assessment			X[3]		X		X	X	X	X	X[6]	
ECOG Performance Status		X					X	X	X	X	X[6]	
Complete Physical Exam (including weight)		X[5]							X		X[6]	
Vital Signs (Temp, BP, Pulse, RR)		X	X	X	X	X	X	X	X	X	X[6]	
Leuprolide acetate 45 mg 6-month injection			X									
Injection Site Examination			X[4]	X	X	X						
Blood draw for LH/testosterone		X	X[3]	X	X	X	X	X	X	X	X[6]	
Blood draw for PSA, PAP		X			X				X		X[6]	
Blood draw for PK of leuprolide (subset only)			X[3,4]	X	X	X	X	X	X	X	X[6]	
Routine Safety Labs		X			X			X	X		X[6]	
Urinalysis		X			X			X	X		X[6]	
Record adverse events/concomitant meds		X	X	X	X	X	X	X	X	X	X[6]	X

1 Pre-trial procedures should be performed within 4 weeks of Day 1.
2 Day of first depot injection.
3 Prior to 1st depot injection.
4 On Day 1 this is required only for subjects participating in the PK schedule, at 2, 4, and 8 hours post-depot injection.
5 Including height at Screening only.
6 Prior to 2nd depot injection.
10 Week 24 represents the end of the first injection cycle AND the first day of the second injection cycle.
11 Additional safety procedures performed at the discretion of the investigator.

		Treatment Period (Activities to be performed post the 2nd leuprolide acetate 45 mg 6-month depot injection)											
	Week	24[10]	25			26	30	34	40	46	48/Final Visit	Follow-Up Period (30 days)	Unscheduled Visit[11]
Trial Time	Day	169	170	171	176	183	211	239	281	323	337		
Symptom Assessment				X	X	X	X	X	X		X		
ECOG Performance Status						X	X	X	X		X		
Complete Physical Exam (including weight)								X			X	X	
Vitals (Temp, BP, Pulse, RR)			X	X	X	X	X	X	X	X	X	X	
Leuprolide acetate 45 mg 6-month injection		X											
Injection Site Examination		X[8]	X	X	X	X							
Blood draw for LH/testosterone		X[7,8]	X	X	X	X	X	X	X	X	X		
Blood draw for PSA, PAP					X		X		X		X		
Blood draw for PK of leuprolide (subset only)		X[7,9]	X	X	X	X	X	X	X	X	X		
Routine Safety Labs					X			X	X		X		
Urinalysis					X			X	X		X		
Record adverse events/concomitant meds			X	X	X	X	X	X	X	X	X	X	X

7 Prior to 2nd depot injection.
8 On Week 24 this is required for all subjects, at 2, 4, and 8 hours post- 2nd depot injection.
9 2, 4, and 8 hours post-depot injection for the PK subset of subjects only.
10 Week 24 represents the end of the first injection cycle AND the first day of the second injection cycle.
11 Additional safety procedures performed at the discretion of the investigator.

Routine safety laboratories included a complete blood count, urinalysis, and chemistry panel. The chemistry panel included albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, calcium, bicarbonate, chloride, GGT, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, HDL, LDL, total protein, triglyceride, uric acid, and magnesium.

A symptom assessment asked patients to rate the severity of bone pain, pain on urination, and urination difficulty based on a 10 point scale, with 1 representing the absence of any symptoms and 10 representing the most severe.

Prohibited Medications

The following concomitant medications were prohibited during the study period and, for the specified period, prior to enrollment.

Table 8: Prohibited Medications

Medication/Therapy	Dose or Timing Requirements
Chemotherapy, immunotherapy, anti-androgen, radiation therapy, cryotherapy, strontium, biological response modifiers	Within 8 weeks prior to Screening and through the Treatment Period
GnRH analogs (≤ 6M depot formulations), estrogen, phytotherapy, Megace GnRH analog (1-year implant)	Within 32 weeks prior to Screening and through the Treatment Period Within 60 weeks prior to Screening and through the Treatment Period
Alternative medical therapies with estrogenic, androgenic, or anti-androgenic effect	Within 12 weeks prior to Screening and through the Treatment Period
Finasteride Dutasteride	Within 1 week prior to Screening and through the Treatment Period Within 25 weeks prior to Screening and through the Treatment Period
Ketoconazole	Within 1 week prior to Screening and through the Treatment Period

Discontinuation of Individual Patients

The investigator may have discontinued any patient's participation in the study without his consent at any time if any of the following occurred.

- It was in the patient's best medical interest.
- There was an adverse event(s) that the investigator felt was detrimental to the patient.
- The patient required treatment with another drug that would have interfered with evaluation of the investigational product.
- The patient had poor compliance with study drug treatments or study procedures.
- The patient refused to continue treatment.
- Serum testosterone was not maintained at a level considered to be therapeutic.

Patients who prematurely discontinued for any reason other than withdrawal of consent were to be followed for safety for 24 weeks following the last injection.

Assessment of Adverse Events

Adverse events were rated as mild, moderate or severe by the investigator. The Common Toxicity Criteria were not used to determine the severity of adverse event.

Statistical Analysis Plan

Primary Endpoint

- The primary endpoint was the suppression of serum testosterone to castrate levels (≤ 50 ng/dL) from Week 4 through Week 48.
- The primary analysis was conducted in patients who received at least one dose of study drug, had at least one post baseline testosterone measurement, and who did not use any treatments that lower testosterone levels. The primary analysis did not include patients whose final testosterone value was before Day 19 and > 50 ng/dL or patients who were suppressed through Week 48 with no escapes, but had no testosterone value at Week 4 (between Days 20 and 32).
- Patients who discontinued prematurely were included as censored observations at their last testosterone measurement.
- The Kaplan-Meier method was used to calculate a point estimate of the percentage of patients suppressed from Weeks 4 to 48 and to calculate the lower bound of the 1 sided 95% confidence interval (see below for calculations of the 2 sided 95% confidence interval). The statistical plan stated that for the formulation to be declared a "success" the lower bound of the 1 sided 95% confidence interval must be at least 87%.
- The applicant conducted an ongoing review of testosterone data with a plan to stop enrollment to Formulation A (or B) or to not administer the second injection if 15 or more subjects were not suppressed by Week 4 (Day 32) or if there were other results (lack of suppression) which precluded achieving the required primary efficacy endpoint. No alpha was assigned to these assessments.

Secondary Endpoints

- Change from baseline in PSA level at each treatment visit
- Mean testosterone concentration at each treatment visit

- "Acute-on-chronic" changes in testosterone and LH levels from just prior to the second (Week 24) injection through the visit 14 days after the second injection.

All analyses and summaries were conducted separately for the 2 treatment groups (Formulation A and Formulation B) and no statistical tests were performed between the two groups.

6 Review of Efficacy

Efficacy Summary

- Leuprolide acetate 45 mg maintained castrate testosterone levels from Week 4 through Week 48 in 93.4% with 95% CI (89.2%, 97.6%) of patients.
- Non-castrate testosterone levels were seen in 10 patients.
- Due to design flaws, the study was not able to demonstrate an improvement in bone pain, pain on urination, or difficulty with urination.

6.1 Indication

The applicant's proposed indication is the palliative treatment of advanced prostate cancer.

6.1.1 Methods

The primary efficacy analysis is based upon a single, open-label, multicenter, non-randomized Phase 3 trial (L-PC07-169). Two separate leuprolide formulations were studied (A and B), and approval is sought only for Formulation A. For Formulation A, enrollment began on February 25, 2008 and was completed on June 19, 2009. For Formulation B, enrollment began on April 28, 2008 and was completed on September 18, 2009.

6.1.2 Demographics

The demographic characteristics of the patients receiving Formulation A are included in the table below. Since information on the patients who received Formulation B or those treated on C02-008 will only be used in the safety analyses, this demographic information is included in Section 7. The demographic characteristics of the patients who received Formulation A are consistent with the patient population that is likely to receive this medication.

Table 9: Patient Demographics (Formulation A)	
Characteristic	Formulation A N = 151
Median Age (range)	76 years (48-92)
< 65 years	18 (11.9%)
≥ 65 years	133 (88.1%)
≥ 75 years	83 (55.0%)
Race/Ethnicity	
White	112 (84.2%)
Black	30 (19.9%)
Hispanic	7 (4.6%)
Asian	1 (0.7%)
Other	1 (0.7%)
Median Body Mass Index (range)	27 kg/m^2 (18.0-41.5)
< 25 kg/m^2	45 (29.8%)
25 to < 30 kg/m^2	68 (45.0%)
≥ 30 kg/m^2	38 (25.2%)

The table below depicts the disease characteristics of the patients receiving Formulation A, including the patient's stage at study entry. Stage IV prostate cancer was present in only 14% of patients and the indication statement, palliative treatment of advanced prostate cancer, applies only to this limited number of patients. The suppression of testosterone, the primary efficacy endpoint, is expected to occur equally in patients with early and advanced disease and will be examined in both patients with early and with advanced disease.

Fifty-five patients were eligible based upon a rising PSA. This includes 26 patients with an increase in PSA of at least 0.2 ng/dL compared to their previous level and 29 patients with a rise in PSA at least 2 ng/dL above their nadir.

Table 10: Prostate Cancer Disease Characteristics (Formulation A)	
Characteristic	Formulation A N = 151
Stage at Entry (TNM)	
II	104 (68.9%)
III	20 (13.2%)
IV	21 (13.9%)
Missing	6 (4.0%)
Median Testosterone at Entry (Baseline range)	401 ng/dL (114-1060)
Median PSA at Entry (range)	9.8 ng/mL (0.2-1517.3)

6.1.3 Subject Disposition

The disposition of patients receiving Formulation A is depicted below. All 151 patients enrolled received at least one injection. Twelve patients discontinued after the 1st injection and the 2nd injection was administered to only 139 patients. Five patients discontinued after the 2nd injection and did not complete the study. There were 7 patients who discontinued due to an adverse event and they are discussed in Section 7. Among the 5 patients who withdrew consent, 2 had adverse events within 30 days of discontinuation (atrial fibrillation/cardiomyopathy and COPD).

While the applicant stated that only 1 patient discontinued due to a protocol violation (use of a prohibited medication), several patients received prohibited medications and are discussed under Protocol Violations. Since these patients did not discontinue due to their protocol violation, they are not included in the table below. Treatment failure was recorded as a cause of discontinuation in 1 patient. However, 10 patients had testosterone levels > 50 ng/mL at some point during the study period. These patients are discussed in the analysis of the primary endpoint. Finally, 1 patient discontinued due to disease progression. This patient had a non-castrate testosterone level and is discussed in the section dealing with the primary endpoint.

Table 11: Patient Disposition (Formulation A)

Patient Disposition	Formulation A N = 151
Completed	134 (88.7%)
Discontinued	17 (11.3%)
Adverse Event	7 (4.6%)
Withdrew Consent[1]	5 (3.3%)
Protocol Violation	1 (0.7%)
Treatment Failure	1 (0.7%)
Disease Progression	1 (0.7%)
Other[2]	2 (1.3%)

[1]Patients 187, 202, 219, 264, 302 [2] Patient 196-Automobile accident, Patient 283-patient moved

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis, testosterone suppression from Week 4 through Week 48, is depicted below.

Table 12: Primary Re-Analysis (Formulation A)

Primary Analysis	Formulation A
	N = 148
Applicant's Re-Analysis (2-sided 95% CI)	93.6% (90.2, 97.0)
	N = 148
FDA's Re-Analysis (2-sided 95% CI)	93.4% (89.2, 97.6)

The applicant excluded 1 patient from the original analysis, patient #145, because a testosterone level was not obtained at Week 4. In the re-analysis, 2 additional patients (#148, 248) were excluded from the primary analysis population as they were missing Week 4 values (missing frozen back up samples). These 2 patients had low testosterone levels after Week 4 (all <17 ng/dL for 1 subject and all <8.7 ng/dL for the other subject).

Ten patients had non-castrate testosterone levels during the treatment period. These patients are included in the table below. One patient (#255) failed to suppress appropriately by Day 32. Three patients (#159, 167, 282) escaped suppression just prior to the second injection at Week 24. Three patients (#153, 192, 318) escaped suppression after the 2nd injection. Finally, 2 patients escaped after the 2nd injection, one at Week 30 (#160) and one at Week 48 (#190). Two escapes were markedly elevated (173, 337 ng/dL). The remainders were < 97 ng/dL. The tenth patient (#200), who was included in the original analysis as castrate, was censored at 57 days in the re-analysis of the primary endpoint. The initial testosterone level (Esoterix Laboratories) in this patient was > 50 ng/dL. The assay was repeated on a back up sample and the result was < 50

ng/dL. All of this patient's other testosterone levels were castrate and it was thought that the initial testosterone level was erroneously drawn from another patient, and was subsequently corrected and accounted for in the original analysis. However, when the back-up frozen samples were transferred to Abbott Laboratories, this patient did not have enough sample left over to run a back-up sample. Rather than include this patient as non-castrate due to this one erroneous draw, the patient was censored at day 57 in the primary analysis.

Table 13: Failure of Testosterone Suppression from Week 4 to 48 (Formulation A)

Reason for Failure	Formulation A N =148
Any Reason	10 (6.8%)
Failure to Suppress by Day 32	1 (0.7%)
Escape Before the 2nd Injection (Week 24)	3 (2.0%)
Escape on the Day of the 2nd injection	3 (2.0%)
Escape at Week 30	1 (0.7%)
Escape at Week 48	1 (0.7%)
Erroneous lab draw at day 57	1 (0.7%)

The major difference in FDA's primary re-analysis was the censoring of patient #200. This patient was not excluded by the applicant in the first evaluation as there was a back-up sample that was able to clarify that the elevated testosterone level found in this patient was due to a mix-up of samples. However, there was no back-up sample for the re-analysis. Rather than treat this patient as a failure, the patient was censored.

The 4 patients who used megace (#281, 171,187, 118) were censored at (60, 52, 57, 49 days), the first days of using megace, respectively; patient #200 was censored at 57 days, the last date of castrate testosterone. The result was 93.5% with 95% CI (89.4%, 97.6%).

All 4 subjects took megestrol acetate after Week 4. The total daily dose of megestrol acetate did not exceed 40 mg in any subject. The testosterone concentrations, prior to initiation of treatment with megestrol acetate, were within the range of 4.50 to 12.00 ng/dL and were well below the threshold level of 50 ng/dL. The decreases in testosterone concentrations after Week 4 for these subjects who took megestrol acetate follow a similar pattern to that seen in the overall study population.

Sensitivity Analyses

In the first sensitivity analysis performed by the applicant, 2 subjects with inadequate frozen back-up samples were treated as failures at Week 4. Serum testosterone was suppressed to ≤ 50 ng/dL from Week 4 through Week 48 in 92.3% of subjects. In this conservative analysis, the 88.7% lower bound of the 2-sided 90% CI, using the Kaplan-Meier method, remained above the prespecified minimum requirement of 87% for Formulation A to be considered successful.

In a second sensitivity analysis performed by the applicant, 4 subjects who took concomitant megestrol acetate after the first 32 days of the study were excluded. The threshold indicating

success for Formulation A was also exceeded in this analysis, with a 90.0% lower bound of the 2-sided 90% CI, using the Kaplan-Meier method.

Table 14: Reanalysis of Testosterone Suppression from Week 4 to Week 48: Sensitivity Analyses for the Primary Efficacy Endpoint (Formulation A)				
Approach to Sensitivity Analyses	N	% Suppressed	Standard Error	2-sided 90% Confidence Interval
Treating 2 subjects with missing week 4 back-up samples as failures at Week 4	150	92.3	2.23	88.7, 96.0
Excluding 4 subjects who took concomitant megace	144	93.4	2.11	90.0, 96.9

Two new sensitivity analyses (not performed in the Original Analysis) on the primary endpoint with different methods of imputing for missing back-up samples were conducted by the applicant to test the validity of using the proposed primary endpoint analysis. One analysis used the Esoterix data when data from the reanalysis was not available. The second used an average of the reanalysis values immediately preceding and following the missing sample. Results of the primary analysis (Reanalysis) were supported by those from these sensitivity analyses, with results nearly identical to the originally analyzed primary endpoint. Specifically, serum testosterone was suppressed to ≤ 50 ng/dL from Week 4 through Week 48 in 93.7% of subjects and the lower bound of the 2-sided 90% CI using the Kaplan-Meier method (90.3%) exceeded the prespecified minimum requirement of 87% for Formulation A to be considered successful.

6.1.5 Analysis of Secondary Endpoints(s)

Change in PSA from Baseline

At entry, 74.2% (112/151) of patients had a PSA > 4 ng/mL. The table below depicts the number of patients with the stated change in PSA from baseline at predetermined visits. By Day 8, most patients had an increase in PSA, but thereafter, all but 3 patients exhibited a decrease in PSA.

Table 15: Change in PSA from Baseline (Formulation A)					
Visit	↓ <50%	↓ 50-90%	↓ 90-95%	↓ >95%	↑
Day 8	43 pts	2	0	0	101
Week 24	2	34	17	92	1
Week 48	1	21	21	88	2

There were 3 patients who had an elevation in PSA compared to baseline. The table below provides information on the patient's prior treatment and stage at study entry as well as their testosterone level. Note that all 3 patients did achieve, at some point, a decrease in PSA from baseline and that none of these patients had a testosterone level > 50 ng/dL.

Table 16: Testosterone Levels at Time of a Rise in PSA (Formulation A)					
Pt #	Visit	PSA level	Testosterone Level	Stage at Entry	Prior Treatment
132	Baseline	6.4 ng/mL	126.0 ng/dL	T2bN1M0	External Beam and
	Week 14	0.5	5.6	Gleason's 9	Brachytherapy

	Week 40	22.6	7.8		
193	Baseline	39.7	586.0	T4N3M0	No record of prior therapy
	Week 24	8.0	4.3		
	Week 40	96.8	5.3		
302	Baseline	86.5	195.0	T2bNxM1b Gleason's 9	TURP
	Week 14	25.7	15.0		
	Week 24	143.3	12.0		

Mean Testosterone Concentration

The table below shows the mean testosterone concentration and standard deviation at each visit. These are mean values and are minimally affected by individual patient values > 50 ng/dL. The table does provide some information on the time course of the initial increase and later decrease in testosterone levels due to receptor down regulation. At Week 34 and at the Final Visit there is a marked increase in standard deviation due to a single outlier (same patient).

Table 17: Mean Testosterone Concentration (Formulation A)

Visit	N	Mean Testosterone (SD)
Baseline	151	434.6 ± 175.1
Day 2	145	608.2 ± 259.4
Day 8	145	467.5 ± 200.1
Week 2	147	126.8 ± 90.1
Week 4	148	15.9 ± 8.5
Week 8	143	9.4 ± 5.6
Week 14	139	9.1 ± 5.4
Week 20	150	8.4 ± 5.5
Prior to 2nd Injection	136	10.8 ± 11.7
2 h After 2nd Injection	129	9.0 ± 9.9
4 h After 2nd Injection	126	9.7 ± 11.4
8 h After 2nd Injection	123	9.7 ± 13.0
1 Day After 2nd Injection	138	10.8 ± 10.1
2 Days After 2nd Injection	135	10.8 ± 9.9
3-10 Days After 2nd Injection	135	10.0 ± 8.0
11-17 Days After 2nd Injection	131	8.9 ± 5.6
Week 24	148	14.2 ± 15.2
Week 26	135	9.1 ± 5.5
Week 30	136	9.9 ± 19.4
Week 34	131	13.0 ± 48.1
Week 40	131	8.7 ± 4.6
Week 46	129	8.7 ± 5.2
Week 48	135	9.9 ± 8.2
Final Visit	151	13.1 ± 45.1

Acute-on-Chronic Changes in Testosterone and LH Following the Second Injection

An additional secondary endpoint was assessment of "acute-on-chronic" changes in testosterone and LH levels from just prior to the 2nd injection and at 2, 4, and 8 hours and at 1, 2, 3 to 10, and 11 to 17 days following the 2nd injection.

The applicant did not define the level of LH or testosterone that represented an "acute-on-chronic" change in these levels. In these analyses, for patients previously maintained at castrate levels, levels of testosterone greater than 50 ng/dL represented an "acute-on-chronic" change in testosterone. There were 3 patients (#153, 192, and 318) who had a castrate testosterone level prior to the 2nd injection and had an increase in testosterone to > 50 ng/dL after the 2nd injection. The associated LH elevation in these 3 patients was 279-470 times their LH level prior to injection.

The definition of an "acute-on-chronic" change in LH is more problematic. A repeat assay on the same sample can vary by 20-25%. Thus, any increase in LH > 25% could represent a real, "acute-on-chronic" change in LH. An "acute-on-chronic" change was, therefore, defined as a > 25% increase in LH compared to the LH level just prior to injection. The table below (# patients with an elevated level/# patients with an LH level at that time point) suggests that a large number of patients had an increase in LH following the 2nd injection. It also suggests that the time course of this increase was prolonged. Most importantly, few patients had an increase in testosterone to non-castrate levels.

Table 18: Acute on Chronic Elevations in LH Level (Formulation A)

Visit	# Patients with an Elevated LH Level
2 Hours After 2nd Injection	113/127 (89.0%)
4 Hours After 2nd Injection	113/126 (89.7%)
8 Hours After 2nd Injection	105/122 (86.1%)
1 Day After 2nd Injection	120/134 (89.6%)
2 Days After 2nd Injection	109/132 (82.6%)
3-10 Days After 2nd Injection	109/134 (81.3%)
11-17 Days After 2nd Injection	88/134 (65.7%)

6.1.6 Other Endpoints

Bone Pain

On a scale ranging from 1 (no pain) to 10 (worst possible pain), the mean bone pain at baseline was 1.6 $\pm$ 1.5. Given this level of pain, an assessment of the improvement in pain following the use of study drug was not meaningful and was not performed. However, there were 9 patients with baseline scores $\geq$ 5. Among these patients, 7 had at least a 2 point improvement in pain score. However, 1 of these 7 had only a single 2 point improvement (patient 163). The reports of bone pain on Day 8 were also examined for evidence of a flare in bone pain following the administration of study drug. Among 150 patients with Day 8 values, 4 had at least a 2 point increase in bone pain when compared to baseline.

Pain on Urination

On a scale ranging from 1 (no pain) to 10 (worst possible pain) on urination, the mean pain on urination at baseline was 1.4 $\pm$ 1.2. Given the level of pain reported at baseline, an assessment of the improvement in pain was not meaningful and was not performed.

Difficulty with Urination

Similarly, on a scale ranging from 1 (no difficulty) to 10 (worst possible difficulty) on urination, the mean score at baseline was 1.6 ± 1.33. Given the level of difficulty reported at baseline, an assessment of the improvement in urination was not meaningful and was not performed.

6.1.7 Subpopulations

The table below provides information on the number of patients with castrate testosterone levels in various subgroups. Here, this analysis, performed for the population as a whole, is included for comparison. Patients ≥ 75 years did slightly better than the population as a whole while Blacks did slightly worse. Further, the percentage of patients with a castrate testosterone level did not decrease with an increase in BMI. This suggests that there is no relationship between BMI and product efficacy. Finally, patients with Stage II disease appeared to do slightly worse than those with more advanced disease. This is unexplained and no information is available about prior exposure to GnRH agonists. Finally, no difference is seen in the percentage of patients with castrate testosterone levels by stage.

Table 19: Subgroup Analyses of Efficacy (Formulation A)

	# in Subgroup	# Patients with Castrate Testosterone
Study Population	150	141 (94.0%)
Age		
< 65	18	17 (94.4%)
≥ 65	133	125 (94.0%)
≥ 75	83	82 (98.8%)
Race		
White	112	107 (95.5%)
Black	30	26 (86.7%)
BMI		
< 25 kg/m^2	45	43 (95.6%)
25 to < 30 kg/m^2	68	63 (92.6%)
≥ 30 kg/m^2	38	36 (94.7%)
Stage at Entry		
II	104	96 (92.3%)
III	20	19 (95.0%)
IV	21	21 (100.0%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All studies have used the 45 mg extended release formulation of leuprolide acetate. In the key study, 151 patients received the first dose of study drug while 139 patients received the second dose of study drug at Week 24 (Day 169). All patients received their 2nd injection by Day 170.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Among the 10 patients who failed to maintain castrate testosterone levels, 3 patients had elevated testosterone levels just prior to the second injection. Three additional patients developed a non-castrate testosterone level (ranging from 51 to 61 ng/dL) in response to the second injection. Finally, 1 patient developed a non-castrate testosterone level at Week 48. This suggests that the

leuprolide release has been extended to the maximum interval for this formulation and that dosing intervals should be no greater than 24 weeks.

6.1.10 Additional Efficacy Issues/Analyses

Protocol Violations

The applicant identified 63 (41.7%) patients with a protocol violation. This includes both major and minor protocol violations. Major protocol violations that may affect study outcome include the following.

- Patients 118, 171, 187, and 281 received megestrol acetate (stated indication-hot flashes, weakness) during the treatment period. These patients were censored in the FDA's primary analysis but were included in the primary re-analysis. However, the FDA did perform a sensitivity re-analysis excluding these patients. In addition, 4 patients received bicalutamide and 2 chronic steroids. Since bicalutamide and steroids were unlikely to lower testosterone levels, these patients were included in the primary analysis (Br J Urol 1995 75:335).
- Patient 145 did not have a Week 4 testosterone level. This patient was excluded from the primary analysis by the applicant's definition of the primary analysis population and was also excluded in the re-analysis.
- Patient 200 was censored at day 57 as this was the last day of castrate testosterone before a mix-up of samples that was unable to be verified by back-up samples.

Patient 207 did not have 2 rising PSAs prior to entry and entered with study with a PSA of 1.3. While it is unclear whether a GnRH agonist was indicated, the presence or absence of changes in his PSA should not have affected his testosterone levels. In addition, the applicant identified 6 patients who, at some point, did not sign the correct version of the informed consent. This includes 1 patient who initialed rather than signed the informed consent. All patients did sign some version of the informed consent.

Efficacy Analyses for Formulation B and C02-0008

Formulation B

Castrate testosterone levels were seen in 86.9% (95% CI; 82.2, 91.7) of patients receiving Formulation B from Week 4 to 48. Non-castrate testosterone levels were seen in 7 patients just prior to the 2nd injection, 10 patients after the 2nd injection, and in 1 patient at Week 4.

C02-0008

Study drug was administered every 26 (rather than every 24 weeks) weeks. Castrate testosterone levels were seen in 82.8% (95% CI; 77.9, UK) of patients on Study C02-0008. At Week 4, 87.8% of patients had castrate testosterone levels. All patients achieved castrate levels by Week 8, but 15 patients subsequently developed non-castrate levels.

7 Review of Safety

Safety Summary

The table below provides a summary of the safety findings for the to-be-marketed formulation.

Table 20: Safety Summary (Formulation A)	
Deaths	
All Causes of Death	Aspiration Pneumonia (1)
Discontinuations	
Overall	4.6%
All Causes of Discontinuation	Fatigue, Hot Flush, Second Primary Neoplasm, Asthenia, Constipation, Coronary Artery Disease, Hyperkalemia, Sleep Disorder
Serious Adverse Events	
Overall Treatment Emergent	20.5%
Treatment Emergent Serious Adverse Events in ≥ 2% of Patients	COPD, Coronary Artery Disease, CVA/TIA, Pneumonia, Heart Failure, Second Primary Neoplasm
Severe Adverse Events	
Overall Treatment Emergent	20.5%
Treatment Emergent Severe Adverse Events in ≥ 2% of Patients	Hot Flush, Atrial Fibrillation/Flutter, COPD, Coronary Artery Disease, Heart Failure
Adverse Events	
Overall Treatment Emergent	94.7%
Treatment Emergent Adverse Events in ≥ 10% of Patients	Hot Flush, Injection Site Pain/Discomfort, Upper Respiratory Infection, Fatigue/Lethargy
Overall Treatment Related	72.8%
Treatment Related Adverse Events in ≥ 5% of Patients	Hot Flush, Fatigue/Lethargy, Injection Site Pain/Discomfort
Laboratory Abnormalities	
CTCAE v 4 Grade 3-4 in ≥ 5% of Patients	None
CTCAE v 4 Grade 1-2 Abnormalities in ≥ 10% of patients	Grade 1-2 abnormalities in which the incidence increased by ≥ 10% when compared to baseline include increased glucose, triglyceride, cholesterol, decreased hemoglobin, creatinine, and ALT.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety information comes from 151 patients who received Formulation A on study L-PC07-169. Formulation A is the to-be-marketed-product under consideration. This information is supplemented by safety data from 159 patients who received Formulation B on L-PC07-169, as well as, information from 164 patients on study C-02-008. The applicant supplied data sets for all patients who received Formulations A or B. However, only data listings were provided for patients on C02-008.

Each of these formulations, Formulations A and B and the formulation used in C-02-008, was intended to be 24 week extended release forms of leuprolide acetate. The composition of each is shown in Table 4. Since the composition of these products and the adverse event profiles of these products are very similar, this information can be used as part of the safety database. Note

that both Formulation B and the formulation used in study C02-008 failed to achieve their efficacy endpoints.

7.1.2 Categorization of Adverse Events

Adverse events were categorized as mild, moderate, or severe. The Common Toxicity Criteria were not used. Serious adverse events followed the definition used in the Code of Federal Regulations.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from L-PC07-169 Formulation A, L-PC07-169 Formulation B, and C-02-008 will not be pooled. Data from Formulations A and B will be displayed side by side and data from C02-008 will be used to further comment on any signals seen. Adverse events from previous studies of the Lupron 3 Month and Lupron 4 Month formulations will also be compared to those seen with Formulation A.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

All studies used a 45 mg extended release formulation of leuprolide acetate.

- Formulation A: 151 patients received the 1st dose and 139 patients the 2nd dose of study drug at Week 24 (Day 169). Among the 139 patients who received 2 doses, all received their 2nd dose by Day 170.
- Formulation B: 159 patients received the 1st dose and 129 patients the 2nd dose of study drug at Week 24. Among the 129 patients who received 2 doses, 127 received their 2nd dose by Day 170.
- C02-008: 164 patients received the 1st dose and 153 patients the 2nd dose of study drug at Week 26 (Day 182). Among the 153 patients who received 2 doses, 151 received their 2nd dose by Day 184.

Demographics and Baseline Characteristics

The table below provides information on the demographics and baseline characteristics of patients who received either Formulation A or B. Information for patients on study C02-008 was provided in a clinical study report and data listings. The median age of patient on C02-008 was

75.0 years (range: 54-91) and 80.5% of patients were White while 14.0% of patients were Black. Clinical stage at study entry included only 9.8% of Jewett D1 or D2 patients.

Table 21: Demographics and Baseline Characteristics (Safety Database)

	Formulation A N = 151	Formulation B N = 159
Median Age (range)	76 years (48-92)	74 years (46-94)
Race/Ethnicity		
White	112 (84.2%)	105 (66.0%)
Black	30 (19.9%)	47 (29.6%)
Hispanic	7 (4.6%)	0
Asian	1 (0.7%)	4 (2.5%)
Other	1 (0.7%)	3 (1.9%)
Median BMI (range)	27.0 kg/m^2 (18-42)	27.7 kg/m^2 (19.0-45.7)
Stage at Entry		
II	104 (68.9%)	117 (73.6%)
III	20 (13.2%)	11 (6.9%)
IV	21 (13.9%)	25 (15.7%)
Missing	6 (4.0%)	6 (3.8%)

The demographics of these patient populations are similar, but not identical (different racial profiles) and are characteristic of patients undergoing palliative treatment for advanced prostate cancer. This suggests that the available safety data will be useful in the following analyses.

7.2.2 Explorations for Dose Response

All formulations used an extended release formulation of 45 mg of leuprolide acetate.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Safety laboratories were obtained at baseline and at weeks 1, 13, 25, 34, 40, and 50. These laboratories included a complete blood count, urinalysis, and chemistry panel.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology review and Section 4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse event profiles of the 3 and 4 month formulations of Lupron were examined and compared to the adverse event profile of Formulation A.

- Adverse events attributed to Lupron Depot-3 Month, by the investigator, in ≥ 10% of patients included generalized pain, injection site reaction, hot flashes, gastrointestinal disorders, joint disorders, testicular atrophy, and urinary disorders.

- Adverse events reported with Lupron Depot-4 Months in ≥ 10% of patients included asthenia, flu syndrome, generalized pain, headache, injection site reaction, hot flashes, gastrointestinal disorders, edema, skin reaction, and urinary disorders.

Product warnings state that both of these products should not be used in patients with impending cord compression or urinary obstruction. Anemia, hyperlipidemia, and decreased bone density have been seen with these products. In the post-marketing setting, mood swings, depression, and suicide have been reported. Anaphylactoid reactions and pituitary apoplexy have also occurred.

The adverse reactions common to products in this class are due to the effects of decreased testosterone levels. These include hot flashes, asthenia, and testicular atrophy as well as anemia, hyperlipidemia, and loss of bone density. Further, generalized pain or joint disorders may, in part, be attributable to the initial testosterone flare seen with these products.

7.3 Major Safety Results

7.3.1 Deaths

None of the deaths listed below were attributed to study drug by the investigator. Note that suicide has been associated with the use of GnRH agonists.

- One patient on Formulation A died due to aspiration pneumonia.

- Causes of death among 6 patients who received Formulation B included hepatocellular carcinoma, CVA, dementia, suicide, intestinal perforation with multi-organ failure, and urosepsis. The patient whose death was attributed to dementia stopped eating and died on Study Day 81. It is unclear if this patient provided adequate informed consent.

- Causes of death among 4 patients enrolled on C02-008 included sepsis, sudden death (2), and intestinal perforation with cholecystitis complicated by MI.

7.3.2 Nonfatal Serious Adverse Events

The nonfatal serious adverse events for patients who received Formulation A and B are included in the table below. Serious adverse events were reported in 26 (15.9%) patients on study C02-008. Events that occurred in ≥ 2% of patients on C02-008 include CVA and second primary malignancy. Events common to these studies include CVA, pneumonia and second primary malignancies. These events may, in part, be related to the patient's age and to the presence of underlying cancer. Among the 151 patients who received Formulation A, 11 (7.3%) patients had a second primary neoplasm. While only 2 of these were considered serious, 4 of the 11 were non-skin cancers. Among the 159 patients who received Formulation B, 9 (5.7%) patients had a

second primary neoplasm. This included 7 patients with non-skin cancers. This can be compared to a study by Brenner et al from the SEER program (1973-1993) in which the incidence of second primary neoplasms in patients with prostate cancer undergoing surgery was 7.2% while the incidence in men undergoing radiation therapy was 6.9% (Cancer 2000 33:398). Thellenberg et al from the Swedish Cancer Registry reported that second primary neoplasms were seen in 7.7% of patients with prostate cancer from 1958 to 1996 (J Urol 2003 169:1345). In studies involving a 6 month formulation of leuprolide acetate, the percentage of patients with a second primary neoplasm was similar to that in the 2 studies cited. However, these events were reported over a 1 year period (as opposed to a period of 38 to 20 years). Second primary malignancy will be included in the table of grade 1-4 events in the package insert and will be further examined with other GnRH antagonists and agonists.

Table 22: Serious Adverse Events in ≥ 2% of Patients (Safety Database)		
Serious Adverse Events	Formulation A N = 151	Formulation B N = 159
All	31 (20.5%)	41 (25.8%)
Cardiac Disorders		
Coronary Artery Disease	3	2
Heart Failure	2	3
Infections and Infestations		
Pneumonia	3	3
Neoplasms, Second Primary	2	5
Nervous System Disorders		
CVA/TIA	3	3
Respiratory Disorders		
COPD	3	0

7.3.3 Dropouts and/or Discontinuations

The adverse events leading to discontinuation for patients receiving Formulation A or B is provided in the table below. The most common adverse events leading to discontinuation were second primary cancers and hot flushes. Little information is available about the development of pancreatitis and its role in patient discontinuation. However, the investigator did state that pancreatitis was unrelated to study drug. Findings from patients on study C02-008 were similar. Here, 5 (3.0%) patients discontinued due to an adverse event. These events included CVA, hot flush (2), esophageal cancer, and sterile abscess. It is unclear if the sterile abscess occurred at the site of injection, but the event was considered probably related to study drug.

Table 23: Adverse Events Leading to Discontinuation (Safety Database)		
	Formulation A N = 151	Formulation B N = 159
All	7 (4.6%)	10 (6.3%)
Cardiac Disorders		
Coronary Artery Disease	1	0
Heart Failure	0	1
Tachycardia	0	1
Gastrointestinal Disorders		
Constipation	1	0
Pancreatitis	0	1

General Disorders		
Asthenia	1	0
Fatigue	2	0
Infections and Infestations		
Urosepsis	0	1
Injury and Procedural Complications		
Bone Fracture	0	1
Metabolism and Nutrition		
Hyperkalemia	1	0
Neoplasms		
Second Primary Neoplasm	2	2
Psychiatric Disorders		
Sleep Disorder	1	0
Panic Attack/Anxiety	0	1
Respiratory Disorders		
Pleural Effusion	0	1
Vascular Disorders		
Hot Flush	2	2

7.3.4 Significant Adverse Events

Severe Adverse Events

As shown in the table below, patients who received Formulation A or B had a similar number of severe adverse events. Severe adverse events that occurred in ≥ 2% of patients included atrial fibrillation or flutter, COPD, hot flushes, heart failure, and pleural effusion. These events are consistent with the age of the patient population.

In C02-008, 34 (20.7%) patients experienced a severe adverse event. Events which occurred in ≥ 2% of patients included pneumonia, sepsis, muscle cramp, CVA, urinary retention, respiratory failure, and hot flush. These are consistent with the events that led to discontinuation or were reported as severe with Formulation A.

Table 24: Severe Adverse Events in ≥ 2% of Patients (Safety Database)

Severe Adverse Event	Formulation A N = 151	Formulation B N = 159
All	31 (20.5%)	33 (20.7%)
Cardiac Disorders		
Atrial Fibrillation/Flutter	3	1
Heart Failure	1	3
Respiratory Disorders		
COPD	3	0
Pleural Effusion	0	3
Vascular Disorders		
Hot Flush	7	3

Injection Site Reactions

The table below provides information on the incidence of injection site reactions in patients who received Formulation A. Since injection site reactions are likely to be formulation specific, only

information from patients who received Formulation A is included in the table below. The percentage of patients who reported injection site reactions with Formulation A is slightly higher than the percentage who reported injection site reactions with Lupron Depot-3 Month (13.8%) and Lupron Depot-4 Month (8.2%). No patient discontinued due to an injection site reaction.

Table 25: Injection Site Reactions (Formulation A)

	Formulation A N = 151
All	35 (23.2%)
Injection Site Pain/Discomfort	29 (19.2%)
Injection Site Swelling/Induration	3
Injection Site Hematoma/Hemorrhage	2
Injection Site Erythema	3
Injection Site Nodule	1
Injection Site Dermatitis	1
Injection Site Warmth	1

QT Prolongation

Since leuprolide acetate was first approved in 1989, QT data have not been collected. Although the sponsor did not perform ECG monitoring, QT data for leuprolide acetate can be found in another submission (NDA 22-201; degarelix for injection). Here, leuprolide 7.5 mg once every 28 days was used as a comparator drug (N = 201). EKGs were obtained at baseline, Days 3 and 84 and then every 84 days. There was no overt prolongation on Day 3 (maximum drug concentration, but not maximum testosterone suppression). However, among the patients treated with leuprolide, 40 patients has a post baseline QTcF $\geq$ 450 msec, 7 had a QTcF $\geq$ 480 msec, and 4 had a QTcF $\geq$ 500 msec. One patient with a QTcF of 503 msec developed syncope 20 d after this EKG. QT prolongation has been added to the Warnings section of the Lupron package insert.

Metabolic Abnormalities Linked to GnRH Use

Androgen deprivation therapy has been linked to insulin resistance, an unfavorable alteration in the lipid profile, and cardiovascular disease. Cardiac adverse events and abnormalities in the lipid profile are included in these safety tables. However, a single arm study in an elderly population cannot determine whether an increase in these events has been seen. Further, while these changes were reported, the study period may be insufficient to detect an increase in these abnormalities compared to control.

7.3.5 Submission Specific Primary Safety Concerns

This submission identified second primary neoplasms as an additional safety concern when compared to the Lupron Depot-3 Month and Lupron Depot-4 Month formulations.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The two tables below provide information on the mild, moderate, or severe adverse events that occurred in at least 5% of patients who received Formulation A or B. The adverse event profiles of both formulations are similar to each other and to the 3 and 4 month formulations of Lupron. The most common treatment emergent adverse events seen with Formulation A (≥ 10%), regardless of relationship, include hot flushes, injection site pain, upper respiratory tract infection, and fatigue/lethargy. The table below also examines the percentage of patients in which the event was considered treatment related (per investigator). Treatment related adverse events that occurred in ≥ 5% of patients included hot flushes, fatigue/lethargy, and injection site pain/discomfort.

Table 26: Adverse Events in ≥ 5% Patients (Formulation A)

	Formulation A N = 151	
Preferred Term	Treatment Emergent	Treatment Related
All	143 (94.7%)	110 (72.8%)
Blood and Lymphatic Disorders		
Anemia/Hemoglobin Decreased	10 (6.6%)	2 (1.3%)
Cardiac Disorders		
Coronary Artery Disease/Angina	8 (5.3%)	1 (0.7%)
Gastrointestinal Disorders		
Constipation	15 (9.9%)	5 (3.3%)
General Disorders		
Fatigue/Lethargy	20 (13.2%)	18 (11.9%)
Injections Site Pain/Discomfort	29 (19.2%)	16 (10.6%)
Peripheral Edema/Pitting Edema	8 (5.3%)	2 (1.3%)
Infections and Infestations		
Upper Respiratory Tract Infection[1]	32 (21.2%)	0
Urinary Tract Infections/Cystitis	9 (6.0%)	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	14 (9.3%)	2 (1.3%)
Back Pain	8 (5.3%)	0
Musculoskeletal Pain/Myalgia	12 (7.9%)	3 (2.0%)
Neoplasms		
Second Primary Neoplasms[2]	11 (7.3%)	0
Nervous System Disorders		
Dizziness	8 (5.3%)	3 (2.0%)
Headache/Sinus Headache	12 (7.9%)	3 (2.0%)
Psychiatric Disorders		
Insomnia/Sleep Disorder	13 (8.6%)	5 (3.3%)
Renal and Urinary Disorders		
Dysuria	9 (6.0%)	1 (0.7%)
Hematuria/Hemorrhagic Cystitis	10 (6.6%)	0
Nocturia	8 (5.3%)	2 (1.3%)
Urinary Incontinence	8 (5.3%)	3 (2.0%)
Respiratory, Thoracic and Mediastinal Disorders		

COPD	8 (5.3%)	0
Cough	10 (6.6%)	2 (1.3%)
Dyspnea/Dyspnea on Exertion	8 (5.3%)	2 (1.3%)
Skin and Subcutaneous Tissue Disorders		
Rash	9 (6.0%)	3 (2.0%)
Vascular Disorders		
Hot Flush/Flushing	89 (58.9%)	88 (58.3%)1
Hypertension/BP Increased	10 (6.6%)	3 (2.0%)

[1]Includes influenza, nasal congestion, nasopharyngitis, rhinorrhea, upper respiratory tract infection, and viral upper respiratory tract infection.
[2]Includes basal cell carcinoma, bladder transitional cell carcinoma, lung neoplasm, malignant melanoma, non-Hodgkin's lymphoma, and squamous cell carcinoma.

Mild, moderate or severe adverse events in patients who received Formulation B were very similar to those in patients who received Formulation A. The most common treatment emergent adverse events (≥ 10%) seen in patients that received Formulation B included hot flushes, injection site pain, upper respiratory tract infection, arthralgia, fatigue/lethargy, hypertension, and constipation.

Table 27: Treatment Emergent Adverse Events in ≥ 5% of Patients (Formulation B)

Preferred Term	Formulation B N = 159
All	144 (90.6%)
Blood and Lymphatic Disorders	
Anemia	10 (6.3%)
Gastrointestinal Disorders	
Constipation	16 (10.1%)
Nausea	8 (5.0%)
General Disorders	
Fatigue/Lethargy	19 (11.9%)
Peripheral Edema	10 (6.3%)
Injection Site Pain/Discomfort	26 (16.4%)
Infections and Infestations	
Upper Respiratory Tract Infection[1]	27 (17.0%)
Urinary Tract Infection	10 (6.3%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	22 (13.8%)
Back Pain	9 (5.7%)
Extremity Pain	9 (5.7%)
Neoplasms	
Second Primary Neoplasm	9 (5.7%)
Nervous System Disorders	
Dizziness	15 (9.4%)
Headache/Migraine	10 (6.3%)
Psychiatric Disorders	
Insomnia	9 (5.7%)
Renal and Urinary Disorders	
Dysuria	8 (5.0%)
Respiratory, Thoracic, and Mediastinal Disorders	
Dyspnea/Dyspnea on Exertion	10 (6.3%)
Skin and Subcutaneous Tissue Disorders	

Rash	8 (5.0%)
Vascular Disorders	
Hot Flush	71 (44.7%)
Hypertension	16 (10.1%)

[1]Includes nasal congestion, nasopharyngitis, rhinitis, rhinorrhea, and upper respiratory tract infection.

Adverse events in C02-008 were collected from day 1 until 3 days after the final study visit (at 52 weeks or at the time of premature discontinuation). Adverse events were reported in 93% of patients. Adverse events that occurred in ≥ 10% of patients included hot flush, injection site pain, fatigue, arthralgia, nasopharyngitis, hypertension, and back pain. This is similar to the adverse event profile seen with Formulation A.

Testicular Atrophy/Hot Flush

While the percentage of patients who reported a hot flush with Formulation A is similar to the percentage who reported a hot flush with Lupron Depot-3 Month or Lupron Depot-4 Month, the percentage of patients who reported other consequences of testosterone deprivation was much lower. For example, 20.2% of patients receiving Lupron Depot-3 Month reported testicular atrophy while this was reported in only 2 patients who received Formulation A. It may be that there was under reporting of events which are known consequences of testosterone deprivation in the study under review.

Renal Failure

Renal failure or acute renal failure was reported in 3 patients who received Formulation A and 4 patients who received Formulation B. These events were considered unrelated in 6 of the patients. In patient 302, renal failure was reported on Day 59 and was considered mild and related to study drug. The patient had a creatinine of 106.08 mcmol/L (normal range: 44.2-132.6 mcmol/L) at baseline and a maximum value of 221 on Day 59. Subsequent values gradually decreased to 176.8 on Day 167. Hypertonic bladder (Day 80) and hydronephrosis (Day 84) were also reported in this patient.

7.4.2 Laboratory Findings

Safety laboratories were obtained at baseline and at weeks 1, 13, 25, 34, 40, and 50. These laboratories included a complete blood count, urinalysis, and chemistry panel. The table below provides information on the percentage of patients receiving Formulation A who developed grade 1-4 (Common Toxicity Criteria Adverse Events v 4.0) laboratory abnormalities. Laboratories of interest included in this table include liver function tests, anemia, elevated blood glucose, and hyperlipidemia. Among these, no grade 3-4 laboratory abnormalities were seen in ≥ 5% of patients. Note that many patients had grade 1-2 abnormalities at baseline, but that the number of patients with grade 1-2 abnormalities increased during the treatment period. Grade 1-2 abnormalities in which the incidence increased by ≥ 10% when compared to baseline included increased glucose, triglyceride, cholesterol, decreased hemoglobin, creatinine, and ALT. Although all laboratories were supposed to be obtained fasting, it is unclear if the presence of grade 1-2 hyperglycemia or triglycerides may be related to food intake. Further, while baseline

levels were assessed at a single time point, on study values were assessed at multiple time points, increasing the likelihood of an abnormal level in laboratories that vary markedly from day-to-day.

Table 28: CTCAE v 4 Grade 1-4 Laboratory Abnormalities of Interest (Formulation A)

		Formulation A N = 151				
		WNL[1]	Grade 1	Grade 2	Grade 3	Grade 4
Decreased Hemoglobin	Baseline	130	19 (12.6%)	2 (1.3%)	0	-
	On Study	81	64 (42.4%)	3 (2.0%)	2 (1.3%)	-
ALT	Baseline	149	2 (1.3%)	0	0	0
	On Study	133	14 (9.3%)	3 (2.0%)	1 (0.7%)	0
Total Bilirubin	Baseline	143	8 (5.3%)	0	0	0
	On Study	142	7 (4.6%)	2 (1.3%)	0	0
Creatinine	Baseline	128	23 (15.2%)	0	0	0
	On Study	110	39 (25.8%)	2 (1.3%)	0	0
Increased Glucose	Baseline	78	69 (45.7%)	4 (2.6%)	0	0
	On Study	23	107 (70.9%)	17 (11.3%)	4 (2.6%)	0
Increased Cholesterol	Baseline	108	43 (28.5%)	0	0	0
	On Study	62	83 (55.0%)	5 (3.3%)	1 (0.7%)	0
Increased Triglyceride	Baseline	109	36 (23.8%)	6 (4.0%)	0	0
	On Study	54	74 (49.0%)	20 (13.2%)	3 (2.0%)	0

[1]Within Normal Limits

Elevated Liver Function Tests

GnRH agonists are not known to cause abnormal liver function tests. However, several patients who received Formulation A had abnormal liver function tests during the study period. One patient, # 200, had concomitant elevations in total bilirubin (>2xULN) and ALT (>3xULN). These abnormalities could not be clearly related to study drug.

- Patient 200 had a total bilirubin of 42.75 mcmol/L (2.1xULN) and an ALT of 168 U/L (3.1xULN) on Day 337. Patient 200 received his 2nd injection of study drug on Day 169. On Day 277, the patient began several concomitant medications. Jaundice or cholestasis have been reported with each of these concomitant medications.

7.4.3 Vital Signs

Vital signs, temperature, pulse, blood pressure, respiratory rate, and weight, were obtained at baseline and at weeks 1, 13, 25, 34, 40, and 50. Since changes in muscle mass and weight have been reported with GnRH agonists, patient weight was examined at baseline and on study. Eleven patients (7.3%) who received Formulation A had an increase in body weight $\geq$ 10% (range: 10-18.8%) during the study period.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not routinely obtained on L-PC07-169 or C02-008.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Adverse events that may indicate an immunologic reaction to Formulation A were examined. These included rash, pruritus, urticaria, hypersensitivity, and injection site dermatitis. Please see Section 7.3.4 concerning injection site reactions. Among the remaining abnormalities, 7 events were considered possibly related to study drug. The timing of these events was then examined. Pruritic rash was reported in patient 135 on Day 169 and pruritus and rash were reported on Day 170 in patient 139. These reactions were considered mild to moderate and did not result in discontinuation of study drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose exploration was not performed with the 24 week leuprolide acetate Lupron formulation.

7.5.2 Time Dependency for Adverse Events

Adverse events reported in patients receiving either Formulation A or Formulation B were examined from the time of the 1st injection to just prior to the 2nd injection (Day 1 to 168) and from the 2nd injection to the end of study (Day 169 to Day 367). Of interest, while the overall percentage of patients reporting adverse events was similar, no individual events were reported in ≥ 10% of patients from Day 169 to 367. Further, while injection site pain was reported in a similar percentage of patients from Day 1-168 and Day 169-367, hot flushes were less commonly reported from Day 169-367.

Table 29: Adverse Events in ≥ 10% of Patients by Time (Safety Database)

Preferred Term	Formulations A and B N = 310	
	Day 1 to Day 168	Day 169 to Day 367
All	270 (87.1%)	202 (65.2%)
Injection Site Pain/Discomfort	38 (12.3%)	29 (9.4%)
Fatigue/Lethargy	33 (10.6%)	7 (2.3%)
Hot Flush	152 (49.0%)	14 (4.5%)

The type of adverse events reported in the first 2 weeks (Day 1-15) following the administration of Formulations A or B was also examined. It was expected that adverse events during this period would be related to testosterone flare. However, on examination, adverse events such as

arthralgia or myalgia were not reported in ≥ 5% of patients during the first 2 weeks of study drug. While adverse events were reported by 44.8% of patients during this period, the only events reported in ≥ 5% of patients were injection site pain/discomfort (9.0%) and hot flush (10.6%).

7.5.3 Drug-Demographic Interactions

Treatment emergent adverse events that occurred in at least 10% of patients receiving Formulation A or Formulation B were examined by age. Few patients were less than age 65 and it is difficult to make comparisons between groups. However, general conclusions can be drawn. Constipation is the only adverse event that was clearly increased in those ≥ 75 years. Hot flushes were less likely to be reported in this age group. Other adverse events did not appear to be age dependent.

Table 30: Treatment-Emergent Adverse Events by Age (Safety Database)

Preferred Term	Formulations A and B N = 310	< 65 years N = 48	65 to < 75 years N = 87	≥ 75 years N = 152
Hot Flush/Flushing	160 (51.6%)	32 (66.7%)	54 (62.1%)	74 (48.7%)
Injection Site Pain/Discomfort	56 (18.1%)	11 (22.9%)	19 (21.8%)	26 (17.1%)
Upper Respiratory Tract Infection[1]	47 (15.2%)	8 (16.7%)	12 (13.8%)	27 (17.8%)
Fatigue/Lethargy	39 (12.6%)	5 (10.4%)	14 (16.1%)	20 (13.2%)
Arthralgia	36 (11.6%)	8 (16.7%)	9 (10.3%)	19 (12.5%)
Constipation	31 (10.0%)	2 (4.2%)	7 (8.0%)	22 (14.5%)
Hypertension/Blood Pressure Increased	26 (8.4%)	7 (14.6%)	11 (12.6%)	8 (5.3%)

[1]Includes nasopharyngitis, pharyngitis, and rhinitis.

Treatment emergent adverse events that occurred in at least 10% of patients receiving Formulation A or Formulation B were also examined by race. Given the small number of patients whose race/ethnicity was listed as Hispanic or Other, these patients were not included in the assessment. For this reason, the number of patients reported in the columns does not sum to the number of patients who received Formulation A or B. Fatigue, arthralgia, and upper respiratory infections were less likely to be reported in Black patients while the incidence of the remaining adverse events was similar between groups.

Table 31: Treatment Emergent Adverse Events by Race (Safety Database)

Preferred Term	Formulations A and B N = 310	White N = 212	Black N = 68
Hot Flush/Flushing	160 (51.6%)	115 (54.2%)	40 (58.8%)
Injection Site Pain/Discomfort	56 (18.1%)	41 (19.3%)	12 (17.6%)
Upper Respiratory Tract Infection[1]	47 (15.2%)	40 (18.9%)	6 (8.8%)
Fatigue/Lethargy	39 (12.6%)	35 (16.5%)	3 (4.4%)
Arthralgia	36 (11.6%)	31 (14.6%)	5 (7.4%)
Constipation	31 (10.0%)	23 (10.8%)	7 (10.3%)
Hypertension/Blood Pressure Increased	26 (8.4%)	20 (9.4%)	5 (7.4%)

[1]Includes nasopharyngitis, pharyngitis, and rhinitis.

7.5.4 Drug-Disease Interactions

All patients had underlying prostate cancer.

7.5.5 Drug-Drug Interactions

Drug-drug interaction studies were not conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

All patients had a history of prostate cancer, although many did not have detectable disease at study entry. The number of patients who developed worsening prostate cancer was not collected. However, the number of patients receiving Formulation A who reported second primary tumors, collected as an adverse event, was 7.3%. In the absence of a control arm, no conclusion can be drawn concerning the increased or decreased incidence of second primary cancers in this population as compared to other elderly patients with underlying prostate cancer.

7.6.2 Human Reproduction and Pregnancy Data

All patients were male and pregnancy was not reported in any of their partners.

7.6.3 Pediatrics and Assessment of Effects on Growth

This formulation has not been studied in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses have been reported with this drug. The drug is packaged as pre-filled syringe and administered in the physician's office decreasing the potential for overdose. In rats, subcutaneous administration of 250 to 500 times the recommended human dose resulted in dyspnea, decreased activity, and local irritation at the injection site. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects which differed from those observed with the 1 mg/day dose.

This drug has no potential for drug abuse. Discontinuation of GnRH agonists in the elderly results in a gradual increase in testosterone.

7.7 Additional Submissions

Not applicable

8 Postmarket Experience

Not applicable

9 Appendices

9.1 Literature Review/References

Please see citations contained within the text.

9.2 Labeling Recommendations

See the final version of the label revised by all of the FDA scientific disciplines.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held.

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

/s/

KATHERINE A DELORENZO
05/17/2011

VIRGINIA E MAHER
05/18/2011

NDA 20-517 **Sequence** #038 **DRUP Tracked Correspondence** #129

Response to Request for Consultation

Date of submission: December 11, 2009
Date consult requested: January 14, 2010
Date consult completed: October 1, 2010

To: Dianne C. Hanner, Regulatory Project Manager
Division of Drug Oncology Products (DDOP)

From: Harry Handelsman, D.O., Medical Officer
Division of Reproductive and Urologic Products (DRUP)

Mark S. Hirsch, M.D., Medical Team Leader, DRUP

George S. Benson, M.D., Deputy Director, DRUP

Drug product: Lupron Depot® (leuprolide acetate for depot suspension)
6-month 45 mg injection

Sponsor: Abbott Laboratories
Abbott Park, IL

Re: Request for DRUP consultation; specifically, "*Brief DRUP input on the adequacy of results from study L-PC07-169*".

1. Recent Background

On November 1, 2007, TAP Pharmaceuticals met with DDOP at an End-of-Phase 2 (EOP2) meeting to discuss the Sponsor's planned Phase 3 study protocol for two (2) new formulations of Lupron 45 mg - 6 month injection. A new, 6-month formulation would offer convenience over the existing 1 month, 3 month, and 4 month Lupron formulations. The Sponsor proposed to conduct a single study in support of approval of the new 6-month drug product, in which a total of 300 subjects (150 subjects per formulation) would be enrolled. The first 150 subjects would receive the first formulation and the next 150 subjects would receive the second formulation. The Sponsor proposed that if results for the 1st formulation (formulation A) were successful, they would file an NDA for formulation A. (b) (4)

(*For additional details of this EOP2 meeting, the reader is referred to the final meeting minutes in DARRTS under IND#27,350, dated November 15, 2007*).

The Sponsor believed that the results for formulation A were successful. Therefore, on December 11, 2009, they submitted a supplemental new drug application (sNDA) for

formulation A. Formulation B was discontinued. Like all previous Lupron products, the proposed indication for the new 6-month product is the palliative treatment of advanced prostate cancer.

The single, Phase 3 ("pivotal") study in support of this submission was Study L-PC07-169, entitled, "*A Phase-3, multicenter, open-label trial to evaluate the efficacy, safety, and pharmacokinetics of two 6-month leuprolide formulations in subjects with prostatic adenocarcinoma*". The protocol for this trial had been discussed at the EOP2 meeting and was agreed upon with the Agency in advance of the trial initiating. This trial included subjects with any stage of cancer, including patients with a rising PSA after radical prostatectomy or after radiation therapy. The primary study objective was to assess the efficacy and safety of the 45 mg formulations over 48 weeks, administered 24 weeks apart, based on suppression of serum testosterone (T) level to ≤ 50 ng/dL from week 4 to week 48. The sNDA contains final results for formulation A, and an interim report for formulation B. The Sponsor seeks approval for formulation A only.

This consultation from DDOP requested "*brief DRUP input on the adequacy of the results from the study L-PC07-169*".

2. Material Reviewed by the Consultant

1. EOP2 meeting minutes - dated November 15, 2007.
2. Original Phase 3 protocol - submitted on December 20, 2007.
3. Statistical analysis plan (SAP) for the phase 3 protocol – submitted on January 31, 2008.
4. Protocol amendment #1 - submitted on April 24, 2008.
5. Protocol amendment #2 – submitted on December 17, 2008.
6. Sponsor's request for DDOP advice regarding upcoming efficacy supplement submission – submitted on January 22, 2009.
7. DDOP responses to sponsor's requests for advice – conveyed to sponsor on June 24, 2009
8. Clinical Study Report for Protocol L-PC07-169 (formulation A): Clinical Overview, Summary of Clinical Efficacy, and Summary of Clinical Safety – submitted on December 11, 2009.

3. Consultant's Brief Summary of the Protocol

L-PC07-169 was a Phase-3. open-label, 48-week, multi-center study designed to evaluate the efficacy, safety and pharmacokinetics of two 6-month formulations of leuprolide 45 mg (A and B) administered as single injections 24 weeks apart. The first 150 subjects were to receive formulation A and the next 150 subjects were to receive formulation B. Subjects would be men ≥ 18 years of age, with histologically-confirmed prostate adenocarcinoma or a rising serum PSA following radical prostatectomy or prostate irradiation. Subjects must have serum testosterone level > 150 ng/dL, a life expectancy of at least 18 months, and a clinical status warranting at least 48 weeks of continuous androgen ablation therapy.

During the first half of the treatment period, study visits were planned on days 1, 2, and 8, and at the end of weeks 2, 4, 8, 14, 20 and 24. During the 2nd half of the treatment period, study visits were planned on days 170, 171, and 176, and at the end of weeks 26, 30, 34, 40, 46 and 48, followed by a 30 day post-treatment visit. The first injection was administered on day 1 and the second injection on day 169 (week 24). In addition to collecting serum concentrations of T and LH in all subjects at each visit, leuprolide concentrations were measured in a subset of patients (n= 24 planned). Serum T was analyzed using a single measurement at each timepoint, using a LC-MS/MS method, at a single central lab (Eosterix, Inc of Calabasas, CA).

The primary endpoint was the percentage of subjects with suppression of serum testosterone to "medically castrate" (≤ 50 ng/dL) from week 4 through week 48. Success for this endpoint for an individual subject required:

- Onset of T suppression (≤ 50 ng/dL) by week 4 (day 32),
- No escapes (T > 50 ng/dL) at any visit, and
- Continued suppression at week 48.

Success for the entire study population was defined as the lower bound of 2-sided 90% confidence interval no less than 87%, reflecting a point estimate success rate of approximately 91%.

The primary endpoint was calculated using a Kaplan-Meier method for right-censored observations where failures counted at the first T > 50 ng/dL, success counted at the last T measurement, and premature terminations counted until the last T measurement. The 2-sided 90% lower confidence bound was also calculated using the standard error from the Kaplan-Meier method. In addition, seven supportive sensitivity analyses were performed to evaluate the effect of different assumptions on the primary endpoint analysis.

4. Consultant's Brief Summary of Study Results (Formulation A)

Reviewer's Comment: The following brief description of study results is based on the original data submitted by sponsor. Subsequent to the original sNDA submission, the Office of Clinical Pharmacology (OCP) requested an inspection of Esoterix, Inc, the laboratory which analyzed all serum T samples from study L-PC07-169. The inspection was conducted by the Division of Scientific Investigation (DSI) and revealed significant laboratory procedural deficiencies at Esoterix. The DSI deficiencies have called into question the reliability of the originally submitted efficacy data. Therefore, the reader should be aware that our comments and conclusions refer to original data that cannot yet be considered reliable for making formal decisions about the efficacy of Lupron 45 mg 6 month injection. Nonetheless, we show these data and provide our comments for completeness sake.

4.1 Efficacy Results

A total of 151 subjects, with a mean age of 75 (range 48 -92 years), participated in the study. A total of 134 subjects (89%) completed the entire study. A total of 17 discontinued prematurely, for the following reasons: adverse event (n=7), withdrew consent (n=5), protocol violation (n=1), disease progression (n=1), serum T not therapeutic (n=1), and "other" (n=2: motor vehicle accident and relocation).

Overall, T suppression was rapid and sustained throughout the study. The primary endpoint was met, with an overall percent of successes of 93.7%. The lower bound of the 2-sided CI was 90.3%.

There were a total of 9 treatment failures. Of these, 1 subject failed to suppress by day 32 (Subject #255, who had a serum T of 69 ng/dL on day 29 with all subsequent values ≤ 50 ng/dL). 8 subjects escaped T suppression after week 4; three after the 1st injection and five after the 2nd injection.

The three escapes after the 1st treatment cycle were as follows:

- 1 escape on day 169 at trough (Subject #159 with T value of 60 ng/dL)

Table 1. Subject #159 – serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*169 (tr)*
296		398	530		148		17		9.3		5.6	5.9				**60**

169	*169*	*169*	*170*	*171*	*172*	*176*	*183*	*211*	*218*	*239*	*281*	*324*	*330*	*337*
60	**67**	**86**	**74**	**70**		50	**51**	5.9		5.3	6.1	6.5		12

- 1 escape on day 167 at trough (Subject #167 with T value of 95 ng/dL)

Table 2. Subject #167 – serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*170 (tr)*
573		364	503	415	100			14	8.1		9.6	8.4				**95**

171	*172*	*176*	*183*	*211*	*218*	*239*	*246*	*281*	*324*	*330*	*337*
5.2	5.8	8.3	7.5	3.6		7.3		11	3.5		6.5

- 1 escape on day 167 at trough (Subject #282 with T value of 67 ng/dL) – and a second escape at Day 337 in the same patient.

Table 3. Subject #282 – serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167 (tr)*
611		521	603	541	85		20		19		36		39	**67**

167	*167*	*167*	*168*	*169*	*170*	*172*	*176*	*183*	*211*	*218*	*239*	*246*	*281*	*324*	*337*
78	**98**	**96**	36	**56**		38		32							**58**

The 5 escapes observed after the 2nd injection were as follows:

- 3 acute-on-chronic responses within 2 weeks of the 2nd injection (Subjects #153, #192, and #318 with maximum serum T of 51, 57, and 74 ng/dL, respectively)

Table 4. Subject #153 – serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*169 (tr)*
146	249	172	351		107		27		26		23	27				33

169	*169*	*169*	*170*	*171*	*172*	*176*	*183*	*211*	*218*	*246*	*281*	*324*	*330*	*337*
51	**51**	30	25	26		27	28	27		31	21		19	23

Table 5. Subject #192 - serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*169 (tr)*
451		544	752		369		22		6		5.8	4.8				8.3

169	*169*	*169*	*170*	*171*	*172*	*176*	*183*	*211*	*218*	*246*	*281*	*324*	*330*	*337*
6.6	10	16	45	**57**		**53**	14	9.5		11	9.2	6.5		5.6

Table 6. Subject #318 - serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*169 (tr)*
325		169	307	378	62		14		13		12	26				27

169	*169*	*169*	*170*	*171*	*172*	*176*	*183*	*211*	*218*	*239*	*246*	*281*	*324*	*330*	*337*
38	**61**	**74**	**73**	32			15	13		13		13	14		43

- 1 escape on day 211 (Subject #160 with T values of 173, 227 and 555 ng/dL)

Table 7. Subject #160 - serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*169 (tr)*
415		497	902	850	164		28		18		14	14				22

169	*169*	*169*	*170*	*171*	*172*	*176*	*183*	*211*	*218*	*239*	*246*	*281*	*324*	*330*	*337*
17	13	9	29	34		12	21	**173**	**227**	**555**					

- 1 escape on day 337 (Subject #190 with T values of 70, 71 and 58 ng/dL)

Table 8. Subject #190 - serum T (ng/dl) by study day. Escape values shown in bold. SC = Screening, tr = trough

SC #1	*SC #2*	*1*	*2*	*8*	*15*	*22*	*29*	*31*	*57*	*85*	*99*	*141*	*143*	*167*	*168*	*169 (tr)*
620		655	1370	619		56	16		4.3	<3		3.2				6.6

169	*169*	*169*	*170*	*171*	*172*	*176*	*183*	*211*	*239*	*246*	*281*	*324*	*330*	*337*	*337*	*337*
3	<3	3	4.7	4.4		6.3	4.2	<3	4.3		4.3	3.6		**70**	**71**	**58**

<u>Reviewer's Comment</u>*: If the data supporting these efficacy results were reliable, then the efficacy of the new product would have been adequately supported. The occurrence of several "low-grade" escapes towards the end of each dosing cycle would not jeopardize approval, but would support a dosing schedule of every 24 weeks (as per protocol), rather than every 6 months.*

4.2 Safety Results

Adverse events (AEs) and laboratory results were consistent with those seen in previous trials using depot leuprolide acetate, and no new safety signals were observed.

The most frequent AE's were:

- Hot flushes 58%
- Injection site pain 18%
- Fatigue 12%
- Asthenia 3%
- Constipation 10%
- Arthralgia 9%
- Insomnia 9%
- Headache 7%
- Cough 7%
- Hematuria 7%
- Nasopharyngitis, Rhinitis, URI 7%

There were 2 serious AEs assessed by the investigators as treatment-related: angina pectoris, and colonic pseudo-obstruction. There were 2 discontinued subjects with serious AEs: coronary artery disease and non-Hodgkin's lymphoma. There was 1 death (aspiration pneumonia, not assessed by the investigator as treatment related).

4.3 Pharmacokinetic Results

Formulation A provided a sustained plasma exposure, and the mean PK profile was similar following both doses.

Following each dose, there was a rapid increase in plasma leuprolide concentrations, with a peak at approximately 2 hours, followed by a rapid decline over the 1st week. The mean C_{max} for the 1st and 2nd doses were 6.7 and 7.4 ng/mL, respectively.

Mean leuprolide concentrations rose between weeks 2 and 4 and then began to slowly decline to week 24. A steady-state concentration was not reported.

The mean trough leuprolide concentration at the end of the 1st and 2nd dosing periods were 0.073 and 0.057 ng/mL, respectively.

The mean AUC_t values were 1282 and 1142 ng·h/mL for the 1st and 2nd doses, respectively. The mean total AUC_t for both doses was 2483 ng·h/mL.

5. Consultant's Overall Comments

If the DSI inspection of Esoterix Labs had not revealed significant deficiencies, then the results from study L-PC07-169 would have adequately supported the efficacy of the new product. This new preparation appeared to achieve the pre-specified efficacy requirements, resulted in no new safety signals, and showed a safety profile consistent with previously approved depot formulations. The occurrence of several "low-grade" escapes towards the end of each dosing cycle would not have jeopardized approval, but would have supported a dosing schedule of every 24 weeks (as per protocol), rather than every 6 months.

However, subsequent to our review, the results of the DSI inspection have called into question the validity of the reviewed data. Therefore, it appears that sponsor will need to present evidence that affirms the validity of the original data or will need to provide additional data for another review. DRUP would be pleased to re-consult as needed.

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/s/

HARRY HANDELSMAN
09/30/2010

MARK S HIRSCH
09/30/2010
I concur.

GEORGE S BENSON
09/30/2010

CLINICAL REVIEW

Application Type	Commercial
Application Number(s)	20-517
Priority or Standard	Standard
Submit Date(s)	December 11, 2010
Received Date(s)	December 11, 2010
PDUFA Goal Date	October 11, 2010
Reviewer Name(s)	Gwynn Ison, MD
Team Leader	V. Ellen Maher, MD
Review Completion Date	September 7, 2010
Established Name	Leuprolide Acetate Injection, Powder, Lyophilized for Suspension
(Proposed) Trade Name	Lupron® Depot
Therapeutic Class	Gonadotropin Releasing Hormone Agonist
Applicant	Abbott Laboratories
Formulation(s)	Injection
Dosing Regimen	45 mg IM every 6 months
Indication(s)	Palliative Treatment of Advanced Prostate Cancer
Intended Population(s)	Patient with Advanced Prostate Cancer

Table of Contents

Table of Tables

Table of Figures

APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Complete response letter

1.2 Risk Benefit Assessment

Risk

Risks associated with leuprolide acetate 45 mg include:

- The key efficacy analyses were based upon the ability of leuprolide acetate 45 mg to achieve castrate serum testosterone levels. Upon inspection of the central laboratory conducting the testosterone assays, the results of these assays were found to be unreliable. The key efficacy analyses cannot, therefore, serve as the basis of approval and the percentage of patients in which leuprolide acetate 45 mg is able to achieve castrate testosterone levels is uncertain.
- Leuprolide acetate 45 mg and other gonadotropin releasing hormone agonists should not be used in patients with impeding spinal cord compression or urinary tract obstruction.
- Treatment emergent adverse events seen in $\geq$ 10% of patients include hot flush, injection site pain/discomfort, upper respiratory infection, and fatigue/lethargy.
- Treatment related adverse events seen in $\geq$ 5% of patients include hot flush, fatigue/lethargy, and injection site pain/discomfort.
- Grade 1-2 laboratory abnormalities in which the incidence increased by $\geq$ 10% when compared to baseline includes hyperglycemia, hypertriglyceridemia, hypercholesterolemia, anemia, increased creatinine, and elevated ALT.
- No anaphylactic or anaphylactoid reactions were seen. Pituitary apoplexy was not seen.

Benefit

- Given the unreliability of the serum testosterone assays, the benefit associated with the approval of this application is unclear. Lupron formulations which are indicated for the palliative treatment of prostate cancer that have a demonstrated effect on serum testosterone levels are currently available and may be administered every 12 or 16 weeks.
- Due to design flaws, the study was not able to demonstrate an improvement in bone pain, pain on urination, or difficulty with urination.

1.3 Recommendations for Postmarket Risk Management Activities

None

1.4 Recommendations for Postmarket Studies/Clinical Trials

None

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Leuprolide Acetate Injection, Powder, Lyophilized for Suspension

Proprietary Name: Lupron Depot®

Applicant: Abbott Endocrine, Inc.
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064

Pharmacological Class: Gonadotropin Releasing Hormone Agonist

Chemical Class: Peptide

Proposed Indication: The proposed indication is for the palliative treatment of advanced prostate cancer.

Proposed Dosage and Administration: Leuprolide acetate 45 mg will be administered every 24 weeks as a single intramuscular injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatment options for patients with hormone responsive advanced prostate cancer include gonadotropin releasing hormone agonists (GnRH), gonadotropin releasing hormone antagonists, and orchiectomy. Anti-androgen therapies such as bicalutamide, flutamide, and nilutamide are sometimes added to these agents. Although the adverse event profile is similar, GnRH agonists and antagonists are typically preferred to orchiectomy. The table below lists the GnRH agonists and antagonists that are available for the treatment of patients with advanced prostate cancer.

Table 1: Available Treatments		
Class	**Product Name**	**Formulations**
GnRH Agonist	Leuprolide (Lupron)	Every 3 months Every 4 months
	Leuprolide (Eligard)	Every month Every 3 months Every 6 months
	Leuprolide (Viadur)	Every 12 months
	Goserelin	Every 28 days Every 12 weeks
	Histrelin	Every 12 months
	Triptorelin	Every 4 weeks Every 12 weeks Every 24 weeks
GnRH Antagonist	Degarelix	Every 28 days
	Abarelix	Not marketed in the US

2.3 Availability of Proposed Active Ingredient in the United States

Several formulations of leuprolide, including those marketed by the applicant, are available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Gonadotropin releasing hormone agonists cause a transient surge in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. This surge desensitizes the LH and FSH receptors and is followed by a sustained decrease in testosterone to levels comparable to those following orchiectomy. Gonadotropin releasing hormone antagonists act by directly interfering with the binding of endogenous GnRH to its receptor and cause a sustained decrease in testosterone. Because GnRH antagonists do not cause an initial testosterone surge, they may be safety used in patients with impending spinal cord compression or urinary tract obstruction. Following the initial surge in testosterone seen with GnRH agonists, the adverse event profiles of these products are very similar and are primarily related to the consequences of androgen deprivation. The direct effects of testosterone deprivation include hot flushes, loss of libido, fatigue, gynecomastia, testicular atrophy, anemia, and osteoporosis.

Androgen deprivation therapy also produces a decrease in muscle mass and an increase in subcutaneous fat. This may results in obesity, insulin resistance, and an unfavorable alteration in the lipid profile (J Urol 2009 181(5):1998). Changes in these risk factors have, in turn, been linked, by some investigators, to an increased incidence of cardiovascular disease (Circulation 2010 121:833) and new onset diabetes (J Clin Oncol 2006 24:4448).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The clinical development of the 24 week formulation of leuprolide acetate was initiated in July 2002 with the submission of protocol C02-008, “Pharmacokinetics, Safety, and Efficacy Study

of a 6-Month Depot Formulation of Leuprolide in Subjects with Advanced Prostatic Adenocarcinoma" for Special Protocol Assessment. A non-agreement letter was issued in August 2002. This study failed to meet its efficacy endpoint and has been included in this efficacy supplement as part of the safety database.

In November 2007, an end of Phase 2 meeting was held to discuss the study design of L-PC07-169, "A Phase 3, Multicenter, Open-label trial to Evaluate the Efficacy, Safety, and PK of Two 6-Month Leuprolide Formulations, in Subjects with Prostatic Adenocarcinoma." This study enrolled 151 patients to Formulation A followed by the enrollment of 159 patients to Formulation B. This protocol was initiated in February of 2008 and the last study visit for patients treated with Formulation A occurred in June 2009. Formulation A met its efficacy endpoint while Formulation B did not. Efficacy and safety data has been submitted from patients who received Formulation A. Safety data has been submitted from patients who received Formulation B.

Pre-NDA questions were submitted to the Agency and were addressed in a communication to the applicant in June 2009. The NDA was submitted in December 2010.

2.6 Other Relevant Background Information

The full regulatory approval of GnRH agonists and antagonists has been based on the achievement and maintenance of castrate testosterone levels (≤ 50 ng/dL). These studies calculate the percentage of patients who achieve castrate testosterone levels and the confidence intervals around this point. The lower bound of the 95% confidence interval is expected to be > 90%. Other marketed leuprolide acetate formulations have achieved castrate testosterone levels in the following percentages of patients.

Table 2: Achieving Castrate Testosterone Levels with Other Lupron Formulations

	Lupron Depot 1 Month 7.5 mg	Lupron Depot 3 Months 22.5 mg	Lupron Depot 4 Months 30 mg
Castration Rate by Day 30	94%	95%	94%

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant certified that the studies in this submission were conducted in accordance with Good Clinical Practice (GCP) as described in the ICH E6 Guideline for Good Clinical Practice and in accordance with CFR Parts 50, 56, 312, and 314.

3.2 Compliance with Good Clinical Practices

Compliance with GCP was assessed by inspection of the following sites by the Division of Scientific Integrity.

Table 3: Inspection Sites			
Site #	Protocol #	Number Randomized	Comments
#50042 David Lipsitz, MD 1084 Vinehaven Drive Concord, NC 28025	L-PC07-169	11	5 subjects with SAEs 20 protocol violations
#11706 Daniel Saltzstein, MD Urology San Antonio Research, PA 7909 Fredericksburg Road, Ste 115 San Antonio, TX 78229	L-PC07-169	14	6 subjects with SAEs 10 protocol violations

Both sites were found to be GCP compliant and no inspection findings were issued.

The Division of Scientific Integrity also inspected Esoterix, the central laboratory used to assay serum testosterone levels. Testosterone levels were the primary endpoint in the key study in this application. Inspection found that 59 analytical runs had quality control deviations of > 15 or 20%. These runs were not rejected by the central laboratory. Further, the central laboratory did not reject 15 analytical runs in which 25% of their calibration standards did not meet the criteria for assay precision described in "Guidance for Industry, Bioanalytical Method Validation."

Establishment inspections of sites of product manufacturing and testing were not carried out. These sites an involved in the manufacture of approved Lupron products and had been inspected as part of their approval.

3.3 Financial Disclosures

Two studies were submitted with this application, C02-008 and L-PC07-169. C02-008 was conducted by TAP Pharmaceuticals and TAP obtained financial disclosure information from all investigators. L-PC07-169 was initiated by TAP Pharmaceuticals and completed by Abbott Laboratories. TAP Pharmaceuticals obtained financial disclosure information from all investigators participating in L-PC07-169 and Abbott attempted to again obtain financial disclosure information from all investigators participating in L-PC07-169. Abbott did not obtain financial disclosure information from 3 principal investigators who did not enroll any patients on L-PC07-169. Abbott states that they exerted due diligence in attempting to contact these investigators.Abbott Laboratories certified that none of the investigators contacted disclosed reportable financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Leuprolide acetate 45 mg is given as an IM injection. Just prior to injection a lyophilized microsphere powder which contains leuprolide acetate, polylactic acid, steric acid, and mannitol

is mixed with the aqueous vehicle containing water for injection, mannitol, carboxymethylcellulose sodium, polysorbate 80, and glacial acetic acid. During formulation, (b) (4) .

On review, the proposed specifications for the product dissolution curve ((b) (4) were not acceptable and this deficiency will be conveyed to the applicant.

The table below presents information on the composition of each of the 24 week formulations of leuprolide acetate that have been studied by the applicant, Abbott Laboratories, or their commercial partners. These formulations differ (b) (4) Both Formulation B and the formulation used in study C02-0008 failed to meet their efficacy endpoint and Formulation A is the to-be-marketed product. Despite this, the formulations and the adverse event profiles of the 3 formulations are very similar and data from all 3 formulations are included in the safety database.

Table 4: Leuprolide Acetate Formulations Used in this Submission

Component	**Formulation A**	Formulation B	C02-0008
Microsphere Powder		(b) (4)	
Leuprolide Acetate	45.0 mg		
Polylactic Acid	169.9 mg[1]		
Mannitol	39.7 mg		
Stearic Acid	(b) (4) mg		
Vehicle			
Mannitol	75.0 mg		
Carboxymethylcellulose Sodium	7.5 mg		
Polysorbate 80	1.5 mg		
Glacial Acetic Acid	qs		
Water for Injection	(b) (4) mL		

(b) (4)

4.2 Clinical Microbiology

The Microbiology division has reviewed sterilization information in the DP manufacturing process and recommended approval.

4.3 Preclinical Pharmacology/Toxicology

This submission included pharmacodynamic and local tolerance studies. In vivo pharmacodynamic studies were completed in the rat and dog. Pharmacokinetic studies showed that after a single subcutaneous (rat) and intramuscular (dog) dose, leuprolide acetate levels were sustained for at least 24 weeks. An additional in vivo study observed no release differences between the pilot lot and the clinical lot. Pharmacodynamic studies showed that testosterone levels were suppressed during the 24 week period post dosing. Local tolerance studies in rabbits did not show local irritation.

Pharmacology and toxicology data have been submitted and reviewed for Lupron (NDA 19010) and Lupron Depot (NDAs 19732 & 19943). These include studies of mutagenicity, carcinogenicity, and fetal effects. Mutagenicity studies in mammalian and bacterial systems have provided no evidence of mutagenic potential. Carcinogenicity studies in rats demonstrated benign pituitary hyperplasia and pituitary adenomas. An increase in pancreatic islet cell adenomas and testicular interstitial cell adenomas was also seen. Carcinogenicity studies in mice demonstrated no pituitary abnormalities or other benign or malignant tumors. Major fetal abnormalities were observed in rabbits but not in rats after administration of an extended release formulation of leuoprolide acetate. However, increased fetal mortality and decreased fetal weights were seen in both rats and rabbits at higher doses.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See Section 2.4.

4.4.2 Pharmacodynamics

A pharmacodynamic assessment was performed using serum testosterone concentrations. Testosterone was measured in singlet by liquid chromatography with mass spectrometry detection after nonpolar solvent extraction. The assay was conducted by Esoterix, Inc. The analytical range of the assay was validated between 2.5 ng/dL and 5000 ng/dL. However, the intra and interassays for precision (CV%) were not met for 25% of calibration standards in 15 analytic runs. Also, the intra and interassays for accuracy (%bias) were > 15% or 20% (at the lower limit of quantitation) in 59 analytic runs. Mean recoveries between 85-115% were observed for three concentrations.

While these assays cannot be relied up, the initial rapid increase of leuprolide concentration appeared to be associated with a rapid increase in testosterone serum concentration. Mean testosterone concentration was found to increase from a baseline value of 433 ng/dL to a peak of 613 ng/dL on Day 2 after dosing. Once continuous plasma leuprolide exposure was sustained the high mean testosterone serum concentration seemed to decrease to reach a very low plateau (by Week 4 after the first injection) that was maintained through the end of the study.

4.4.3 Pharmacokinetics

The pharmacokinetics (PK) of leuprolide acetate 45 mg was determined in a subset of patients (N=26) in study L-PC07-169. Each patient received two intramuscular injections, Day 1 and Day 169. Pharmacokinetic parameters, including the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), the concentration at the end of the dosing period (C_{trough}) and the area under the plasma concentration-time curve (AUC), were determined using noncompartmental methods. Leuprolide plasma concentrations were determined by a liquid chromatography/tandem mass spectrometry (LC/MS/MS). This method is applicable to the quantitation of leuprolide

within a range of 0.0250 to 25.0 ng/mL. Intra or interassay precision (CV%) was less than 15%, and intra or interaccuracy (%bias) was within ±15%.

The PK profiles exhibited two phases. After dosing, an initial rapid increase of plasma leuprolide concentration was observed, followed by a rapid decline over the first 7 days post dose. The maximum leuprolide concentration occurred at approximately 2 hours after injection. The mean C_{max} value was 6.7 ng/mL after first dose. Leuprolide appeared to be released continuously by the third week after dosing with steady plasma concentrations through the 24 week dosing interval. The mean AUC was 1282 $\pm$ 551 ng·hr/mL and the mean leuprolide concentration declined to 0.07 ng/mL at 24 weeks. Mean leuprolide plasma concentration-time profiles were similar after the first and second dose.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5: Leuprolide Acetate 45 mg Clinical Studies

Study	Design and Population	Dose and Regimen	Patients Evaluated	Duration
L-PC07-169	Single arm, multicenter study in men with prostate cancer or rising PSA post-radical prostatectomy	Formulation A 45 mg IM q 24 weeks x 2 Formulation B 45 mg IM q 24 week x 2	Formulation A: 151 Formulation B: 159	48 weeks
C02-008	Single arm, multicenter study in men with prostate cancer whose disease warrants therapy with a GnRH agonist	45 mg IM q 26 weeks x 2	164	52 weeks

All safety and efficacy data were submitted for both studies and the following data will be used in the review of this application:

- Efficacy data from Formulation A (to-be-marketed product); and
- Safety data from Formulation A, Formulation B, and C02-008.

5.2 Review Strategy

The Division of Scientific Integrity verified the source data collected at 2 clinical sites in the US and compared this data with that included in the case report forms. Adverse event (AE) and serious adverse event (SAE) reports in a portion of the case report forms included with the NDA were reviewed and compared with the supplied datasets. The primary efficacy endpoint was unable to be verified by inspection of Esoterix Laboratories and this data cannot be relied upon to form conclusions about the efficacy of leuprolide acetate 45 mg.

5.3 Discussion of Individual Studies/Clinical Trials

L-PC07-169, the key study, was conducted at 58 sites in the US from February 2008 until September 2009.

Study Title

A Phase 3, Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Two 6-Month Leuprolide Formulations, in Subjects with Prostatic Adenocarcinoma

Study Milestones

The table below provides the study milestones. The administrative letter referred to in the table changed the study sponsor to Abbott Laboratories.

Table 6: Study Milestones

Milestone	Date	Formulation A
Original Protocol 1	December 7, 2007	43
Amendment #1	March 31, 2008	108
Administrative Letter	July 31, 2008	0
Amendment #2	October 31, 2008	0
Final Statistical Analysis Plan	July 17, 2009	0
First Visit for 1st Subject	February 25, 2008 (Formulation A) April 28, 2008 (Formulation B)	-
Last Visit for Any Subject	June 19, 2009 (Formulation A) September 18, 2009 (Formulation B)	-

Amendment 1: The following substantive changes were made in Amendment 1.

- Defined a rising PSA following radical prostatectomy or prostate irradiation.
- Entry criterion for serum creatinine was changed to ≤ 1.9 mg/dL.
- Cryotherapy was excluded within 8 weeks of Screening.
- Use of 1-year GnRH implants was excluded within 60 weeks of Screening.
- Defined different washout periods for finasteride and dutasteride.
- Ketoconazole was added as an excluded medication.

Amendment #2: No substantive changes were included in Amendment 2.

Study Objectives

1) To assess the efficacy and safety of two new leuprolide acetate 45 mg formulations over 48 weeks. Each formulation will be delivered as 2 single injections 24 weeks apart, in patients with prostate cancer.
2) To establish a PK profile of serum leuprolide for the two new 45 mg formulations in a subset of subjects with prostate cancer.

Inclusion Criteria

1) Prior to any study specific procedures being performed, the subject voluntarily signed the IRB approved informed consent form and any required privacy statement/authorization

form (i.e., Health Information Portability and Accountability Act) after having its content fully explained and all questions answered.
2) Subject was male, ≥ 18 years of age, with a pre-study serum testosterone > 150 ng/dL.
3) Subject had a histologically-confirmed prostatic adenocarcinoma in any of the following clinical stages (clinical staging should have been based on information available to the clinical investigator at the time of screening, and not necessarily at the time of diagnosis):

Jewett:	A_2, B, C, D
TNM:	cT_{1b}-$4N_{any}M_{any}$

Subjects with a rising PSA following radical prostatectomy were defined as patients with an increase of 0.2 ng/dL from the previous test on 2 consecutive assessments or rising PSA following prostate irradiation. Patients who met the Phoenix definition: a rise of ≥ 2.0 ng/dL above the nadir (lowest PSA achieved following radiation therapy) were also eligible.

4) In the opinion of the clinical investigator, prostate cancer status and general clinical status was sufficient to warrant at least 48 weeks of continuous androgen deprivation treatment, without concomitant anti-androgen treatment.
5) Subject had ECOG performance status grade 0-2.
6) Subject's life expectancy was at least 18 months.
7) Subject had serum creatinine ≤ 1.9 mg/dL, bilirubin ≤ 2.0 mg/dL (unless Gilbert's syndrome) and AST and ALT ≤ 2.5 times the ULN.
8) Subject was willing to complete all phases and all procedures of the study.

Exclusion Criteria

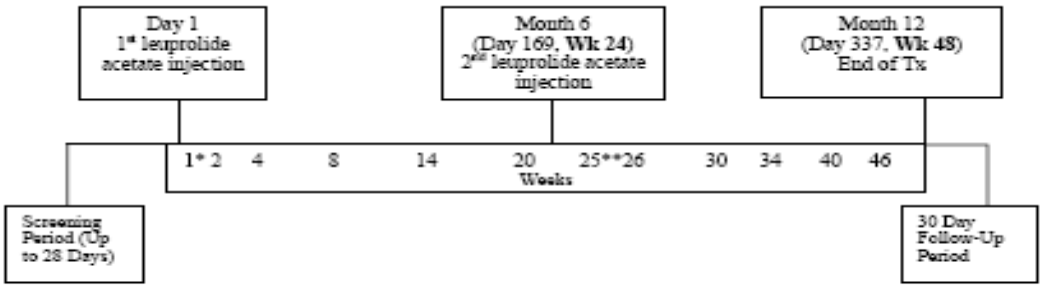
1) The clinical investigator anticipated the subject's need for radical prostatectomy or radiotherapy (including conventional electron beam radiation therapy, 3-D conformal radiation therapy, intensity modulated radiation therapy, proton beam radiation therapy or brachytherapy) or cryotherapy of local disease within the 48 week study period following the initial administration of the investigational leuprolide acetate 45 mg formulation.
2) Subject had historical, clinical, or radiographic evidence of central nervous system metastases, including spinal cord metastases.
3) Subject had clinical evidence of urinary tract obstruction, which, in the judgment of the clinical investigator, would have put the subject at significant risk, should disease flare have occurred.
4) Subject had a history of bilateral orchiectomy, adrenalectomy, or hypophysectomy.
5) History of clinical hypogonadism (testosterone < 150 ng/dL).
6) Subject had a current malignancy or history of malignancy within 5 years prior to screening with the exception of the following: prostate cancer or treated basal or squamous cell carcinoma of the skin.
7) Subject had clinical laboratory evidence of any severe underlying disease state (excluding prostate cancer) that would have placed subjects in additional jeopardy by participating in this study.
8) Subject had hypersensitivity to leuprolide, polylactic acid, or any excipient of the drug.
9) Subject had not completely recovered from the effects of any major surgery.

10) Subject had history of administration of the following prostate cancer therapies within 8 weeks prior to Screening Visit: chemotherapy, immunotherapy, anti-androgen, radiation therapy or brachytherapy), cryotherapy, strontium, or biological response modifiers.
11) Subject had a history of prostatic surgery (includes transurethral resection of the prostate and radical prostatectomy) within 4 weeks prior to the Screening Visit.
12) Subject had history of administration of hormonal therapy, including GnRH analogs (≤ 6 month depot formulation), estrogen, Megace and phytotherapy, within 32 weeks prior to the Screening Visit and through the treatment period or GnRH analog 1 year implants within 60 weeks prior to the Screening visit and through the treatment period.
13) Subject had a history of use of alternative medical therapies which have an estrogenic, androgenic, or anti-androgenic effect within 12 weeks prior to the Screening Visit and through the treatment period.
14) Subject had exposure to finasteride or ketoconazole within 1 week prior to the Screening Visit and through the treatment period; dutasteride within 25 weeks prior to the Screening Visit and through the treatment period.
15) Subject had exposure to experimental/investigational medication, device, or biologic within 5 half-lives of its pharmacologic effect or 3 months, whichever is longer, prior to the initial depot injection.
16) Subject required the chronic use of systemic corticosteroids or anticonvulsants that may have affected bone loss such as carbamazepine, phenobarbital, phenytoin, valproic acid, or primidone.
17) Subject had anticipated need for anti-androgen, immunotherapy, or surgical therapy for prostate cancer during the study.
18) Subject consumed >14 alcoholic beverages per week or had a history of alcoholism or illicit drug use within the 12 months prior to screening.
19) Employees and family members of the investigator, subinvestigator, or study coordinator were ineligible to participate. Employees or students of the institution/research facility who under the supervision of, or in a hierarchical subordinate role to, the investigator were also ineligible.

Treatment Plan

The first 150 patients enrolled were to receive Formulation A for both injections (injections are given 24 weeks apart). The next 150 patients were to receive Formulation B for both injections.

The trial included a Screening Period (up to 4 weeks), the 12 month Treatment Period (two 24 week treatment cycles) and a Follow-Up Period (30 days). During the first half of the treatment period, trial visits occurred on Days 1, 2, 8, and at the end of Weeks 2, 4, 8, 14, 20, and 24. During the second half of the treatment period, trial visits occurred at Weeks 24, 25 (on Days 170, 171, and 176) and at the end of Weeks 26, 30, 34, 40, 46, and 48, followed by a 30 day Post Treatment Follow up Visit. Figure 1 depicts the Trial Schematic.



* During Weeks 1, visits to take place on Days 1, 2, and 8.
** During Week 25, visits to take place on Days 170, 171, and 176.

Figure 1 Trial Schematic

The magnitude of the initial burst effect and the steady state leuprolide acetate systemic concentration was examined in a subset of patients following the 1st injection. Testosterone suppression was measured in all patients. The second IM injection of the same formulation (A or B) allowed assessment of possible elevations in testosterone concentrations and LH due to an acute-on-chronic effect on the hypothalamus-pitiutary-gonadal axis. The second injection also permitted further observation of the duration of testosterone suppression.

Trial Procedures/Schedule of Visits

After signing the informed consent, patients underwent a Screening Period of up to 4 weeks. Blood draws (including pharmacokinetics), physical exam, and adverse events were assessed at pre-specified time points and are depicted in the Study Calendar shown below. Pharmacokinetic studies were conducted in 48 patients (24 Formulation A, 24 Formulation B).

Table 7: Schedule of Activities

	Week	Screening Visit[1]	Treatment Period									Unscheduled Visit[11]
		-4	1			2	4	8	14	20	24[10]	
Trial Time	Day	-28	1[2]	2	8	15	29	57	99	141	169	
Medical, Surgical and Social History		X										
Prostate Cancer History		X										
Admission Criteria		X										
Symptom Assessment			X[3]		X		X	X	X	X	X[6]	
ECOG Performance Status		X					X	X	X	X	X[6]	
Complete Physical Exam (including weight)		X[5]							X		X[6]	
Vital Signs (Temp, BP, Pulse, RR)		X	X	X	X	X	X	X	X	X	X[6]	
Leuprolide acetate 45 mg 6-month injection			X									
Injection Site Examination			X[4]	X	X	X						
Blood draw for LH/testosterone		X	X[3]	X	X	X	X	X	X	X	X[6]	
Blood draw for PSA, PAP		X			X				X		X[6]	
Blood draw for PK of leuprolide (subset only)			X[3,4]	X	X	X	X	X	X	X	X[6]	
Routine Safety Labs		X			X			X	X		X[6]	
Urinalysis		X			X			X	X		X[6]	
Record adverse events/concomitant meds		X	X	X	X	X	X	X	X	X	X[6]	X

1 Pre-trial procedures should be performed within 4 weeks of Day 1.
2 Day of first depot injection.
3 Prior to 1st depot injection.
4 On Day 1 this is required only for subjects participating in the PK schedule, at 2, 4, and 8 hours post-depot injection.
5 Including height at Screening only.
6 Prior to 2nd depot injection.
10 Week 24 represents the end of the first injection cycle AND the first day of the second injection cycle.
11 Additional safety procedures performed at the discretion of the investigator.

		Treatment Period (Activities to be performed post the 2nd leuprolide acetate 45 mg 6-month depot injection)											
	Week	24[10]	25			26	30	34	40	46	48/Final Visit	Follow-Up Period (30 days)	Unscheduled Visit[11]
Trial Time	Day	169	170	171	176	183	211	239	281	323	337		
Symptom Assessment				X	X	X	X	X	X		X		
ECOG Performance Status						X	X	X	X		X		
Complete Physical Exam (including weight)								X			X	X	
Vitals (Temp, BP, Pulse, RR)			X	X	X	X	X	X	X	X	X	X	
Leuprolide acetate 45 mg 6-month injection		X											
Injection Site Examination		X[8]	X	X	X	X							
Blood draw for LH/testosterone		X[7,8]	X	X	X	X	X	X	X	X	X		
Blood draw for PSA, PAP					X		X		X		X		
Blood draw for PK of leuprolide (subset only)		X[7,9]	X	X	X	X	X	X	X	X	X		
Routine Safety Labs					X			X	X		X		
Urinalysis					X			X	X		X		
Record adverse events/concomitant meds			X	X	X	X	X	X	X	X	X	X	X

7 Prior to 2nd depot injection.
8 On Week 24 this is required for all subjects, at 2, 4, and 8 hours post- 2nd depot injection.
9 2, 4, and 8 hours post-depot injection for the PK subset of subjects only.
10 Week 24 represents the end of the first injection cycle AND the first day of the second injection cycle.
11 Additional safety procedures performed at the discretion of the investigator.

Routine safety laboratories included a complete blood count, urinalysis, and chemistry panel. The chemistry panel included albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, calcium, bicarbonate, chloride, GGT, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, HDL, LDL, total protein, triglyceride, uric acid, and magnesium.

A symptom assessment asked patients to rate the severity of bone pain, pain on urination, and urination difficulty based on a 10 point scale, with 1 representing the absence of any symptoms and 10 representing the most severe.

Prohibited Medications

The following concomitant medications were prohibited during the study period and, for the specified period, prior to enrollment.

Table 8: Prohibited Medications

Medication/Therapy	Dose or Timing Requirements
Chemotherapy, immunotherapy, anti-androgen, radiation therapy, cryotherapy, strontium, biological response modifiers	Within 8 weeks prior to Screening and through the Treatment Period
GnRH analogs (≤ 6M depot formulations), estrogen, phytotherapy, Megace GnRH analog (1-year implant)	Within 32 weeks prior to Screening and through the Treatment Period Within 60 weeks prior to Screening and through the Treatment Period
Alternative medical therapies with estrogenic, androgenic, or anti-androgenic effect	Within 12 weeks prior to Screening and through the Treatment Period
Finasteride Dutasteride	Within 1 week prior to Screening and through the Treatment Period Within 25 weeks prior to Screening and through the Treatment Period
Ketoconazole	Within 1 week prior to Screening and through the Treatment Period

Discontinuation of Individual Patients

The investigator may have discontinued any patient's participation in the study without his consent at any time if any of the following occurred:

- It was in the patient's best medical interest.
- There were adverse event(s) that the investigator felt was detrimental to the patient.
- The patient required treatment with another drug that would have interfered with evaluation of the investigational product.
- The patient had poor compliance with study drug treatments or study procedures.
- The patient refused to continue treatment.
- Serum testosterone was not maintained at a level considered to be therapeutic.

Patients who prematurely discontinued for any reason other than withdrawal of consent were to be followed for safety for 24 weeks following the last injection.

Assessment of Adverse Events

Adverse events were rated as mild, moderate or severe by the investigator. The Common Toxicity Criteria were not used to determine the severity of adverse event.

Statistical Analysis Plan

Primary Endpoint

- The primary endpoint was the suppression of serum testosterone to castrate levels (≤ 50 ng/dL) from Week 4 through Week 48.
- The primary analysis was conducted in patients who received at least one dose of study drug, had at least one post baseline testosterone measurement, and who did not use any treatments that lower testosterone levels. The primary analysis did not include patients whose final testosterone value was before Day 19 and > 50 ng/dL or patients who were suppressed through Week 48 with no escapes, but had no testosterone value at Week 4 (between Days 20 and 32).
- Patients who discontinued prematurely were included as censored observations at their last testosterone measurement.
- The Kaplan-Meier method was used to calculate a point estimate of the percentage of patients suppressed from Weeks 4 to 48 and to calculate the lower bound of the 1 sided 95% confidence interval. The statistical plan stated that for the formulation to be declared a "success" the lower bound of the 1 sided 95% confidence interval must be at least 87%.
- The applicant conducted an ongoing review of testosterone data with a plan to stop enrollment to Formulation A (or B) or to not administer the second injection if 15 or more subjects were not suppressed by Week 4 (Day 32) or if there were other results (lack of suppression) which precluded achieving the required primary efficacy endpoint. No alpha was assigned to these assessments.

Secondary Endpoints

- Change from baseline in PSA level at each treatment visit
- Mean testosterone concentration at each treatment visit

- "Acute-on-chronic" changes in testosterone and LH levels from just prior to the second (Week 24) injection through the visit 14 days after the second injection.

All analyses and summaries were conducted separately for the 2 treatment groups (Formulation A and Formulation B) and no statistical tests were performed between the two groups.

6 Review of Efficacy

Efficacy Summary

- Leuprolide acetate 45 mg maintained castrate testosterone levels from Week 4 through Week 48 in 93.7% (89.7, 97.7) of patients.
- Non-castrate testosterone levels were seen in 9 patients. Two patients escaped suppression just prior to the second injection. Four patients escaped suppression on the day of the Week 24 injection.
- Due to design flaws, the study was not able to demonstrate an improvement in bone pain, pain on urination, or difficulty with urination.

6.1 Indication

The applicant's proposed indication is the palliative treatment of advanced prostate cancer.

6.1.1 Methods

The primary efficacy analysis is based upon a single, open-label, multicenter, non-randomized Phase 3 trial (L-PC07-169). Two separate leuprolide formulations were studied (A and B), and approval is sought only for Formulation A. For Formulation A, enrollment began on February 25, 2008 and was completed on June 19, 2009. For Formulation B, enrollment began on April 28, 2008 and was completed on September 18, 2009.

6.1.2 Demographics

The demographic characteristics of the patients receiving Formulation A are included in the table below. Since information on the patients who received Formulation B or those treated on C02-008 will only be used in the safety analyses, this demographic information is included in Section 7. The demographic characteristics of the patients who received Formulation A are consistent with the patient population that is likely to receive this medication.

Table 9: Patient Demographics (Formulation A)	
Characteristic	Formulation A N = 151
Median Age (range)	76 years (48-92)
< 65 years	18 (11.9%)
≥ 65 years	133 (88.1%)
≥ 75 years	83 (55.0%)
Race/Ethnicity	
White	112 (84.2%)
Black	30 (19.9%)
Hispanic	7 (4.6%)
Asian	1 (0.7%)
Other	1 (0.7%)
Median Body Mass Index (range)	27 kg/m^2 (18.0-41.5)
< 25 kg/m^2	45 (29.8%)
25 to < 30 kg/m^2	68 (45.0%)
≥ 30 kg/m^2	38 (25.2%)

The table below depicts the disease characteristics of the patients receiving Formulation A, including the patient's stage at study entry. Stage IV prostate cancer was present in only 14% of patients and the indication statement, palliative treatment of advanced prostate cancer, applies only to this limited number of patients. The suppression of testosterone, the primary efficacy endpoint, is expected to occur equally in patients with early and advanced disease and will be examined in both patients with early and with advanced disease.

Fifty-five patients were eligible based upon a rising PSA. This includes 26 patients with an increase in PSA of at least 0.2 ng/dL compared to their previous level and 29 patients with a rise in PSA at least 2 ng/dL above their nadir.

Table 10: Prostate Cancer Disease Characteristics (Formulation A)	
Characteristic	Formulation A N = 151
Stage at Entry (TNM)	
II	104 (68.9%)
III	20 (13.2%)
IV	21 (13.9%)
Missing	6 (4.0%)
Median Testosterone at Entry (range)	398 ng/dL (67-1060)
Median PSA at Entry (range)	9.8 ng/mL (0.2-1517.3)

6.1.3 Subject Disposition

The disposition of patients receiving Formulation A is depicted below. All 151 patients enrolled received at least one injection. Twelve patients discontinued after the 1st injection and the 2nd injection was administered to only 139 patients. Five patients discontinued after the 2nd injection and did not complete the study. There were 7 patients who discontinued due to an adverse event and they are discussed in Section 7. Among the 5 patients who withdrew consent, 2 had adverse events within 30 days of discontinuation (atrial fibrillation/cardiomyopathy and COPD).

While the applicant stated that only 1 patient discontinued due to a protocol violation (use of a prohibited medication), several patients received prohibited medications and are discussed under Protocol Violations. Since these patients did not discontinue due to their protocol violation, they are not included in the table below. Treatment failure was recorded as a cause of discontinuation in 1 patient. However, 9 patients had testosterone levels > 50 ng/mL at some point during the study period. These patients are discussed in the analysis of the primary endpoint. Finally, 1 patient discontinued due to disease progression. This patient had a non-castrate testosterone level and is included in the discussion of the primary endpoint.

Table 11: Patient Disposition (Formulation A)	
Patient Disposition	Formulation A N = 151
Completed	134 (88.7%)
Discontinued	17 (11.3%)
Adverse Event	7 (4.6%)
Withdrew Consent[1]	5 (3.3%)
Protocol Violation	1 (0.7%)
Treatment Failure	1 (0.7%)
Disease Progression	1 (0.7%)
Other[2]	2 (1.3%)

[1]Patients 187, 202, 219, 264, 302 [2] Patient 196-Automobile accident, Patient 283-patient moved

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis, testosterone suppression from Week 4 through Week 48, is depicted below. As noted above, these testosterone levels cannot be relied upon to reflect the efficacy of leuprolide acetate 45 mg.

Table 12: Primary Analysis (Formulation A)	
Primary Analysis	Formulation A
	N = 150
Applicant's Analysis (1-sided 95% CI)	93.7% (90.3, …)
	N = 146
FDA's Analysis (2-sided 95% CI)	93.7% (89.7, 97.7)

The applicant excluded 1 patient from the analysis, patient #145, because a testosterone level was not obtained at Week 4. In the FDA analysis, patient #145 was excluded along with 4 patients who received megesterol acetate, patients 118, 171, 187, and 281. None of these 4 patients had a testosterone level > 50 ng/dL.

Nine patients had non-castrate testosterone levels during the treatment period. These patients are included in the table below. One patient (#255) failed to suppress appropriately by Day 32. Two patients (#159, 167, 282) escaped suppression just prior to the second injection at Week 24. Four patients (#153, 192, 318) escaped suppression after the day of the 2nd injection. Finally, 2 patients escaped after the 2nd injection, one at Week 30 (#160) and one at Week 48 (#190). Two escapes were marked elevated (105, 227 ng/dL). The remainders were < 70 ng/dL.

Table 13: Failure of Testosterone Suppression from Week 4 to 48 (Formulation A)	
Reason for Failure	Formulation A N =146
Any Reason	9 (6.2%)
Failure to Suppress by Day 32	1 (0.7%)
Escape Before the 2nd Injection (Week 24)	2 (1.4%)
Escape on the Day of the 2nd injection	4 (2.7%)
Escape at Week 30	1 (0.7%)
Escape at Week 48	1 (0.7%)

Sensitivity Analyses

Sensitivity analyses had not been completed prior to receipt of the report from the Division of Scientific Integrity concerning the central laboratory conducting the testosterone assays. Given the unreliability of the results of these testosterone assays, sensitivity analyses were not conducted.

6.1.5 Analysis of Secondary Endpoints(s)

Change in PSA from Baseline

At entry, 74.2% (112/151) of patients had a PSA > 4 ng/mL. The table belowTable 14: depicts the number of patients with the stated change in PSA from baseline at predetermined visits. By Day 8, most patients had an increase in PSA, but thereafter, all but 3 patients exhibited a decrease in PSA.

Table 14: Change in PSA from Baseline (Formulation A)					
Visit	↓ <50%	↓ 50-90%	↓ 90-95%	↓ >95%	↑
Day 8	43 pts	2	0	0	101
Week 24	2	34	17	92	1
Week 48	1	21	21	88	2

There were 3 patients who had an elevation in PSA compared to baseline. The table below provides information on the patient's prior treatment and stage at study entry as well as their testosterone level. Note that all 3 patients did achieve, at some point, a decrease in PSA from baseline and that none of these patients had a testosterone level > 50 ng/dL.

Table 15: Testosterone Levels at Time of a Rise in PSA (Formulation A)					
Pt #	Visit	PSA level	Testosterone Level	Stage at Entry	Prior Treatment
132	Baseline	6.4 ng/mL	126.0 ng/dL	T2bN1M0 Gleason's 9	External Beam and Brachytherapy
	Week 14	0.5	5.6		
	Week 40	22.6	7.8		
193	Baseline	39.7	586.0	T4N3M0	No record of prior therapy
	Week 24	8.0	4.3		
	Week 40	96.8	5.3		
302	Baseline	86.5	195.0	T2bNxM1b Gleason's 9	TURP
	Week 14	25.7	15.0		
	Week 24	143.3	12.0		

Mean Testosterone Concentration

The table below shows the mean testosterone concentration and standard deviation at each visit. These are mean values and are minimally affected by individual patient values > 50 ng/dL. The table does provide some information on the time course of the initial increase and later decrease in testosterone levels due to receptor down regulation. Again note that these values cannot be considered reliable. At Week 34 and at the Final Visit there is a marked increase in standard deviation due to a single outlier (same patient).

Table 16: Mean Testosterone Concentration (Formulation A)

Visit	N	Mean Testosterone (SD)
Baseline	151	432.9 ± 176.3
Day 2	146	613.1 ± 260.1
Day 8	146	468.2 ± 200.0
Week 2	148	127.1 ± 89.5
Week 4	150	16.0 ± 8.5
Week 8	148	9.6 ± 5.6
Week 14	148	9.2 ± 5.6
Week 20	151	8.5 ± 5.6
Prior to 2nd Injection	136	10.8 ± 11.7
2 h After 2nd Injection	129	9.1 ± 9.9
4 h After 2nd Injection	126	9.8 ± 11.6
8 h After 2nd Injection	123	9.7 ± 12.9
1 Day After 2nd Injection	138	10.8 ± 10.0
2 Days After 2nd Injection	136	10.9 ± 9.9
3-10 Days After 2nd Injection	137	10.0 ± 7.9
11-17 Days After 2nd Injection	136	8.8 ± 5.6
Week 24	148	14.3 ± 15.2
Week 26	138	9.0 ± 5.5
Week 30	136	9.9 ± 19.4
Week 34	133	13.0 ± 47.7
Week 40	131	8.8 ± 4.7
Week 46	129	8.8 ± 5.3
Week 48	136	10.0 ± 8.4
Final Visit	151	13.3 ± 45.1

Acute-on-Chronic Changes in Testosterone and LH Following the Second Injection

An additional secondary endpoint was assessment of "acute-on-chronic" changes in testosterone and LH levels from just prior to the 2nd injection and at 2, 4, and 8 hours and at 1, 2, 3 to 10, and 11 to 17 days following the 2nd injection.

The applicant did not define the level of LH or testosterone that represented an "acute-on-chronic" change in these levels. In these analyses, for patients previously maintained at castrate levels, levels of testosterone greater than 50 ng/dL represented an "acute-on-chronic" change in testosterone. There were 3 patients (153, 192, and 318) who had a castrate testosterone level prior to the 2nd injection had an increase in testosterone to > 50 ng/dL after the 2nd injection. The associated LH elevation in these 3 patients was 279-470 times their LH level prior to injection.

The definition of an "acute-on-chronic" change in LH is more problematic. A repeat assay on the same sample can vary by 20-25%. Thus, any increase in LH > 25% could represent a real, "acute-on-chronic" change in LH. An "acute-on-chronic" change was, therefore, defined as a > 25% increase in LH compared to the LH level just prior to injection. The table below (# patients with an elevated level/# patients with an LH level at that time point) suggests that a large number of patients had an increase in LH following the 2nd injection. It also suggests that the time course of this increase was prolonged. Most importantly, few patients had an increase in testosterone to non-castrate levels.

Table 17: Acute on Chronic Elevations in LH Level (Formulation A)	
Visit	# Patients with an Elevated LH Level
2 Hours After 2nd Injection	113/127 (89.0%)
4 Hours After 2nd Injection	113/126 (89.7%)
8 Hours After 2nd Injection	105/122 (86.1%)
1 Day After 2nd Injection	120/134 (89.6%)
2 Days After 2nd Injection	109/132 (82.6%)
3-10 Days After 2nd Injection	109/134 (81.3%)
11-17 Days After 2nd Injection	88/134 (65.7%)

6.1.6 Other Endpoints

Bone Pain

On a scale ranging from 1 (no pain) to 10 (worst possible pain), the mean bone pain at baseline was 1.6 $\pm$ 1.5. Given this level of pain, an assessment of the improvement in pain following the use of study drug was not meaningful and was not performed. However, there were 9 patients with baseline scores $\geq$ 5. Among these patients, 7 had at least a 2 point improvement in pain score. However, 1 of these 7 had only a single 2 point improvement (patient 163). The reports of bone pain on Day 8 were also examined for evidence of a flare in bone pain following the administration of study drug. Among 150 patients with Day 8 values, 4 had at least a 2 point increase in bone pain when compared to baseline.

Pain on Urination

On a scale ranging from 1 (no pain) to 10 (worst possible pain) on urination, the mean pain on urination at baseline was 1.4 $\pm$ 1.2. Given the level of pain reported at baseline, an assessment of the improvement in pain was not meaningful and was not performed.

Difficulty with Urination

Similarly, on a scale ranging from 1 (no difficulty) to 10 (worst possible difficulty) on urination, the mean score at baseline was 1.6 $\pm$ 1.33. Given the level of difficulty reported at baseline, an assessment of the improvement in urination was not meaningful and was not performed.

6.1.7 Subpopulations

The table below provides information on the number of patients with castrate testosterone levels in various subgroups. Again, no conclusions can be drawn about the subgroup analyses given the unreliability of the testosterone assays. Here, this analysis, performed for the population as a whole, is included for comparison. Patients ≥ 75 years did slightly better than the population as a whole while Blacks did slightly worse. Further, the percentage of patients with a castrate testosterone level did not decrease with an increase in BMI. This suggests that there is no relationship between BMI and product efficacy. Finally, patients with Stage II disease appeared to do slightly worse than those with more advanced disease. This is unexplained and no information is available about prior exposure to GnRH agonists. Finally, no difference is seen in the percentage of patients with castrate testosterone levels by stage.

Table 18: Subgroup Analyses of Efficacy (Formulation A)

	# in Subgroup	# Patients with Castrate Testosterone
Study Population	150	141 (94.0%)
Age		
< 65	18	17 (94.4%)
≥ 65	133	125 (94.0%)
≥ 75	83	82 (98.8%)
Race		
White	112	107 (95.5%)
Black	30	26 (86.7%)
BMI		
< 25 kg/m^2	45	43 (95.6%)
25 to < 30 kg/m^2	68	63 (92.6%)
≥ 30 kg/m^2	38	36 (94.7%)
Stage at Entry		
II	104	96 (92.3%)
III	20	19 (95.0%)
IV	21	21 (100.0%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All studies have used the 45 mg extended release formulation of leuprolide acetate. In the key study, 151 patients received the first dose of study drug while 139 patients received the second dose of study drug at Week 24 (Day 169). All patients received their 2nd injection by Day 170.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Among the 9 patients who failed to maintain castrate testosterone levels, 2 patients had elevated testosterone levels just prior to the second injection. Three additional patients developed a non-castrate testosterone level (ranging from 51 to 61 ng/dL) in response to the second injection. Finally, 1 patient developed a non-castrate testosterone level at Week 48. This suggests that the leuprolide release has been extended to the maximum interval for this formulation and that dosing intervals should be no greater than 24 weeks.

6.1.10 Additional Efficacy Issues/Analyses

Protocol Violations

The applicant identified 63 (41.7%) patients with a protocol violation. This includes both major and minor protocol violations. Major protocol violations that may affect study outcome include the following.

- Patients 118, 171, 187, and 281 received megestrol acetate (stated indication-hot flashes, weakness) during the treatment period. These patients were excluded from the FDA's primary analysis. In addition, 2 patients received bicalutamide and 2 chronic steroids. Since bicalutamide and steroids were unlikely to affect testosterone levels, these patients were included in the primary analysis.
- Patient 145 did not have a Week 4 testosterone level. This patient was excluded from the primary analysis by the applicant's definition of the primary analysis population.

Patient 207 did not have 2 rising PSAs prior to entry and entered with study with a PSA of 1.3. While it is unclear whether a GnRH agonist was indicated, the presence or absence of changes in his PSA should not have affected his testosterone levels. In addition, the applicant identified 6 patients who, at some point, did not sign the correct version of the informed consent. This includes 1 patient who initialed rather than signed the informed consent. All patients did sign some version of the informed consent.

Efficacy Analyses for Formulation B and C02-0008

Formulation B

Castrate testosterone levels were seen in 86.9% (95% CI; 82.2, 91.7) of patients receiving Formulation B from Week 4 to 48. Non-castrate testosterone levels were seen in 7 patients just prior to the 2nd injection, 10 patients after the 2nd injection, and in 1 patient at Week 4.

C02-0008

Study drug was administered every 26 (rather than every 24 weeks) weeks. Castrate testosterone levels were seen in 82.8% (95% CI; 77.9, UK) of patients on Study C02-0008. At Week 4, 87.8% of patients had castrate testosterone levels. All patients achieved castrate levels by Week 8, but 15 patients subsequently developed non-castrate levels.

7 Review of Safety

Safety Summary

The table below provides a summary of the safety findings for the to-be-marketed formulation.

Table 19: Safety Summary (Formulation A)	
Deaths	
All Causes of Death	Aspiration Pneumonia (1)
Discontinuations	
Overall	4.6%
All Causes of Discontinuation	Fatigue, Hot Flush, Second Primary Neoplasm, Asthenia, Constipation, Coronary Artery Disease, Hyperkalemia, Sleep Disorder
Serious Adverse Events	
Overall Treatment Emergent	20.5%
Treatment Emergent Serious Adverse Events in ≥ 2% of Patients	COPD, Coronary Artery Disease, CVA/TIA, Pneumonia, Heart Failure, Second Primary Neoplasm
Severe Adverse Events	
Overall Treatment Emergent	20.5%
Treatment Emergent Severe Adverse Events in ≥ 2% of Patients	Hot Flush, Atrial Fibrillation/Flutter, COPD, Coronary Artery Disease, Heart Failure
Adverse Events	
Overall Treatment Emergent	94.7%
Treatment Emergent Adverse Events in ≥ 10% of Patients	Hot Flush, Injection Site Pain/Discomfort, Upper Respiratory Infection, Fatigue/Lethargy
Overall Treatment Related	72.8%
Treatment Related Adverse Events in ≥ 5% of Patients	Hot Flush, Fatigue/Lethargy, Injection Site Pain/Discomfort
Laboratory Abnormalities	
CTCAE v 4 Grade 3-4 in ≥ 5% of Patients	None
CTCAE v 4 Grade 1-2 Abnormalities in ≥ 10% of patients	Grade 1-2 abnormalities in which the incidence increased by ≥ 10% when compared to baseline include increased glucose, triglyceride, cholesterol, decreased hemoglobin, creatinine, and ALT.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety information comes from 151 patients who received Formulation A on study L-PC07-169. Formulation A is the to-be-marketed-product under consideration. This information is supplemented by safety data from 159 patients who received Formulation B on L-PC07-169, as well as, information from 164 patients on study C-02-008. The applicant supplied data sets for all patients who received Formulations A or B. However, only data listings were provided for patients on C02-008.

Each of these formulations was intended to be 24 week extended release forms of leuprolide acetate. The composition of each of these products is shown in Table 4. Since the composition of these products and the adverse event profiles of these products are very similar, this

information could be used as part of the safety database. Note that both Formulation B and the formulation used in study C02-008 failed to achieve their efficacy endpoints.

7.1.2 Categorization of Adverse Events

Adverse events were categorized as mild, moderate, or severe. The Common Toxicity Criteria were not used. Serious adverse events followed the definition used in the Code of Federal Regulations.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from L-PC07-169 Formulation A, L-PC07-169 Formulation B, and C-02-008 will not be pooled. Data from Formulations A and B will be displayed side by side and data from C02-008 will be used to further comment on any signals seen. Adverse events from previous studies of the Lupron 3 Month and Lupron 4 Month formulations will also be compared to those seen with Formulation A.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

All studies used a 45 mg extended release formulation of leuprolide acetate.

- Formulation A: 151 patients received the 1st dose and 139 patients the 2nd dose of study drug at Week 24 (Day 169). Among the 139 patients who received 2 doses, all received their 2nd dose by Day 170.
- Formulation B: 159 patients received the 1st dose and 129 patients the 2nd dose of study drug at Week 24. Among the 129 patients who received 2 doses, 127 received their 2nd dose by Day 170.
- C02-008: 164 patients received the 1st dose and 153 patients the 2nd dose of study drug at Week 26 (Day 182). Among the 153 patients who received 2 doses, 151 received their 2nd dose by Day 184.

Demographics and Baseline Characteristics

The table below provides information on the demographics and baseline characteristics of patients who received either Formulation A or B. Information for patients on study C02-008 was provided in a clinical study report and data listings. The median age of patient on C02-008 was

75.0 years (range: 54-91) and 80.5% of patients were White while 14.0% of patients were Black. Clinical stage at study entry included only 9.8% of Jewett D1 or D2 patients.

Table 20: Demographics and Baseline Characteristics (Safety Database)

	Formulation A N = 151	Formulation B N = 159
Median Age (range)	76 years (48-92)	74 years (46-94)
Race/Ethnicity		
White	112 (84.2%)	105 (66.0%)
Black	30 (19.9%)	47 (29.6%)
Hispanic	7 (4.6%)	0
Asian	1 (0.7%)	4 (2.5%)
Other	1 (0.7%)	3 (1.9%)
Median BMI (range)	27.0 kg/m^2 (18-42)	27.7 kg/m^2 (19.0-45.7)
Stage at Entry		
II	104 (68.9%)	117 (73.6%)
III	20 (13.2%)	11 (6.9%)
IV	21 (13.9%)	25 (15.7%)
Missing	6 (4.0%)	6 (3.8%)

The demographics of these patient populations are similar, but not identical (different racial profiles) and are characteristic of patients undergoing palliative treatment for advanced prostate cancer. This suggests that the available safety data will be useful in the following analyses.

7.2.2 Explorations for Dose Response

All formulations used an extended release formulation of 45 mg of leuprolide acetate.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Safety laboratories were obtained at baseline and at weeks 1, 13, 25, 34, 40, and 50. These laboratories included a complete blood count, urinalysis, and chemistry panel.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology review and Section 4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The 3 and 4 month formulations of Lupron were examined and compared to the adverse event profile of Formulation A.

- Adverse events attributed to Lupron Depot-3 Month, by the investigator, in ≥ 10% of patients included generalized pain, injection site reaction, hot flashes, gastrointestinal disorders, joint disorders, testicular atrophy, and urinary disorders.

- Adverse events reported with Lupron Depot-4 Months in ≥ 10% of patients included asthenia, flu syndrome, generalized pain, headache, injection site reaction, hot flashes, gastrointestinal disorders, edema, skin reaction, and urinary disorders.

Product warnings state that both of these products should not be used in patients with impending cord compression or urinary obstruction. Anemia, hyperlipidemia, and decreased bone density have been seen with these products. In the post-marketing setting, mood swings, depression, and suicide have been reported. Anaphylactoid reactions and pituitary apoplexy have also occurred.

The adverse reactions common to products in this class are due to the effects of decreased testosterone levels. These include hot flashes, asthenia, and testicular atrophy as well as anemia, hyperlipidemia, and loss of bone density. Further, generalized pain or joint disorders may, in part, be attributable to the initial testosterone flare seen with these products.

7.3 Major Safety Results

7.3.1 Deaths

None of the deaths listed below were attributed to study drug by the investigator. Note that suicide has been associated with the use of GnRH agonists.

- One patient on Formulation A died due to aspiration pneumonia.

- Causes of death among 6 patients who received Formulation B included hepatocellular carcinoma, CVA, dementia, suicide, intestinal perforation with multi-organ failure, and urosepsis. The patient whose death was attributed to dementia stopped eating and died on Study Day 81. It is unclear if this patient provided adequate informed consent.

- Causes of death among 4 patients enrolled on C02-008 included sepsis, sudden death (2), and intestinal perforation with cholecystitis complicated by MI.

7.3.2 Nonfatal Serious Adverse Events

The nonfatal serious adverse events for patients who received Formulation A and B are included in the table below. Serious adverse events were reported in 26 (15.9%) patients on study C02-008. Events that occurred in ≥ 2% of patients on C02-008 include CVA and second primary malignancy. Events common to these studies include CVA, pneumonia and second primary malignancies. These events may, in part, be related to the patient's age and to the presence of underlying cancer. That is, patients with cancer are more likely, than the general population, to develop cancer. Among the 151 patients who received Formulation A, 11 (7.3%) patients had a second primary neoplasm. While only 2 of these were considered serious, 4 of the 11 were non-

skin cancers. Among the 159 patients who received Formulation B, 9 (5.7%) patients had a second primary neoplasm. This included 7 patients with non-skin cancers.

Table 21: Serious Adverse Events in ≥ 2% of Patients (Safety Database)		
Serious Adverse Events	Formulation A N = 151	Formulation B N = 159
All	31 (20.5%)	41 (25.8%)
Cardiac Disorders		
Coronary Artery Disease	3	2
Heart Failure	2	3
Infections and Infestations		
Pneumonia	3	3
Neoplasms, Second Primary	2	5
Nervous System Disorders		
CVA/TIA	3	3
Respiratory Disorders		
COPD	3	0

7.3.3 Dropouts and/or Discontinuations

The adverse events leading to discontinuation for patients receiving Formulation A or B is provided in the table below. The most common adverse events leading to discontinuation were second primary cancers and hot flushes. Little information is available about the development of pancreatitis and its role in patient discontinuation. However, the investigator did state that pancreatitis was unrelated to study drug. Findings from patients on study C02-008 were similar. Here, 5 (3.0%) patients discontinued due to an adverse event. These events included CVA, hot flush (2), esophageal cancer, and sterile abscess. It is unclear if the sterile abscess occurred at the site of injection, but the event was considered probably related to study drug.

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Table 22: Adverse Events Leading to Discontinuation (Safety Database)		
	Formulation A N = 151	Formulation B N = 159
All	7 (4.6%)	10 (6.3%)
Cardiac Disorders		
Coronary Artery Disease	1	0
Heart Failure	0	1
Tachycardia	0	1
Gastrointestinal Disorders		
Constipation	1	0
Pancreatitis	0	1
General Disorders		
Asthenia	1	0
Fatigue	2	0
Infections and Infestations		
Urosepsis	0	1
Injury and Procedural Complications		
Bone Fracture	0	1
Metabolism and Nutrition		
Hyperkalemia	1	0
Neoplasms		
Second Primary Neoplasm	2	2
Psychiatric Disorders		
Sleep Disorder	1	0
Panic Attack/Anxiety	0	1
Respiratory Disorders		
Pleural Effusion	0	1
Vascular Disorders		
Hot Flush	2	2

7.3.4 Significant Adverse Events

Severe Adverse Events

As shown in the table below, patients who received Formulation A or B had a similar number of severe adverse events. Severe adverse events that occurred in ≥ 2% of patients included atrial fibrillation or flutter, COPD, hot flushes, heart failure, and pleural effusion. These events are consistent with the age of the patient population.

In C02-008, 34 (20.7%) patients experienced a severe adverse event. Events which occurred in ≥ 2% of patients included pneumonia, sepsis, muscle cramp, CVA, urinary retention, respiratory failure, and hot flush. These are consistent with the events that led to discontinuation or were reported as severe with Formulation A.

Table 23: Severe Adverse Events in ≥ 2% of Patients (Safety Database)		
Severe Adverse Event	Formulation A N = 151	Formulation B N = 159
All	31 (20.5%)	33 (20.7%)
Cardiac Disorders		
Atrial Fibrillation/Flutter	3	1
Heart Failure	1	3
Respiratory Disorders		
COPD	3	0
Pleural Effusion	0	3
Vascular Disorders		
Hot Flush	7	3

Injection Site Reactions

The table below provides information on the incidence of injection site reactions in patients who received Formulation A. Since injection site reactions are likely to be formulation specific, only information from patients who received Formulation A is included in the table below. The percentage of patients who reported injection site reactions with Formulation A is slightly higher than the percentage who reported injection site reactions with Lupron Depot-3 Month (13.8%) and Lupron Depot-4 Month (8.2%). No patient discontinued due to an injection site reaction.

Table 24: Injection Site Reactions (Formulation A)	
	Formulation A N = 151
All	35 (23.2%)
Injection Site Pain/Discomfort	29 (19.2%)
Injection Site Swelling/Induration	3
Injection Site Hematoma/Hemorrhage	2
Injection Site Erythema	3
Injection Site Nodule	1
Injection Site Dermatitis	1
Injection Site Warmth	1

QT Prolongation

Since leuprolide acetate was first approved in 1989, QT data have not been collected. Although the sponsor did not perform ECG monitoring, QT data for leuprolide acetate can be found in another submission (NDA 22-201; degarelix for injection). Here, leuprolide 7.5 mg once every 28 days was used as a comparator drug (N = 201). EKGs were obtained at baseline, Days 3 and 84 and then every 84 days. There was no overt prolongation on Day 3 (maximum drug concentration, but not maximum testosterone suppression). However, among the patients treated with leuprolide, 40 patients has a post baseline QTcF $\geq$ 450 msec, 7 had a QTcF $\geq$ 480 msec, and 4 had a QTcF $\geq$ 500 msec. One patient with a QTcF of 503 msec developed syncope 20 d after this EKG.

Metabolic Abnormalities Linked to GnRH Use

Androgen deprivation therapy has been linked to insulin resistance, an unfavorable alteration in the lipid profile, and cardiovascular disease. Cardiac adverse events and abnormalities in the lipid profile are included in these safety tables. However, a single arm study in an elderly population cannot determine whether an increase in these events has been seen. Further, while these changes were reported, the study period may be insufficient to detect an increase in these abnormalities compared to control.

7.3.5 Submission Specific Primary Safety Concerns

This submission identified no new safety concerns when compared to the Lupron Depot-3 Month and Lupron Depot-4 Month formulations.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The two tables below provide information on the mild, moderate, or severe adverse events that occurred in at least 5% of patients who received Formulation A or B. The adverse event profiles of both formulations are similar to each other and to the 3 and 4 month formulations of Lupron. The most common treatment emergent adverse events seen with Formulation A ($\geq$ 10%), regardless of relationship, include hot flushes, injection site pain, upper respiratory tract infection, and fatigue/lethargy. The table below also examines the percentage of patients in which the event was considered treatment related (per investigator). Treatment related adverse events that occurred in $\geq$ 5% of patients included hot flushes, fatigue/lethargy, and injection site pain/discomfort.

Table 25: Adverse Events in ≥ 5% Patients (Formulation A)		
	Formulation A N = 151	
Preferred Term	Treatment Emergent	Treatment Related
All	143 (94.7%)	110 (72.8%)
Blood and Lymphatic Disorders		
Anemia/Hemoglobin Decreased	10 (6.6%)	2 (1.3%)
Cardiac Disorders		
Coronary Artery Disease/Angina	8 (5.3%)	1 (0.7%)
Gastrointestinal Disorders		
Constipation	15 (9.9%)	5 (3.3%)
General Disorders		
Fatigue/Lethargy	20 (13.2%)	18 (11.9%)
Injections Site Pain/Discomfort	29 (19.2%)	16 (10.6%)
Peripheral Edema/Pitting Edema	8 (5.3%)	2 (1.3%)
Infections and Infestations		
Upper Respiratory Tract Infection[1]	32 (21.2%)	0
Urinary Tract Infections/Cystitis	9 (6.0%)	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	14 (9.3%)	2 (1.3%)
Back Pain	8 (5.3%)	0
Musculoskeletal Pain/Myalgia	12 (7.9%)	3 (2.0%)
Neoplasms		
Second Primary Neoplasms	11 (7.3%)	0
Nervous System Disorders		
Dizziness	8 (5.3%)	3 (2.0%)
Headache/Sinus Headache	12 (7.9%)	3 (2.0%)
Psychiatric Disorders		
Insomnia/Sleep Disorder	13 (8.6%)	5 (3.3%)
Renal and Urinary Disorders		
Dysuria	9 (6.0%)	1 (0.7%)
Hematuria/Hemorrhagic Cystitis	10 (6.6%)	0
Nocturia	8 (5.3%)	2 (1.3%)
Urinary Incontinence	8 (5.3%)	3 (2.0%)
Respiratory, Thoracic and Mediastinal Disorders		
COPD	8 (5.3%)	0
Cough	10 (6.6%)	2 (1.3%)
Dyspnea/Dyspnea on Exertion	8 (5.3%)	2 (1.3%)
Skin and Subcutaneous Tissue Disorders		
Rash	10 (6.6%)	4 (2.6%)
Vascular Disorders		
Hot Flush/Flushing	89 (58.9%)	88 (58.3%)1
Hypertension/BP Increased	10 (6.6%)	3 (2.0%)

[1]Includes influenza, nasal congestion, nasopharyngitis, rhinorrhea, upper respiratory tract infection, and viral upper respiratory tract infection.

Mild, moderate or severe adverse events in patients who received Formulation B were very similar to those in patients who received Formulation A. The most common treatment emergent adverse events (≥ 10%) seen in patients that received Formulation B included hot flushes, injection site pain, upper respiratory tract infection, arthralgia, fatigue/lethargy, hypertension, and constipation.

Table 26: Treatment Emergent Adverse Events in ≥ 5% of Patients (Formulation B)	
Preferred Term	Formulation B N = 159
All	144 (90.6%)
Blood and Lymphatic Disorders	
Anemia	10 (6.3%)
Gastrointestinal Disorders	
Constipation	16 (10.1%)
Nausea	8 (5.0%)
General Disorders	
Fatigue/Lethargy	19 (11.9%)
Peripheral Edema	10 (6.3%)
Injection Site Pain/Discomfort	26 (16.4%)
Infections and Infestations	
Upper Respiratory Tract Infection[1]	27 (17.0%)
Urinary Tract Infection	10 (6.3%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	22 (13.8%)
Back Pain	9 (5.7%)
Extremity Pain	9 (5.7%)
Neoplasms	
Second Primary Neoplasm	9 (5.7%)
Nervous System Disorders	
Dizziness	15 (9.4%)
Headache/Migraine	10 (6.3%)
Psychiatric Disorders	
Insomnia	9 (5.7%)
Renal and Urinary Disorders	
Dysuria	8 (5.0%)
Respiratory, Thoracic, and Mediastinal Disorders	
Dyspnea/Dyspnea on Exertion	10 (6.3%)
Skin and Subcutaneous Tissue Disorders	
Rash	8 (5.0%)
Vascular Disorders	
Hot Flush	71 (44.7%)
Hypertension	16 (10.1%)

[1]Includes nasal congestion, nasopharyngitis, rhinitis, rhinorrhea, and upper respiratory tract infection.

Adverse events in C02-008 were collected from day 1 until 3 days after the final study visit (at 52 weeks or at the time of premature discontinuation). Adverse events were reported in 93% of patients. Adverse events that occurred in ≥ 10% of patients included hot flush, injection site pain, fatigue, arthralgia, nasopharyngitis, hypertension, and back pain. This is similar to the adverse event profile seen with Formulation A.

Testicular Atrophy/Hot Flush

While the percentage of patients who reported a hot flush with Formulation A is similar to the percentage who reported a hot flush with Lupron Depot-3 Month or Lupron Depot-4 Month, the percentage of patients who reported other consequences of testosterone deprivation was much

lower. For example, 20.2% of patients receiving Lupron Depot-3 Month reported testicular atrophy while this was reported in only 2 patients who received Formulation A. It may be that there was under reporting of events which are known consequences of testosterone deprivation in the study under review.

Renal Failure

Renal failure or acute renal failure was reported in 3 patients who received Formulation A and 4 patients who received Formulation B. These events were considered unrelated in 6 of the patients. In patient 302, renal failure was reported on Day 59 and was considered mild and related to study drug. The patient had a creatinine of 106.08 mcmol/L (normal range: 44.2-132.6 mcmol/L) at baseline and a maximum value of 221 on Day 59. Subsequent values gradually decreased to 176.8 on Day 167. Hypertonic bladder (Day 80) and hydronephrosis (Day 84) were also reported in this patient.

7.4.2 Laboratory Findings

Safety laboratories were obtained at baseline and at weeks 1, 13, 25, 34, 40, and 50. These laboratories included a complete blood count, urinalysis, and chemistry panel. The table below provides information on the percentage of patients receiving Formulation A who developed grade 1-4 (Common Toxicity Criteria Adverse Events v 4.0) laboratory abnormalities. Laboratories of interest included in this table include liver function tests, anemia, elevated blood glucose, and hyperlipidemia. Among these, no grade 3-4 laboratory abnormalities were seen in $\geq$ 5% of patients. Note that many patients had grade 1-2 abnormalities at baseline, but that the number of patients with grade 1-2 abnormalities increased during the treatment period. Grade 1-2 abnormalities in which the incidence increased by $\geq$ 10% when compared to baseline included increased glucose, triglyceride, cholesterol, decreased hemoglobin, creatinine, and ALT. Although all laboratories were supposed to be obtained fasting, it is unclear if the presence of grade 1-2 hyperglycemia or triglycerides may be related to food intake. Further, while baseline levels were assessed at a single time point, on study values were assessed at multiple time points, increasing the likelihood of an abnormal level in laboratories that vary markedly from day-to-day.

Table 27: CTCAE v 4 Grade 1-4 Laboratory Abnormalities of Interest (Formulation A)						
Formulation A N = 151						
		WNL[1]	Grade 1	Grade 2	Grade 3	Grade 4
Decreased Hemoglobin	Baseline	130	19 (12.6%)	2 (1.3%)	0	-
	On Study	81	64 (42.4%)	3 (2.0%)	2 (1.3%)	-
ALT	Baseline	149	2 (1.3%)	0	0	0
	On Study	133	14 (9.3%)	3 (2.0%)	1 (0.7%)	0
Total Bilirubin	Baseline	143	8 (5.3%)	0	0	0
	On Study	142	7 (4.6%)	2 (1.3%)	0	0
Creatinine	Baseline	128	23 (15.2%)	0	0	0
	On Study	110	39 (25.8%)	2 (1.3%)	0	0
Increased Glucose	Baseline	78	69 (45.7%)	4 (2.6%)	0	0
	On Study	23	107 (70.9%)	17 (11.3%)	4 (2.6%)	0
Increased Cholesterol	Baseline	108	43 (28.5%)	0	0	0
	On Study	62	83 (55.0%)	5 (3.3%)	1 (0.7%)	0
Increased Triglyceride	Baseline	109	36 (23.8%)	6 (4.0%)	0	0
	On Study	54	74 (49.0%)	20 (13.2%)	3 (2.0%)	0

[1]Within Normal Limits

Elevated Liver Function Tests

GnRH agonists are not known to cause abnormal liver function tests. However, several patients who received Formulation A had abnormal liver function tests during the study period. One patient, # 200, had concomitant elevations in total bilirubin (>2xULN) and ALT (>3xULN). These abnormalities could not be clearly related to study drug.

- Patient 200 had a total bilirubin of 42.75 mcmol/L (2.1xULN) and an ALT of 168 U/L (3.1xULN) on Day 337. Patient 200 received his 2nd injection of study drug on Day 169. On Day 277, the patient began several concomitant medications. Jaundice or cholestasis have been reported with each of these concomitant medications.

7.4.3 Vital Signs

Vital signs, temperature, pulse, blood pressure, respiratory rate, and weight, were obtained at baseline and at weeks 1, 13, 25, 34, 40, and 50. Since changes in muscle mass and weight have been reported with GnRH agonists, patient weight was examined at baseline and on study. Eleven patients (7.3%) who received Formulation A had an increase in body weight $\geq$ 10% (range: 10-18.8%) during the study period.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not routinely obtained on L-PC07-169 or C02-008.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Adverse events that may indicate an immunologic reaction to Formulation A were examined. These included rash, pruritus, urticaria, hypersensitivity, and injection site dermatitis. Please see Section 7.3.4 concerning injection site reactions. Among the remaining abnormalities, 7 events were considered possibly related to study drug. The timing of these events was then examined. Pruritic rash was reported in patient 135 on Day 169 and pruritus and rash were reported on Day 170 in patient 139. These reactions were considered mild to moderate and did not result in discontinuation of study drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose exploration was not performed with the 24 week leuprolide acetateLupron formulation.

7.5.2 Time Dependency for Adverse Events

Adverse events reported in patients receiving either Formulation A or Formulation B were examined from the time of the 1st injection to just prior to the 2nd injection (Day 1 to 168) and from the 2nd injection to the end of study (Day 169 to Day 367). Of interest, while the overall percentage of patients reporting adverse events was similar, no individual events were reported in ≥ 10% of patients from Day 169 to 367. Further, while injection site pain was reported in a similar percentage of patients from Day 1-168 and Day 169-367, hot flushes were less commonly reported from Day 169-367.

Table 28: Adverse Events in ≥ 10% of Patients by Time (Safety Database)

Preferred Term	Formulations A and B N = 310	
	Day 1 to Day 168	Day 169 to Day 367
All	270 (87.1%)	202 (65.2%)
Injection Site Pain/Discomfort	38 (12.3%)	29 (9.4%)
Fatigue/Lethargy	33 (10.6%)	7 (2.3%)
Hot Flush	152 (49.0%)	14 (4.5%)

The type of adverse events reported in the first 2 weeks (Day 1-15) following the administration of Formulations A or B was also examined. It was expected that adverse events during this period would be related to testosterone flare. However, on examination, adverse events such as arthralgia or myalgia were not reported in ≥ 5% of patients during the first 2 weeks of study drug. While adverse events were reported by 44.8% of patients during this period, the only events reported in ≥ 5% of patients were injection site pain/discomfort (9.0%) and hot flush (10.6%).

7.5.3 Drug-Demographic Interactions

Treatment emergent adverse events that occurred in at least 10% of patients receiving Formulation A or Formulation B were examined by age. Few patients were less than age 65 and it is difficult to make comparisons between groups. However, general conclusions can be drawn. Constipation is the only adverse event that was clearly increased in those ≥ 75 years. Hot flushes were less likely to be reported in this age group. Other adverse events did not appear to be age dependent.

Table 29: Treatment-Emergent Adverse Events by Age (Safety Database)

Preferred Term	Formulations A and B N = 310	< 65 years N = 48	65 to < 75 years N = 87	≥ 75 years N = 152
Hot Flush/Flushing	160 (51.6%)	32 (66.7%)	54 (62.1%)	74 (48.7%)
Injection Site Pain/Discomfort	56 (18.1%)	11 (22.9%)	19 (21.8%)	26 (17.1%)
Upper Respiratory Tract Infection[1]	47 (15.2%)	8 (16.7%)	12 (13.8%)	27 (17.8%)
Fatigue/Lethargy	39 (12.6%)	5 (10.4%)	14 (16.1%)	20 (13.2%)
Arthralgia	36 (11.6%)	8 (16.7%)	9 (10.3%)	19 (12.5%)
Constipation	31 (10.0%)	2 (4.2%)	7 (8.0%)	22 (14.5%)
Hypertension/Blood Pressure Increased	26 (8.4%)	7 (14.6%)	11 (12.6%)	8 (5.3%)

[1]Includes nasopharyngitis, pharyngitis, and rhinitis.

Treatment emergent adverse events that occurred in at least 10% of patients receiving Formulation A or Formulation B were also examined by race. Given the small number of patients whose race/ethnicity was listed as Hispanic or Other, these patients were not included in the assessment. For this reason, the number of patients reported in the columns does not sum to the number of patients who received Formulation A or B. Fatigue, arthralgia, and upper respiratory infections were less likely to be reported in Black patients while the incidence of the remaining adverse events was similar between groups.

Table 30: Treatment Emergent Adverse Events by Race (Safety Database)

Preferred Term	Formulations A and B N = 310	White N = 212	Black N = 68
Hot Flush/Flushing	160 (51.6%)	115 (54.2%)	40 (58.8%)
Injection Site Pain/Discomfort	56 (18.1%)	41 (19.3%)	12 (17.6%)
Upper Respiratory Tract Infection[1]	47 (15.2%)	40 (18.9%)	6 (8.8%)
Fatigue/Lethargy	39 (12.6%)	35 (16.5%)	3 (4.4%)
Arthralgia	36 (11.6%)	31 (14.6%)	5 (7.4%)
Constipation	31 (10.0%)	23 (10.8%)	7 (10.3%)
Hypertension/Blood Pressure Increased	26 (8.4%)	20 (9.4%)	5 (7.4%)

[1]Includes nasopharyngitis, pharyngitis, and rhinitis.

7.5.4 Drug-Disease Interactions

All patients had underlying prostate cancer.

7.5.5 Drug-Drug Interactions

Drug-drug interaction studies were not conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

All patients had a history of prostate cancer, although many did not have detectable disease at study entry. The number of patients who developed worsening prostate cancer was not collected. However, the number of patients receiving Formulation A who reported second primary tumors, collected as an adverse event, was 7.3%. In the absence of a control arm, no conclusion can be drawn concerning the increased or decreased incidence of second primary cancers in this population as compared to other elderly patients with underlying prostate cancer.

7.6.2 Human Reproduction and Pregnancy Data

All patients were male and pregnancy was not reported in any of their partners.

7.6.3 Pediatrics and Assessment of Effects on Growth

This formulation has not been studied in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses have been reported with this drug. The drug is packaged as pre-filled syringe and administered in the physician's office decreasing the potential for overdose. In rats, subcutaneous administration of 250 to 500 times the recommended human dose resulted in dyspnea, decreased activity, and local irritation at the injection site. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects which differed from those observed with the 1 mg/day dose.

This drug has no potential for drug abuse. Discontinuation of GnRH agonists in the elderly results in a gradual increase in testosterone.

7.7 Additional Submissions

Not applicable

8 Postmarket Experience

Not applicable

9 Appendices

9.1 Literature Review/References

Please see citations contained within the text.

9.2 Labeling Recommendations

A final label was not developed.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held.

ADDENDUM 9/15/10:
On August 17, 2010, DSI conducted an inspection of Esoterix, Inc. analytical laboratory in Calabasas, CA and issued a Form FDA-483. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from the single Phase 3 clinical study (Study L-PC-7-169). The deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of the drug product being considered for approval.

The deficiency of critical importance was that many analytical runs had > 33.3% of the total QCs and/or > 50% of the QCs at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations. The firm used the Westgard rules to accept or reject analytical runs, rather than the acceptance criteria listed in the 'FDA Guidance for Industry- Bioanalytical Method Validation'. During inspection, the firm was requested to recalculate the QC results in each run using criteria listed in the FDA guidance (i.e. reject a run when > 33.3 % of total # of QCs and/or > 50% of QCs at the same concentration with deviations > 15% (for MS based assays) or 20% (for ligand based assays) from the nominal concentrations. Many runs failed the run acceptance criteria used in the FDA guidance.

On September 7, 2010, Abbott Endocrine, Inc. provided a response to the Esoterix Form FDA-483 observations. The response addresses only the validation of the testosterone assay. The response does not address the extensive in-study failures of the testosterone calibration curve and QC accuracy. Abbott's response has been discussed with the NDA review team. The FDA plans to advise Abbott that adequate and reliable data must be provided to assess the safety and efficacy of this drug product. The failed runs identified in the DSI audit should be re-analyzed. If these deficiencies cannot be adequately addressed, new Phase 3 data will be required.

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/s/

GWYNN C Ison
09/29/2010

VIRGINIA E MAHER
09/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

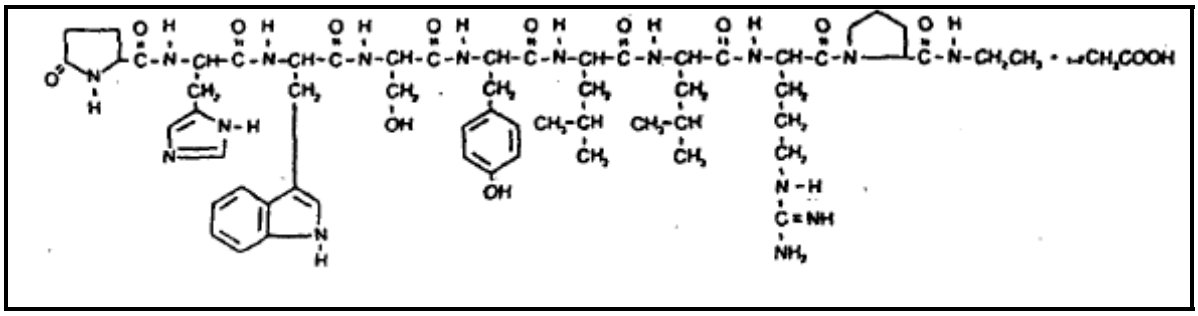
APPLICATION NUMBER:

20-517/S030

CHEMISTRY REVIEW(S)

Chemistry Review # 4	**ONDQA Division** I- **Branch** III	**2. NDA Number** 20-517
3. Name and Address of Applicant: Abbott Laboratories 200 Abbott Park Road Abbott Park, IL 60064-6188		**4.Supplement# Date:** S-030 11-DEC-2009 and Resubmission: 17-DEC-2010 **Goal Date**: 17-JUN-2011
5. Name of Drug (b) (4)	**6. Nonproprietary Name** (b) (4)	
7. Supplement Provides for 45 mg Lupron Depot 6 month DP in the same DP manufacturing site		**8. Amendment(s)** Biopharm Response of 12/17/2010 & 11-MAY-2011(labeling-constitution stability data)
9. Pharmacological Category: Treatment of Endometriosis and uterine fibroids	**10. How Dispensed** Rx	**11. Related Documents** DMF 9365
12. Dosage Form: Sterile depot suspension for injection	**13. Strength** (currently approved)**:** 3M 22.5 mg and 4M 30 mg	

14. Chemical Name and Structure: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-Ltyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-Lprolinamide acetate.



15. Comments: This Review #4 provides an update to deal with the documentation and assessment of the EA considerations since this control matter was not previous addressed in other reviews.

OND: HFD-150: P.M. - D. Mesmer

16. Conclusions and Recommendations: From the standpoint of a CMC assessment, provide approval for this NDA 20-517/S-030.

17. Name **Signature** **Date: 15**-JUN-11

Stuart Zimmerman, Ph.D., (ONDQA, Division I, Branch III)

Hasmukh Patel, Ph.D., Branch Chief (ONDQA, Division I, Branch III)

File N20517_S-030_W(15-JUN-2011)

REVIEW NOTES:

Concerning the question regarding the necessity to have EA documentation submitted to this S-030, it is realized that it is current FDA policy not to require such information if a new indication is not proposed. In this S-030 case, the only change is to provid for an additional strength, a 45 mg Luron Dpot 6 month drug product at th same manufacturing site. Hence, on this basis, it is not expected that basic EA documentation is appropriate.

There was submitted supporting informati that showed that the projected expected introduction concentration (EIC) of leuprolide acetate into the aquatic environment may be calculated. The value is as follows: EIC-Aquatic (mcg/l) = (b) (4) mcg/liter as based on 5-yearsales estimates. The EIC calculated for leuprolide acetate is significantly less than the 1 mcg/l (1 ppb) threshold and thus, qualifies this application for a claim of a categorical exclusion.

The claim for an exclusion of leuprolide acetate from an Environmental Assessment (EA) is made (per 21 CFR Parts 25.30 and 25.31) without reference to CFR Parts 25.20 and 24.21. The drug product is a nanopeptide (polypeptide) and such qualifies to have respective categorical exclusion. As assessed, the actual CFR Part expected to be cited is 25.31 (b) which indicates an increased use of the drug product without exceeding 1 ppb threshold limit.

CONCLUSION: The expected EA documentation requirements for this S-030 have been met to assure there are no potential risk effects to the environment.

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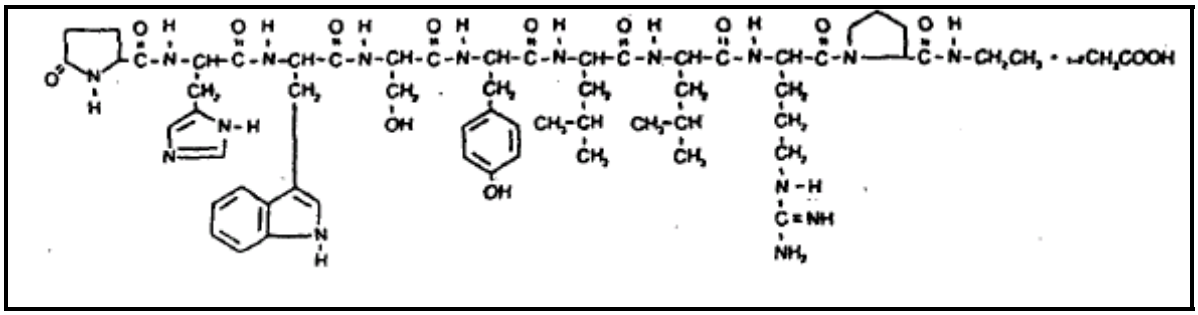
/s/

STUART E ZIMMERMAN
06/15/2011

NALLAPERUM CHIDAMBARAM
06/15/2011
For Dr. Hasmukh Patel

Chemistry Review # 3	**ONDQA Division** I- **Branch** III	**2. NDA Number** 20-517
3. Name and Address of Applicant: Abbott Laboratories 200 Abbott Park Road Abbott Park, IL 60064-6188		**4.Supplement# Date:** S-030 11-DEC-2009 and Resubmission: 17-DEC-2010 **Goal Date**: 17-JUN-2011
5. Name of Drug (b) (4)	**6. Nonproprietary Name** (b) (4)	
7. Supplement Provides for 45 mg Lupron Depot 6 month DP in the same DP manufacturing site		**8. Amendment(s)** Biopharm Response of 12/17/2010 & 11-MAY-2011(labeling-constitution stability data)
9. Pharmacological Category: Treatment of Endometriosis and uterine fibroids	**10. How Dispensed** Rx	**11. Related Documents** DMF 9365
12. Dosage Form: Sterile depot suspension for injection	**13. Strength** (currently approved)**:** 3M 22.5 mg and 4M 30 mg	

14. Chemical Name and Structure: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-Ltyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-Lprolinamide acetate.



15. Comments: This Review #3 follows the CMC Review #2 of 9/14/2010. The Office of Compliance has provided an adequate report as documented. Additional amendments have been provided to this submission as related to other reviewer disciplines: 1) Biopharmaceutics (i.e., Review of submission of 12/17/2010 as by John Duan, 2) Microbiology (Reviewer: John Arigo as relative to the respective DMF 9365 issues), 3) Compliance investigations (i.e., as based on a finalized decision in the OC EER Report) and 4) Labeling with related changes (e.g., PI text with involvements in various group meetings) and resolution of DMEPA recommendation.
OND: HFD-150: P.M. - D. Mesmer

16. Conclusions and Recommendations: From the standpoint of a CMC assessment, provide approval for this NDA 20-517/S-030.

17. Name **Signature** **Date:** 20-May-11
Stuart Zimmerman, Ph.D., (ONDQA, Division I, Branch III)

Hasmukh Patel, Ph.D., Branch Chief (ONDQA, Division I, Branch III)

File N20517_S-030_W(20-MAY-2011)

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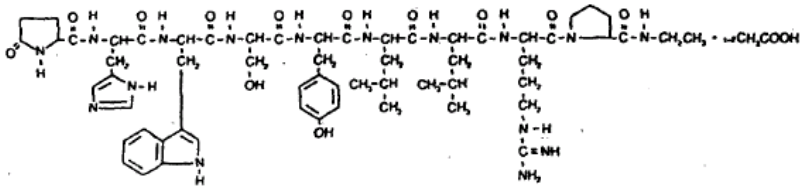
/s/

STUART E ZIMMERMAN
05/20/2011

HASMUKH B PATEL
05/20/2011

CHEMIST'S REVIEW #2	1. ORGANIZATION ONDQA/HFD-150	2. NDA NUMBER 20-517	
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Abbott Laboratories 200 Abbott Park Road Abbott Park, IL 60064-6188		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Lupron Depot-6 Month 45 mg	7. NONPROPRIETARY NAME Leuprolide Acetate for depot suspension	SCS-30	12/11/2009
8. SUPPLEMENT PROVIDES FOR: 45 mg Lupron Depot 6 month DP in the same DP manufacturing site		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Treatment of Endometriosis and uterine fibroids	11. HOW DISPENSED RX . OTC	12. RELATED IND/NDA/DMF DMF 9365	
13. DOSAGE FORM(S) Sterile depot suspension for injection	14. POTENCY 3M 22.5 mg and 4M 30 mg		
15. CHEMICAL NAME AND STRUCTURE  5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.		16. RECORDS AND REPORTS CURRENT YES . NO REVIEWED YES . NO	

17. COMMENTS

In the CMC review 1, the supplement was recommended for Not Approval due to micro and biopharm deficiencies. Micro division has reviewed additional information upon the request from agency and the micro deficiencies have been satisfactorily addressed. The only remaining issue is the deficiency of in-vitro release specification from Biopharm reviewer (Dr. John Duan).

18. CONCLUSIONS AND RECOMMENDATIONS

This supplement is still recommended for Not Approval based on the remaining Biopharm deficiency.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		9/14/2010

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: C.Y. Liang		Branch Chief H. Patelh

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

CHENG YI LIANG
09/14/2010

HASMUKH B PATEL
09/15/2010

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
ONDQA	20-517

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6188

4. AF NUMBER

5. SUPPLEMENT (S)
NUMBER(S) DATES(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME		
Lupron Depot-6 Month 45 mg	Leuprolide Acetate for depot suspension	SCS-30	12/11/2009

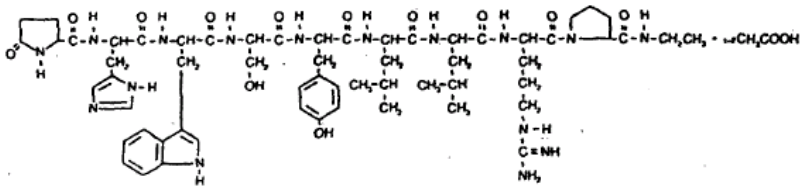
8. SUPPLEMENT PROVIDES FOR: 45 mg Lupron Depot 6 month DP in the same DP manufacturing site

9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Treatment of Endometriosis and uterine fibroids	RX . OTC	DMF 9365

13. DOSAGE FORM(S)	14. POTENCY
Sterile depot suspension for injection	3M 22.5 mg and 4M 30 mg

15. CHEMICAL NAME AND STRUCTURE



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

16. RECORDS AND REPORTS

CURRENT YES . NO
REVIEWED YES . NO

17. COMMENTS
See review notes

18. CONCLUSIONS AND RECOMMENDATIONS

This supplement is recommended for Not Approval due to the deficiencies of DP in-vitro release specification and DP sterility assurance. The drug name is recommended as **Lupron Depot (leuprolide acetate for depot suspension) 45 mg 6-month.**

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		8/12/2010

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: C.Y. Liang		Branch Chief H. Patelh

REVIEW NOTES

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

CHENG YI LIANG
08/26/2010

HASMUKH B PATEL
08/26/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

PHARMACOLOGY REVIEW(S)

MEMORANDUM

From:	Haleh Saber, Ph.D. Supervisory Pharmacologist Division of Hematology Products (DHP)
For:	Division of Drug Oncology Products (DDOP)
Subject:	PLR Labeling Revisions
Date:	5/23/2011
NDA:	20517, S-030
Drug:	Lupron Depot
Applicant:	Abbott Laboratories
Indication:	Palliative treatment of advanced prostatic cancer

Background:

In 2009, Abbott Laboratories submitted supplement S-030 to add a new dosage form (Lupron Depot 45 mg; 6-month administration). In support of this dosage form the Applicant submitted results of pharmacokinetic (PK)/pharmacodynamic (PD) and local tolerance studies. The studies were reviewed by Kimberly Ringgold, Ph.D. (see APPENDIX, excerpted from Dr. Ringgold's review). In summary, *in vivo* PK/PD studies were completed in rats and dogs. Pharmacokinetic studies showed that after a single subcutaneous (rat) and intramuscular (dog) dose, leuprolide acetate levels were sustained for approximately 22 weeks in rats and 24 weeks in dogs. Testosterone levels were suppressed during the 24-week period post-dosing. There were no significant PK/PD differences observed between the pilot lot and the clinical lot. Local tolerance studies were completed in rabbits; no major concerns were identified.

A complete response letter was issued on October 5, 2010 due to a clinical deficiency (DSI audit) and a product quality deficiency (drug release acceptance criteria).

On December 17, 2010, the Agency received the resubmission, which was considered Class 2 response to the October 5, 2010 action letter. The nonclinical labeling review and negotiation started during the 2009 supplemental submission cycle and was completed during the December 17 resubmission review cycle. In the following section, major changes in the label are discussed and the final version of the PLR label is presented.

PLR label:

Nonclinical sections of the label have been updated to comply with 21CFR201.56 and 21CFR201.57 on PLR formatting. In addition, the following changes were made to the label:

- The pharmacologic class of the drug is defined as "gonadotropin releasing hormone (GnRH) agonist", to be consistent with other products of the same class.
- The dosage form used in animal studies (e.g. monthly depot) and the schedule of administration in animals are added to sections 8.1, Pregnancy; 10, Overdosage;

and 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility. This will allow for appropriate animal-to-human dose extrapolations when necessary.

- Two assumptions were made for animal-to-human dose extrapolations:
  - All dosage forms result in a constant/steady release of the drug per day.
  - At the end of the exposure period (e.g. 3, 4, or 6 months as defined by the dosage form), no drug is left at the injection site or in the plasma.

  Based on the assumptions above, the estimated daily human dose is 0.154 mg/m^2/day. This number could be based on any of the depot formulations presented in the label. For instance, for "Lupron Depot 45 mg for 6-month administration", the human daily dose on a body surface area will be (45 mg/ 60 kg/ 180 days)* 37 or 0.154 mg/m^2/day. The estimated human daily dose is the same value (0.154 mg/m^2/day) for Lupron Depot 22.5 mg for 3-month administration or Lupron Depot 30 mg for 4-month administration.

  Assumptions above were used to estimate the daily dose in animals. When a monthly depot formulation was used in animals, the dose was divided by 30 for an estimation of daily dose, and then this dose was converted to the body surface area for animal-to-human dose extrapolation based on body surface area.
  - Section 8.1 dose extrapolation: A single monthly Lupron Depot of 0.00024 mg/kg in rabbits will result in an estimated daily leuprolide dose of (0.00024/30)*12 or 0.000096 mg/m^2/day. Hence the animal-to-human dose ratio will be 0.000096/0.154 or 1/1600. Similar calculations were done for relevant sections of the label.

Of note, pregnancy Category X is assigned to Lupron Depot, since this drug is indicated for use in men. If this drug is used in pregnant women, expected hormonal changes that occur after receiving this drug may result in fetal mortalities or abnormalities. These effects were observed in pregnant animals that received the drug.

<u>The following represents the final version for nonclinical sections of the label.</u>

4.2 Pregnancy

LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Expected hormonal changes that occur with LUPRON DEPOT treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. LUPRON DEPOT is contraindicated in women who are or may become pregnant. If this drug is 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.

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.2)]*.

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. Expected hormonal changes that occur with LUPRON DEPOT

treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman. If this drug is 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.
Major fetal abnormalities were observed in rabbits after a single administration of the monthly formulation of LUPRON DEPOT on day 6 of pregnancy at doses of 0.00024, 0.0024, and 0.024 mg/kg (approximately 1/1600 to 1/16 the human dose based on body surface area using an estimated daily dose in animals and humans). Since a depot formulation was utilized in the study, a sustained exposure to leuprolide was expected throughout the period of organogenesis and to the end of gestation. Similar studies in rats did not demonstrate an increase in fetal malformations, however, there was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.3 Nursing Mothers
LUPRON DEPOT is not indicated for women *[see Indications and Usage (1)]*. It is not known whether leuprolide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from LUPRON DEPOT, a decision should be made to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

10 OVERDOSAGE
There is no experience of overdosage in clinical trials. In rats, a single subcutaneous dose of 100 mg/kg (approximately 4,000 times the estimated daily human dose based on body surface area), resulted in dyspnea, decreased activity, and excessive scratching. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

12.1 Mechanism of Action
Leuprolide acetate, a GnRH agonist, acts as an inhibitor of gonadotropin secretion. Animal studies indicate that following an initial stimulation, continuous administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect was reversible upon discontinuation of drug therapy.
Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in

females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Genotoxicity studies were conducted with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of mutagenic effects or chromosomal aberrations.

Leuprolide may reduce male and female fertility. Administration of leuprolide acetate to male and female rats at dose of 0.024, 0.24, and 2.4 mg/kg as monthly depot formulation for up to 3 months (approximately as low as 1/30 of the highest human dose based on body surface area using an estimated daily dose in animals and humans) caused atrophy of the reproductive organs, and suppression of reproductive function. These changes were reversible upon cessation of treatment. Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

APPENDIX
Review of nonclinical studies by Kimberly Ringgold, Ph.D.

Study title: In Vivo Release and Pharmacokinetics and Pharmacodynamics of TAP-144 in Rats and Dogs after Administration of TAP-144-MC (6M PLA IP2) Powder

Study no.:	TAP-144SR(6M)IP/ 00015.001R
Study report location:	4.2.1.1
Conducting laboratory and location:	(b) (4)
Drug, lot #:	TAP-144, OW6M-MC-SA-L02
Vehicle:	Carboxmethylcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

Methods: In vivo release profile, pharmacokinetics, and pharmacodynamic of TAP-144-MC (6M PLA IP2) powder was investigated in male rats and male dogs up to week 28. Injections were given in the back of male rats subcutaneously. In the dog, injections were given intramuscularly in the hind legs.

Dosing:

Species:	Sprague-Dawley rats and Beagle dogs
Number of animals:	Rats: n = 4; dogs: n = 4
Age/weight:	Rats: 7 weeks/NA; dogs: 6 – 9 months/NA
Dose:	Rats: 9 mg; dogs: 45 mg
Frequency:	Single dose
Route:	Rats: SC; dogs: IM
Dose volume:	Rats: 0.4 mL; dogs: 1.3 mL
Vehicle:	Carboxmethulcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

NA: not available

Observations and times:

Rat: blood samples were collected from the jugular vein at pre-dose, hour 1, 2, 4, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Dog: blood samples were collected from the jugular vein at pre-dose, hour 1, 2, 4, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Results: The following tables and figures are excerpted from Applicant's submission.

Serum Concentrations of TAP-144 (including the metabolite I (M-I))

Rat:

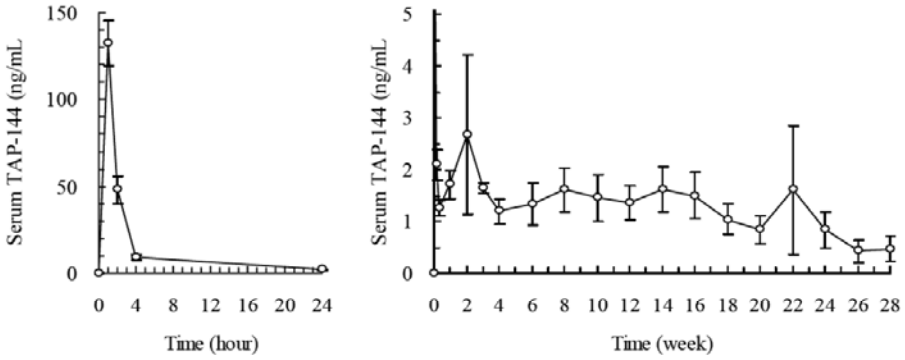
Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-053)

Time			pre	H 1	H 2	H 4	D 1	D 2
Serum TAP-144 (ng/mL)		Mean	0.00	132.63	48.00	9.31	2.10	1.25
		SD	0.00	13.01	8.20	1.61	0.29	0.15
	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	1.72	2.67	1.64	1.20	1.34	1.61	1.46	1.36
SD	0.27	1.54	0.10	0.24	0.42	0.42	0.44	0.33
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	1.61	1.49	1.04	0.84	1.61	0.84	0.43	0.47
SD	0.43	0.45	0.31	0.27	1.24	0.35	0.21	0.24

H: Hour, D: Day, W: Week

Each value represents the mean and SD (n=4).



Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.

Each point represents the mean ± SD

○: Lot No. OW6M-MC-SA-L02

Dog:

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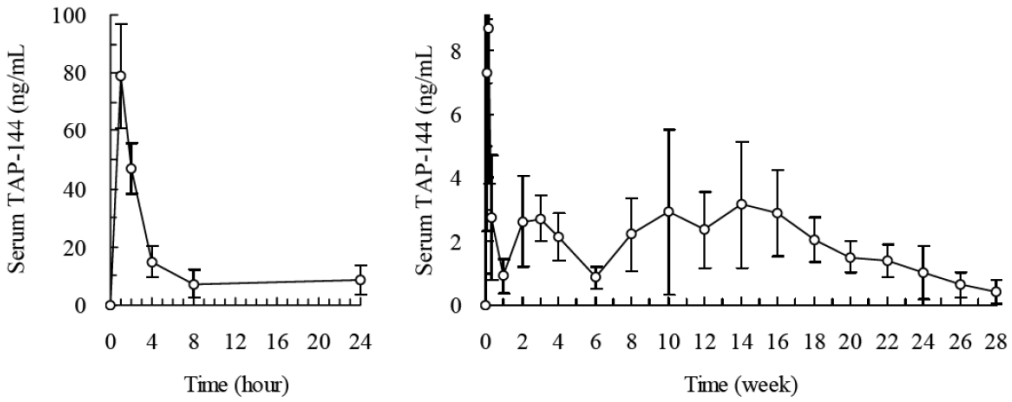
Serum concentrations of TAP-144 (including the M-I) in male dogs after intramuscular injection at a single dose of 45 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-042)

Time				pre	H 1	H 2	H 4	H 8	D 1
Serum TAP-144 (ng/mL)			Mean	0.00	78.95	47.10	14.97	7.33	8.72
			SD	0.00	18.19	8.61	5.19	4.98	4.90
	D 2	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	2.75	0.93	2.63	2.73	2.14	0.87	2.22	2.92	2.36
SD	1.98	0.54	1.44	0.72	0.75	0.33	1.15	2.59	1.21
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	
Mean	3.15	2.88	2.06	1.51	1.40	1.02	0.64	0.42	
SD	2.00	1.35	0.69	0.50	0.53	0.84	0.41	0.37	

H: Hour, D: Day, W: Week
Each value represents the mean and SD (n=4).



Serum concentrations of TAP-144 (including the M-I) in male dogs after intramuscular injection at a single dose of 45 mg TAP-144.
Each point represents the mean ± SD
○: Lot No. OW6M-MC-SA-L02

Serum Concentrations of Testosterone

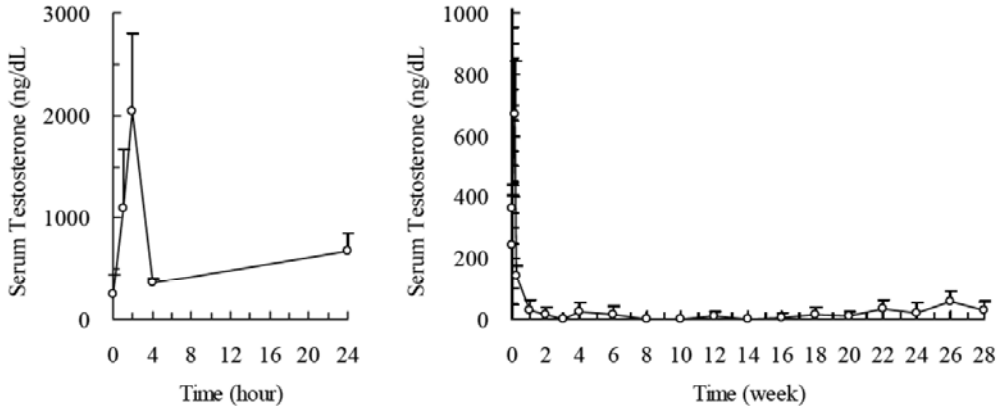
Rats:

Serum concentrations of testosterone in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-053)

Time			pre	H 1	H 2	H 4	D 1	D 2
Serum testosterone (ng/dL)	Mean		242	1096	2032	366	672	143
	SD		197	564	764	42	171	35
	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	29	13	0	24	14	0	0	8
SD	34	26	0	28	28	0	0	15
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	0	7	13	9	35	17	56	27
SD	0	14	26	17	28	34	38	31

H: Hour, D: Day, W: Week
Each value represents the mean and SD (n=4).



Serum concentrations of testosterone in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.
Each point represents the mean + SD (n=4)

Dog:

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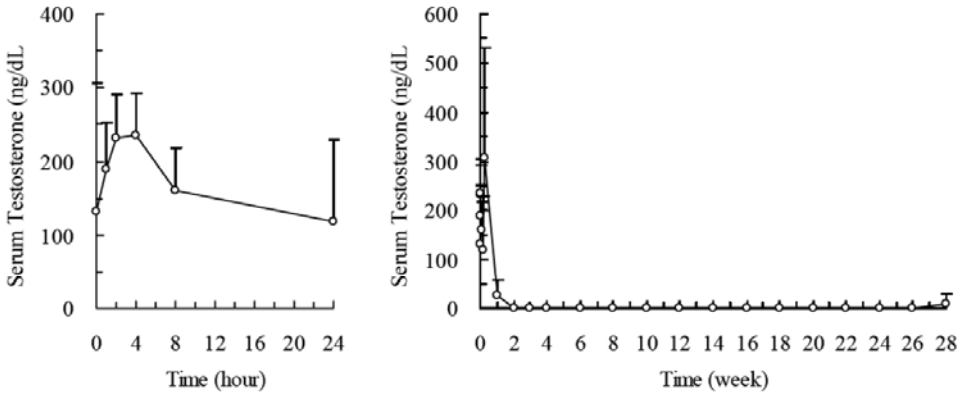
Serum concentrations of testosterone in male dogs after intramuscular injection at a single dose of 45 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-042)

Time				pre	H 1	H 2	H 4	H 8	D 1
Serum testosterone (ng/dL)			Mean	133	190	232	236	160	120
			SD	172	63	60	58	57	109
	D 2	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	309	26	0	0	0	0	0	0	0
SD	221	31	0	0	0	0	0	0	0
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	
Mean	0	0	0	0	0	0	0	10	
SD	0	0	0	0	0	0	0	20	

H: Hour, D: Day, W: Week
Each value represents the mean and SD (n=4).

Each point represents the mean ± SD
○: Lot No. OW6M-MC-SA-L02



Serum concentrations of testosterone in male dogs after intramuscular injection at a single dose of 45 mg TAP-144.
Each point represents the mean + SD (n=4)
○: Lot No. OW6M-MC-SA-L02

Conclusion: Serum concentrations of TAP-144 were maintained at nearly constant levels for approximately 22 weeks after administration of 9 mg to rats subcutaneously and for 24 weeks after administration of 45 mg intramuscularly to dogs. Serum concentrations of testosterone were maintained at ≤ 35 ng/dL in rats and at ≤ 26 ng/dL in dogs from week 1 to week 24.

Study title: Pharmacokinetics and Pharmacodynamics of TAP-144 in Rats and Dogs after Administration of TAP-144-MC (6M PLA IP2) Powder

Study no.:	RD091340
Study report location:	4.2.2.7.1
Conducting laboratory and location:	(b) (4)
Drug, lot #, and % purity:	TAP-144-MC (6M PLA IP2) – pilot lot, OW6M-MC-SA-L02,
Vehicle:	Carboxmethylcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

Key Findings:

- No toxicologically significant PK differences were observed between the pilot lot (6M PLA IP2) and the clinical lot

Methods: The profile, pharmacokinetics, and pharmacodynamic of TAP-144-MC (6M PLA IP2) powder was investigated in this study. The pilot (OW6M-MC-SA-L02) and clinical (Z327802) lots were subcutaneously injected into the backs of male rats at a dose of 9 mg TAP-144-MC. Only the pilot lot was tested in dogs. TAP-144 and testosterone levels in the dog are reviewed in the previous study (TAP-144SR(6M)IP/ 00015.001R).

Dosing:

Species:	Sprague-Dawley rats Beagle dog
Number of animals:	Rats = Pilot lot: n = 4; Clinical lot: n = 5 Dog = Pilot lot: n = 4
Age/weight:	7 weeks/NA
Dose:	9 mg
Frequency:	Single dose
Route:	Rats: SC
Dose volume:	Rats: 0.4 mL; dogs: 1.3 mL
Vehicle:	Carboxmethylcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

Observations and times:

Rat: blood samples were collected from the jugular vein at pre-dose, hour 1, 2, 4, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Dog: blood samples were collected fore-arm at pre-dose, hour 1, 2, 4, 8, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Results: The following tables and figures are excerpted from Applicant's submission. Results from the pilot lot were also presented in the previous study (TAP-144SR(6M)IP/ 00015.001R).

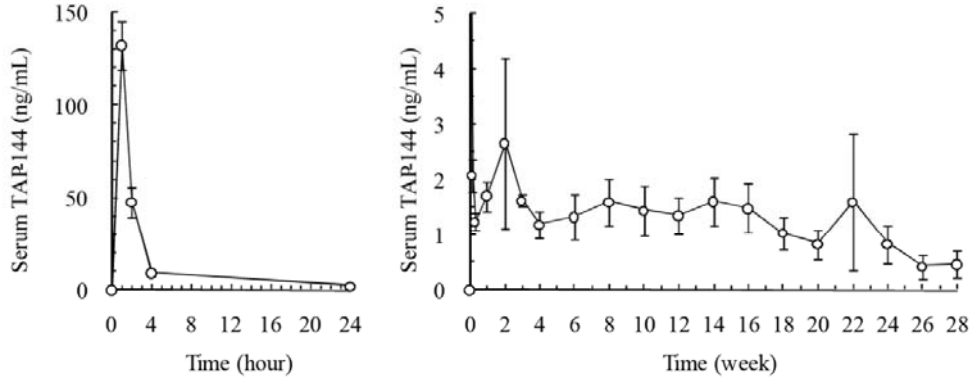
Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-053)

Time			pre	H 1	H 2	H 4	D 1	D 2
Serum TAP-144 (ng/mL)		Mean	0.00	132.63	48.00	9.31	2.10	1.25
		SD	0.00	13.01	8.20	1.61	0.29	0.15
	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	1.72	2.67	1.64	1.20	1.34	1.61	1.46	1.36
SD	0.27	1.54	0.10	0.24	0.42	0.42	0.44	0.33
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	1.61	1.49	1.04	0.84	1.61	0.84	0.43	0.47
SD	0.43	0.45	0.31	0.27	1.24	0.35	0.21	0.24

H: Hour, D: Day, W: Week

Each value represents the mean and SD (n=4).



Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.

Each point represents the mean ± SD

○: Lot No. OW6M-MC-SA-L02

Clinical lot:

Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. Z327802 (Protocol No. ZALE2007-KS-004)

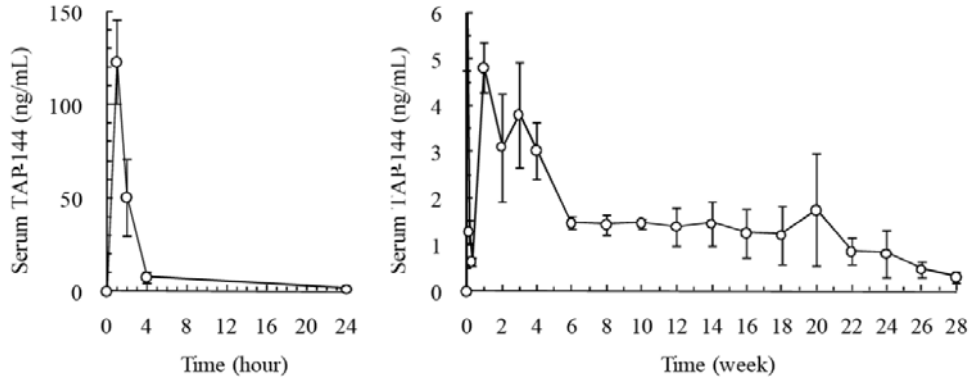
Time		pre	H 1	H 2	H 4	D 1	D 2
Serum TAP-144 (ng/mL)	Mean	0.00	123.59	50.68	7.56	1.29	0.64
	SD	0.00	22.45	20.48	2.78	0.26	0.10

	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	4.83	3.12	3.82	3.05	1.49	1.44	1.47	1.40
SD	0.54	1.17	1.15	0.62	0.13	0.21	0.11	0.42

	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	1.47	1.27	1.22	1.76	0.87	0.82	0.48	0.31
SD	0.46	0.52	0.62	1.21	0.29	0.51	0.16	0.11

H: Hour, D: Day, W: Week

Each value represents the mean and SD (n=5).



Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.

Each point represents the mean ± SD

○: Lot No. Z327802

Conclusion: In the pilot lot, the serum concentrations of TAP-144 (including the M-I) in male rats elevated to 132.63 ng/mL one hour post-dose and decreased to 2.10 ng/mL about 24 hours post-dose. Serum concentrations were maintained 0.8 and 2.67 ng/mL for 24 weeks after dosing. In the clinical lot, serum concentrations of TAP-144 (including the M-I) in male rats elevated to 123.59 ng/mL one hour post-dose and decreased to 1.29 ng/mL. Levels decreased to 0.31 ng/mL by 28 weeks post-dose. No toxicologically significant differences were observed in the PK profiles between the pilot lot and the clinical lot.

Local Irritation Study

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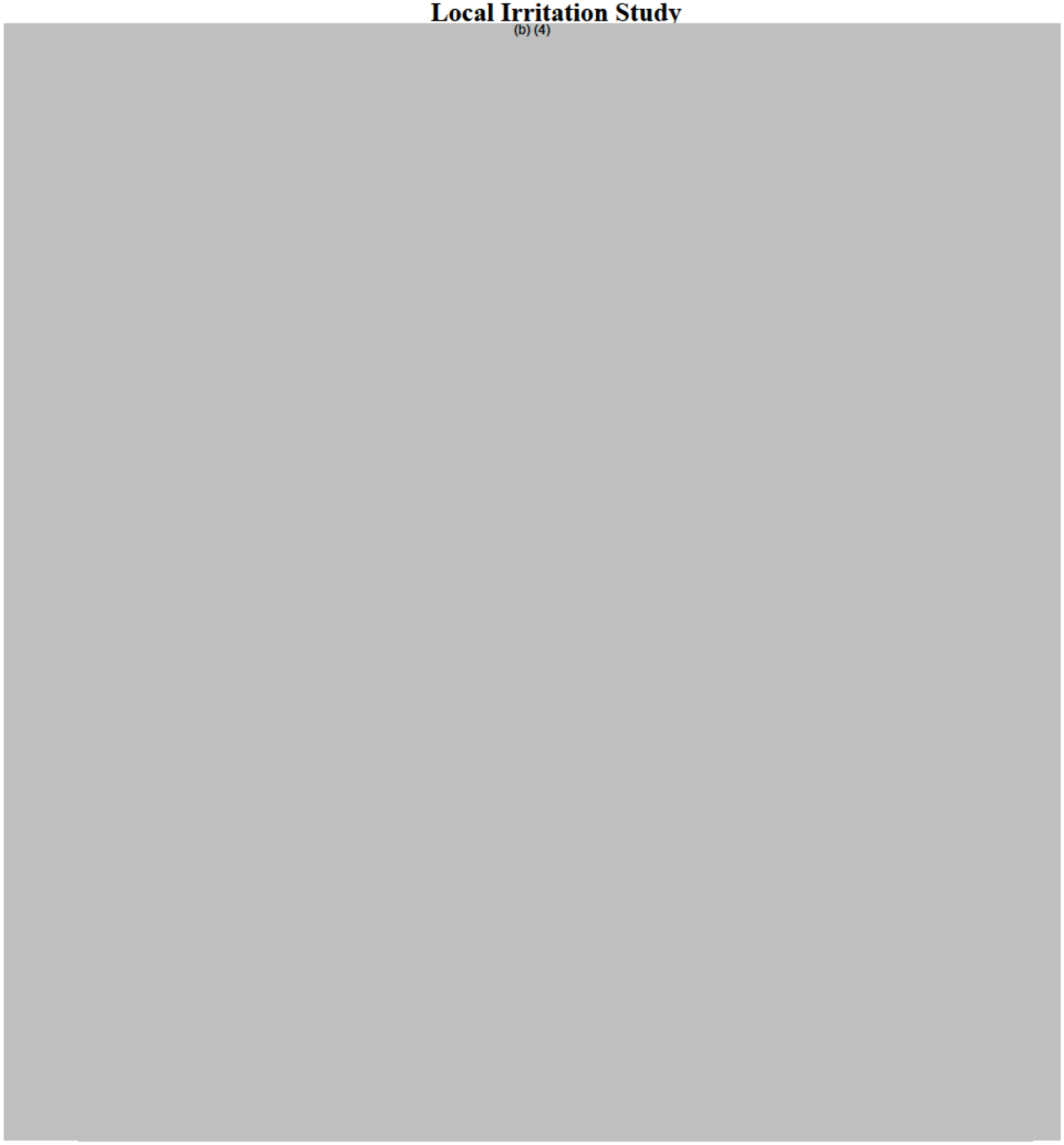

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/s/

HALEH SABER
05/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	20517
Supplemental application:	S-030
Supporting documents:	161
submission date:	12/11/2009
Received date:	12/11/2009
Product:	Lupron Depot® (leuprolide acetate for depot suspension) 6 month 45 mg injection
Indication:	Palliative treatment of advanced prostate cancer
Applicant:	Abbott Laboratories
Review Division:	Division of Drug Oncology Products
Reviewer:	Kimberly Ringgold, PhD
Supervisor/Team Leader:	Haleh Saber, PhD
Division Director:	Robert Justice, MD
Project Manager:	Dianne Hanner

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

There are no nonclinical issues to preclude the approval of this supplemental NDA for the addition of the new dosage (Lupon Depot 45 mg, every 24 weeks administration).

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Refer to section 12 (Appendix/Attachments) for labeling recommendations
*Of note, the label has not been finalized due to clinical quality control issues and the potential for a complete response letter

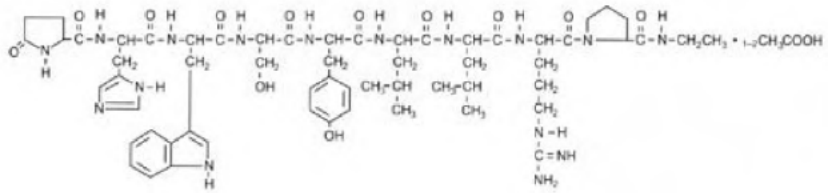
1.2 Discussion of Nonclinical Findings

Pharmacology and toxicology data has been submitted and reviewed for Lupron (NDA 19010) and Lupron Depot (NDAs 19732 & 19943). In the present submission, the Applicant submitted pharmacodynamic and local tolerance studies with this application. In vivo pharmacodynamic studies were completed in the rat and dog. Pharmacokinetics studies show that after a single subcutaneous (rat) and intramuscular (dog) dose, leuprolide acetate levels were sustained for approximately 22 weeks in rats and 24 weeks in dogs. They also showed that testosterone levels were suppressed during the 24-week period post dosing. There were no release differences observed between the pilot lot and the clinical lot. Local tolerance studies were completed in rabbits. The results show that treatment did not increase local irritation effects (summary provided).

2 Drug Information

2.1 Lupron

2.1.1 CAS Registry Number:	74381-53-6
2.1.2 Generic Name:	leuprolide acetate
2.1.3 Code Name:	TAP-144
2.1.4 Chemical Name:	5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-

	prolinamide acetate (salt)
2.1.5 Molecular Formula/Molecular Weight	$C_{59}H_{84}N_{16}O_2$/1269.47
2.1.6 Structure 	
2.1.7 Pharmacologic class:	gonadotropin-releasing hormone agonist

2.2 Relevant IND/s, NDA/s, and DMF/s

NDAs 19732, 19943, 20011, 20708

2.3 Clinical Formulation

2.3.1 Drug Formulation

Composition of Leuprolide Acetate Depot 6 Month, 45 mg

Component	Quality Standard	Function	Amount/Unit
Component for MC Powder[1] (b) (4)			

2.3.2 Comments on Novel Excipients: none

2.3.3 Comments on Impurities/Degradants of Concern: none

2.4 Proposed Clinical Population and Dosing Regimen

Palliative treatment of advanced prostate cancer

2.5 Regulatory Background

Date Introduced	Formulation	Indication
April 1985	Lupron Injection	Palliative treatment of advanced prostate cancer
January 1989	Lupron Depot 7.5 mg	Palliative treatment of advanced prostate cancer
October 1990	Lupron Depot 3.75 mg	Endometriosis
April 1993	Lupron Depot-PED 7.5, 11.25, and 15 mg and Lupron Injection	Central precocious puberty
March 1995	Lupron Depot 3.75 mg	Anemia associated with leiomyoma uteri
December 1995	Lupron Depot – 3 Month 22.5 mg	Palliative treatment of advanced prostate cancer
March 1997	Lupron Depot – 3 Month 11.25 mg	Endometriosis and anemia associated with leiomyoma uteri
May 1997	Lupron Depot – 4 Month 30 mg	Palliative treatment of advanced prostate cancer

3 Studies Submitted

3.1 Studies Reviewed

Type	Study Title	Study #
In Vivo PK/PD	In vivo release and pharmacokinetics and pharmacodynamics of TAP-144 in rats and dogs after administration of TAP-144 (6M PLA IP2) Powder	TAP-07-013729-1.0
In Vivo Pk/PD	Pharmacokinetics and Pharmacodynamics of TAP-144 in Rats and Dogs after Administration of TAP-144-MC (6M PLA IP2) Powder	RD091340

3.2 Studies Not Reviewed

Type	Study Title	Study #
(b) (4)		

3.3 Previous Reviews Referenced

Non-clinical reviews under NDAs 19010, 19732, and 20517 (S-002)

4 Pharmacology

4.1 Primary Pharmacology

Lupron Depot contains leuprolide acetate, a gonadotropin releasing hormone agonist. GnRH agonist inhibits gonadotropin secretion by suppressing ovarian and testicular steroidogenesis. Pharmacology studies were reviewed under NDA 19-010.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 ADME

See the label approved on 6/2/2009:

5.2 In Vivo Pharmacokinetics and Pharmacodynamics

Study title: In Vivo Release and Pharmacokinetics and Pharmacodynamics of TAP-144 in Rats and Dogs after Administration of TAP-144-MC (6M PLA IP2) Powder

Study no.:	TAP-144SR(6M)IP/ 00015.001R
Study report location:	4.2.1.1
Conducting laboratory and location:	(b) (4)
Drug, lot #:	TAP-144, OW6M-MC-SA-L02
Vehicle:	Carboxmethylcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

Methods: In vivo release profile, pharmacokinetics, and pharmacodynamic of TAP-144-MC (6M PLA IP2) powder was investigated in male rats and male dogs up to week 28. Injections were given in the back of male rats subcutaneously. In the dog, injections were given intramuscularly in the hind legs.

Dosing:

Species:	Sprague-Dawley rats and Beagle dogs
Number of animals:	Rats: n = 4; dogs: n = 4
Age/weight:	Rats: 7 weeks/NA; dogs: 6 – 9 months/NA
Dose:	Rats: 9 mg; dogs: 45 mg
Frequency:	Single dose
Route:	Rats: SC; dogs: IM
Dose volume:	Rats: 0.4 mL; dogs: 1.3 mL
Vehicle:	Carboxmethulcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

NA: not available

Observations and times:

Rat: blood samples were collected from the jugular vein at pre-dose, hour 1, 2, 4, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Dog: blood samples were collected from the jugular vein at pre-dose, hour 1, 2, 4, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Results: The following tables and figures are excerpted from Applicant's submission.

Serum Concentrations of TAP-144 (including the metabolite I (M-I))

Rat:

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Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-053)

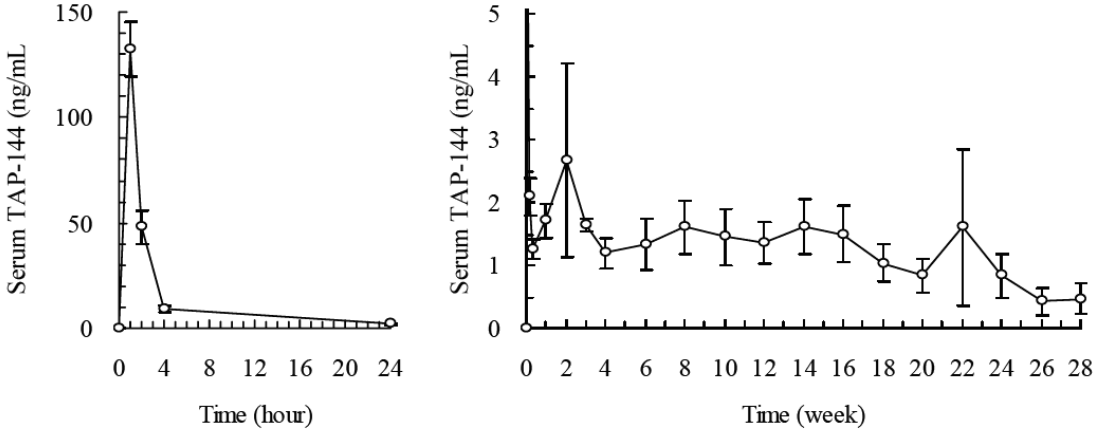
Time		pre	H 1	H 2	H 4	D 1	D 2
Serum TAP-144 (ng/mL)	Mean	0.00	132.63	48.00	9.31	2.10	1.25
	SD	0.00	13.01	8.20	1.61	0.29	0.15

	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	1.72	2.67	1.64	1.20	1.34	1.61	1.46	1.36
SD	0.27	1.54	0.10	0.24	0.42	0.42	0.44	0.33

	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	1.61	1.49	1.04	0.84	1.61	0.84	0.43	0.47
SD	0.43	0.45	0.31	0.27	1.24	0.35	0.21	0.24

H: Hour, D: Day, W: Week

Each value represents the mean and SD (n=4).



Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.

Each point represents the mean ± SD

○: Lot No. OW6M-MC-SA-L02

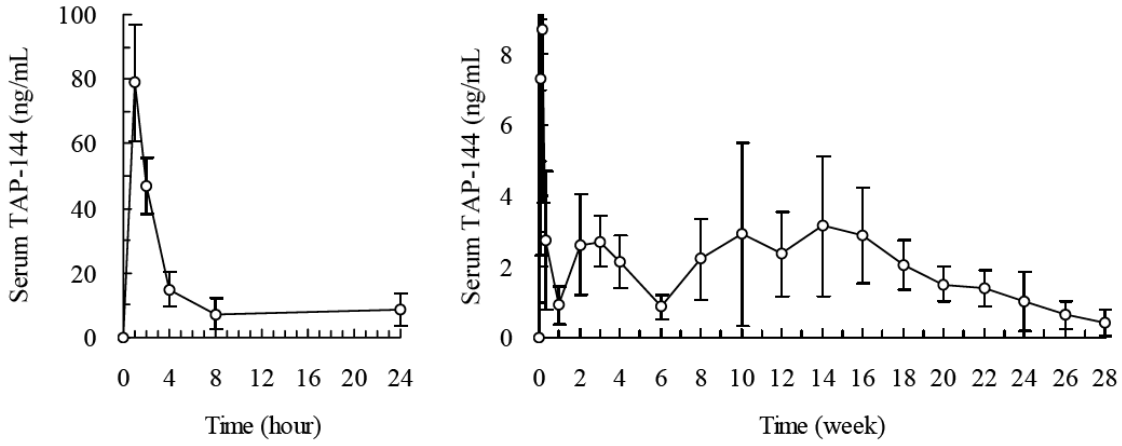
Dog:

Serum concentrations of TAP-144 (including the M-I) in male dogs after intramuscular injection at a single dose of 45 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-042)

Time				pre	H 1	H 2	H 4	H 8	D 1
Serum TAP-144 (ng/mL)			Mean	0.00	78.95	47.10	14.97	7.33	8.72
			SD	0.00	18.19	8.61	5.19	4.98	4.90
	D 2	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	2.75	0.93	2.63	2.73	2.14	0.87	2.22	2.92	2.36
SD	1.98	0.54	1.44	0.72	0.75	0.33	1.15	2.59	1.21
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	
Mean	3.15	2.88	2.06	1.51	1.40	1.02	0.64	0.42	
SD	2.00	1.35	0.69	0.50	0.53	0.84	0.41	0.37	

H: Hour, D: Day, W: Week
Each value represents the mean and SD (n=4).



Serum concentrations of TAP-144 (including the M-I) in male dogs after intramuscular injection at a single dose of 45 mg TAP-144.
Each point represents the mean ± SD
○: Lot No. OW6M-MC-SA-L02

Serum Concentrations of Testosterone

Rats:

Serum concentrations of testosterone in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

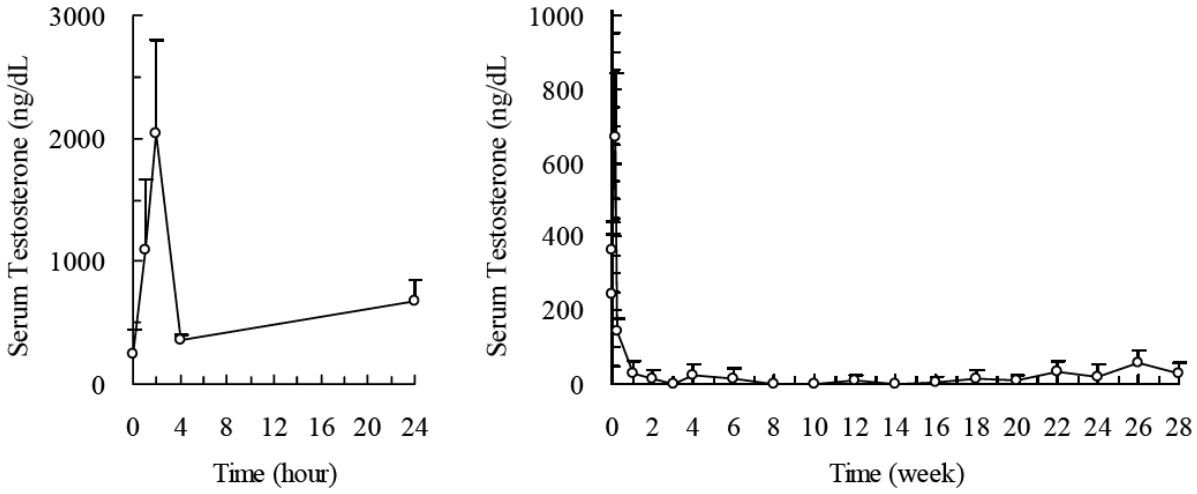
Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-053)

Time		pre	H 1	H 2	H 4	D 1	D 2
Serum testosterone (ng/dL)	Mean	242	1096	2032	366	672	143
	SD	197	564	764	42	171	35

	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	29	13	0	24	14	0	0	8
SD	34	26	0	28	28	0	0	15

	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	0	7	13	9	35	17	56	27
SD	0	14	26	17	28	34	38	31

H: Hour, D: Day, W: Week
Each value represents the mean and SD (n=4).



Serum concentrations of testosterone in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.
Each point represents the mean + SD (n=4)

Dog:

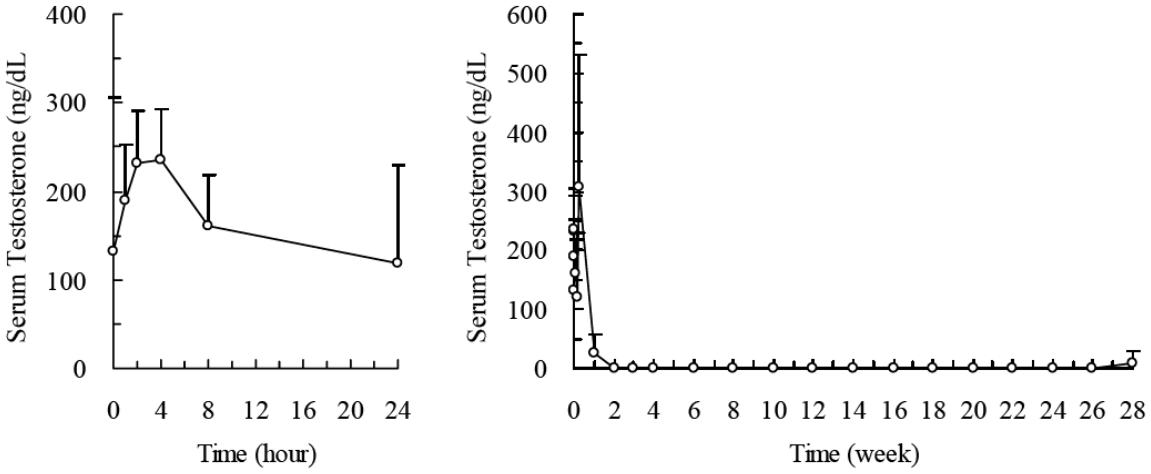
Serum concentrations of testosterone in male dogs after intramuscular injection at a single dose of 45 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-042)

Time				pre	H 1	H 2	H 4	H 8	D 1
Serum testosterone (ng/dL)			Mean	133	190	232	236	160	120
			SD	172	63	60	58	57	109
	D 2	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	309	26	0	0	0	0	0	0	0
SD	221	31	0	0	0	0	0	0	0
	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	
Mean	0	0	0	0	0	0	0	10	
SD	0	0	0	0	0	0	0	20	

H: Hour, D: Day, W: Week
Each value represents the mean and SD (n=4).

Each point represents the mean ± SD
○: Lot No. OW6M-MC-SA-L02



Serum concentrations of testosterone in male dogs after intramuscular injection at a single dose of 45 mg TAP-144.
Each point represents the mean + SD (n=4)
○: Lot No. OW6M-MC-SA-L02

Conclusion: Serum concentrations of TAP-144 were maintained at nearly constant levels for approximately 22 weeks after administration of 9 mg to rats subcutaneously and for 24 weeks after administration of 45 mg intramuscularly to dogs. Serum concentrations of testosterone were maintained at ≤ 35 ng/dL in rats and at ≤ 26 ng/dL in dogs from week 1 to week 24.

Study title: Pharmacokinetics and Pharmacodynamics of TAP-144 in Rats and Dogs after Administration of TAP-144-MC (6M PLA IP2) Powder

Study no.:	RD091340
Study report location:	4.2.2.7.1
Conducting laboratory and location:	(b) (4)
Drug, lot #, and % purity:	TAP-144-MC (6M PLA IP2) – pilot lot, OW6M-MC-SA-L02,
Vehicle:	Carboxmethylcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

Key Findings:

- No toxicologically significant PK differences were observed between the pilot lot (6M PLA IP2) and the clinical lot

Methods: The profile, pharmacokinetics, and pharmacodynamic of TAP-144-MC (6M PLA IP2) powder was investigated in this study. The pilot (OW6M-MC-SA-L02) and clinical (Z327802) lots were subcutaneously injected into the backs of male rats at a dose of 9 mg TAP-144-MC. Only the pilot lot was tested in dogs. TAP-144 and testosterone levels in the dog are reviewed in the previous study (TAP-144SR(6M)IP/ 00015.001R).

Dosing:

Species:	Sprague-Dawley rats Beagle dog
Number of animals:	Rats = Pilot lot: n = 4; Clinical lot: n = 5 Dog = Pilot lot: n = 4
Age/weight:	7 weeks/NA
Dose:	9 mg
Frequency:	Single dose
Route:	Rats: SC
Dose volume:	Rats: 0.4 mL; dogs: 1.3 mL
Vehicle:	Carboxmethylcellulose sodium, mannitol, polysorbate 80, water, and glacial acetic acid (pH adjustment)

Observations and times:

Rat: blood samples were collected from the jugular vein at pre-dose, hour 1, 2, 4, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Dog: blood samples were collected fore-arm at pre-dose, hour 1, 2, 4, 8, day 1, 2, week 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-dose.

Results: The following tables and figures are excerpted from Applicant's submission. Results from the pilot lot were also presented in the previous study (TAP-144SR(6M)IP/ 00015.001R).

Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. OW6M-MC-SA-L02 (Protocol No. ZALE2006-KS-053)

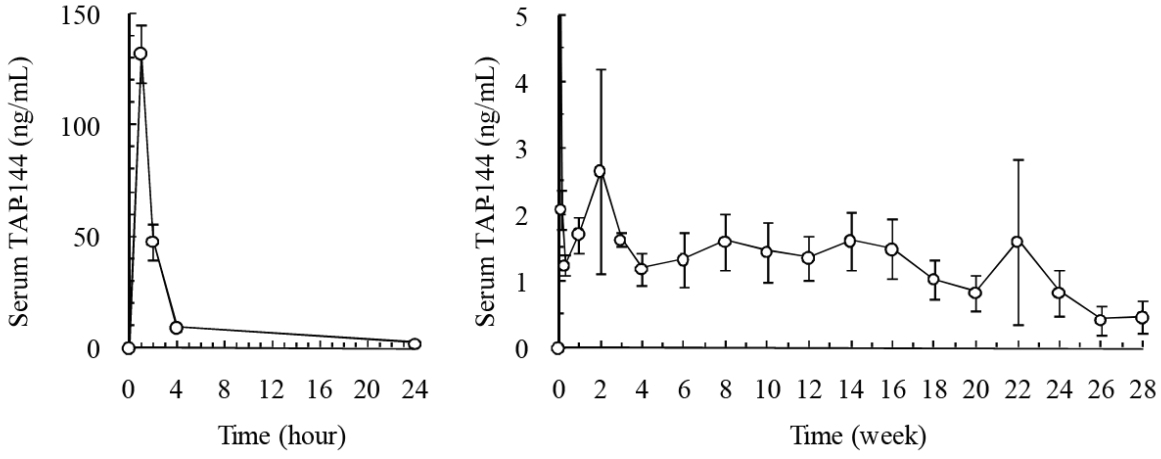
Time		pre	H 1	H 2	H 4	D 1	D 2
Serum TAP-144	Mean	0.00	132.63	48.00	9.31	2.10	1.25
(ng/mL)	SD	0.00	13.01	8.20	1.61	0.29	0.15

	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	1.72	2.67	1.64	1.20	1.34	1.61	1.46	1.36
SD	0.27	1.54	0.10	0.24	0.42	0.42	0.44	0.33

	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	1.61	1.49	1.04	0.84	1.61	0.84	0.43	0.47
SD	0.43	0.45	0.31	0.27	1.24	0.35	0.21	0.24

H: Hour, D: Day, W: Week

Each value represents the mean and SD (n=4).



Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.

Each point represents the mean ± SD

○: Lot No. OW6M-MC-SA-L02

Clinical lot:

Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144

Lot No. Z327802 (Protocol No. ZALE2007-KS-004)

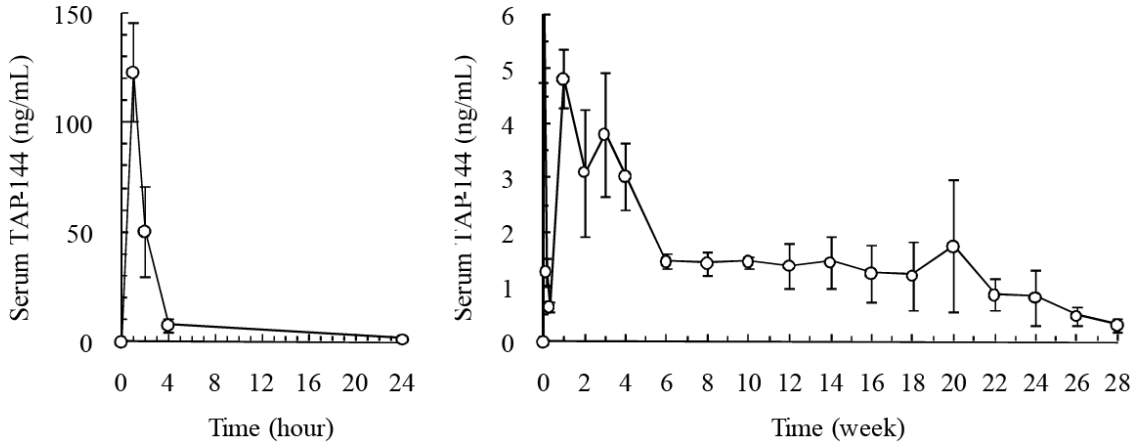
Time		pre	H 1	H 2	H 4	D 1	D 2
Serum TAP-144 (ng/mL)	Mean	0.00	123.59	50.68	7.56	1.29	0.64
	SD	0.00	22.45	20.48	2.78	0.26	0.10

	W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12
Mean	4.83	3.12	3.82	3.05	1.49	1.44	1.47	1.40
SD	0.54	1.17	1.15	0.62	0.13	0.21	0.11	0.42

	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28
Mean	1.47	1.27	1.22	1.76	0.87	0.82	0.48	0.31
SD	0.46	0.52	0.62	1.21	0.29	0.51	0.16	0.11

H: Hour, D: Day, W: Week

Each value represents the mean and SD (n=5).



Serum concentrations of TAP-144 (including the M-I) in male rats after subcutaneous injection at a single dose of 9 mg TAP-144.

Each point represents the mean ± SD

○: Lot No. Z327802

Conclusion: In the pilot lot, the serum concentrations of TAP-144 (including the M-I) in male rats elevated to 132.63 ng/mL one hour post-dose and decreased to 2.10 ng/mL about 24 hours post-dose. Serum concentrations were maintained 0.8 and 2.67 ng/mL for 24 weeks after dosing. In the clinical lot, serum concentrations of TAP-144 (including the M-I) in male rats elevated to 123.59 ng/mL one hour post-dose and decreased to 1.29 ng/mL. Levels decreased to 0.31 ng/mL by 28 weeks post-dose. No toxicologically significant differences were observed in the PK profiles between the pilot lot and the clinical lot.

6 General Toxicology

Studies reviewed under NDAs 19010 and 19732

7 Genetic Toxicology

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential. Information available in label approved on 6/2/2009.

8 Carcinogenicity

Information from label approved on 6/2/2009 is as follows:

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. 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.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Studies reviewed under NDA 19943. Information available in label approved on 6/2/2009.

9.2 Embryonic Fetal Development

Studies reviewed under NDA 19943. Information available in label approved on 6/2/2009.

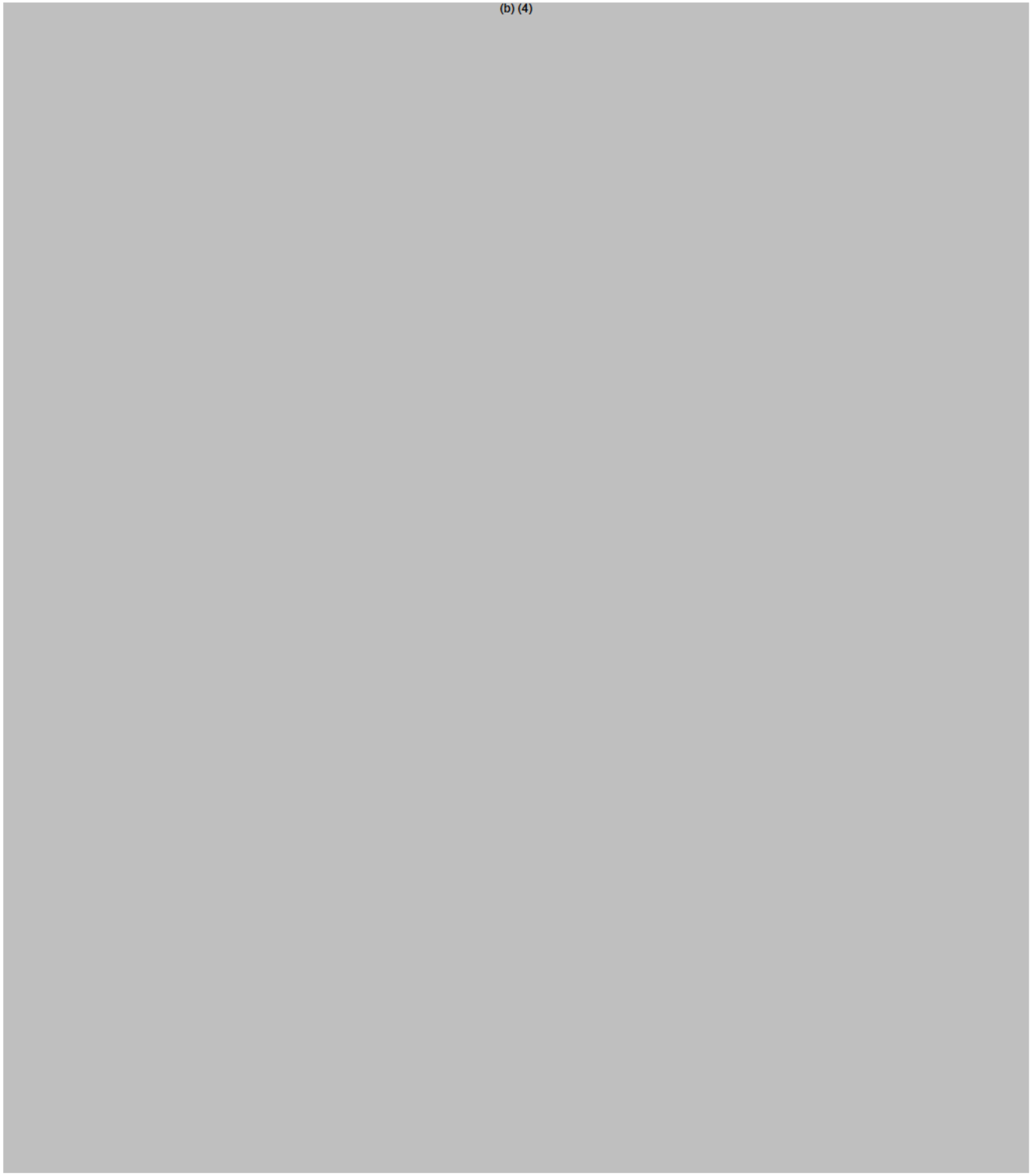
9.3 Prenatal and Postnatal Development

Studies reviewed under NDA 19943. Information available in label approved on 6/2/2009.

10 Special Toxicology Studies

10.1 Local Irritation

(b) (4)



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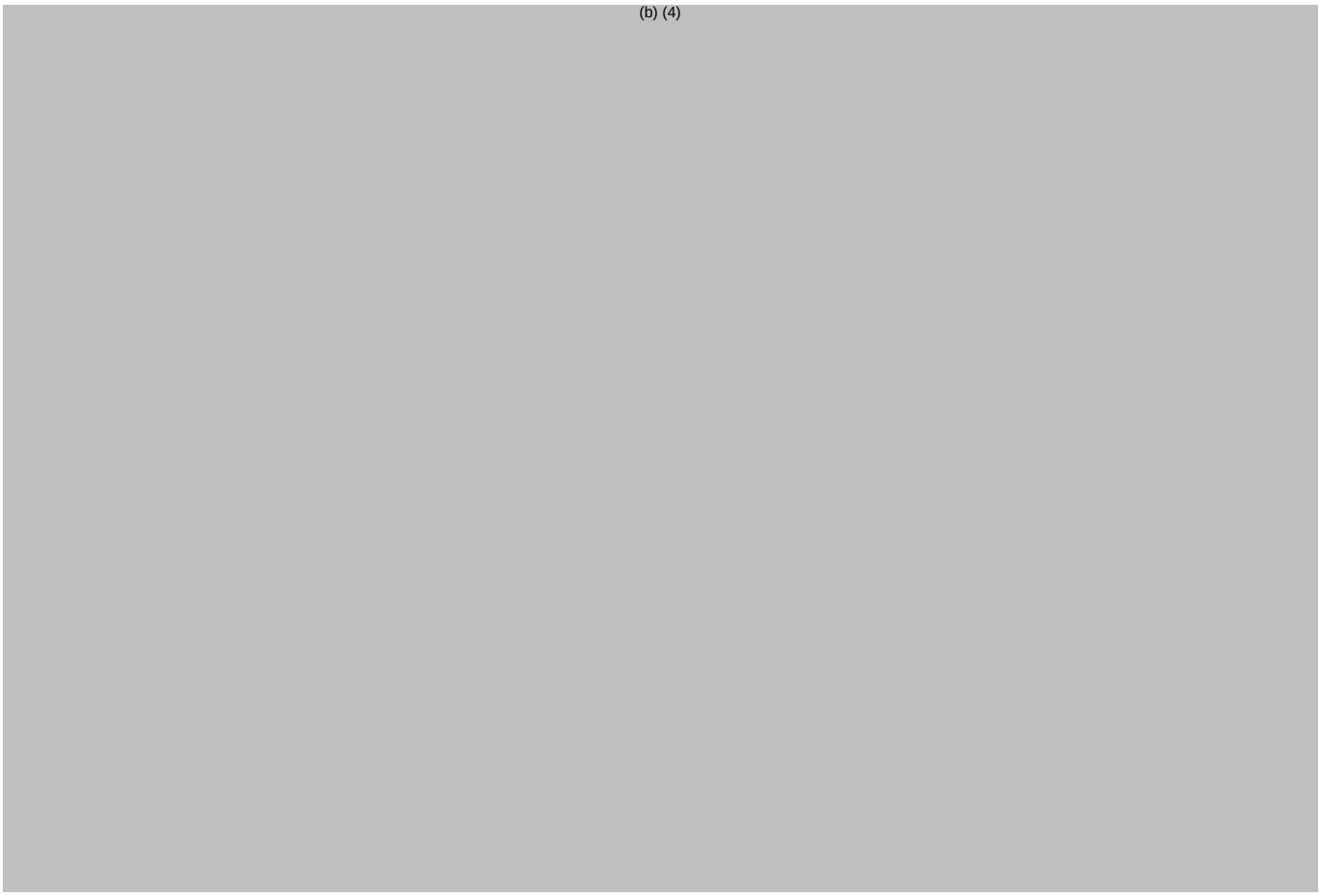

11 Integrated Summary and Safety Evaluation

Lupron Depot® is a gonadotropin releasing hormone agonist currently approved in 3 and 4 month formulations for the palliative treatment of advanced prostate cancer. This supplemental NDA was submitted to support the Applicant's proposed 45 mg dose of Lupron Depot intended to be administered at 6 month intervals. There are no nonclinical issues to preclude the approval of the new dosage form.

12 Appendix/Attachments

12.1 Labeling

The following section will contain the Applicant's proposed wording for the label followed by the FDA recommendation with a rationale for the recommended changes. Most changes were made to comply with 21CFR 201.57 on PLR content and formatting and recent practices. The label was not finalized during this submission period because of the potential for a complete response letter.

The Applicant's proposed:

(b) (4)

FDA recommends:

4 CONTRAINDICATIONS
4.1 HYPERSENSITIVITY
LUPRON DEPOT is contraindicated in individuals with a known hypersensitivity to GnRH agonists or any of the excipients in LUPRON DEPOT. Reports of anaphylactic reactions to GnRH agonists have been reported in the medical literature. 1,2

4.2 PREGNANCY
LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Expected hormonal changes that occur with LUPRON DEPOT treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].* LUPRON DEPOT is contraindicated in women who are or may become pregnant. If this drug is 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.

Rationale: The recommended changes are in compliance with CFR and current practices. Due to known embryofetal effects (lethality) associated with these drugs and the lack of benefit to pregnant women, Lupron Depot is assigned Category X.

The Applicant's proposed:

(b) (4)

FDA recommends:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see 'Contraindications' section'].*

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. Expected hormonal changes that occur with LUPRON DEPOT treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman. If this drug is 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.

Major fetal abnormalities were observed in rabbits after administration of the monthly formulation of LUPRON on day 6 of pregnancy at doses of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 times the human dose). This resulted in exposure to leuprolide throughout the period of organogenesis and to the end of gestation. Similar studies in rats did not demonstrate an increase in fetal malformations, however, there was

increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of LUPRON in rabbits and with the highest dose (0.024 mg/kg) in rats.

Rationale:

- The recommended changes are in compliance with CFR and current practices. Values were updated to represent the monthly formulation.
- Presently, hormonal agents such as GnRH agonists are assigned Pregnancy Category X, if indicated in male malignancies only. This is mainly due to known embryofetal effects (lethality) associated with these drugs and the lack of benefit to pregnant women.
- Human dose extrapolation values were updated based on monthly formulation.

A comment was sent to applicant regarding dose extrapolation:

(b) (4)

Result: Since labeling had not been completed, no changes were made to the label based on the Applicant's response to question 1.A. For question 1.B. Changes made to the label by the Applicant's were not reviewed.

FDA recommends the addition of:

8.3 Nursing Mothers

LUPRON DEPOT is not indicated for use in women [see Indications and Usage (1)]. It is not known whether LUPRON DEPOT is excreted in human milk. Because many drugs are excreted in human milk and because the effects of LUPRON DEPOT on lactation and/or the breast-fed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

Rationale: The recommended changes are in compliance with CFR and current practices.

The Applicant's proposed:

(b) (4)

FDA Recommends:

10 OVERDOSAGE

There is no experience of overdosage in clinical trials. In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose. If overdosage occurs, therapy should be discontinued immediately and the appropriate supportive and symptomatic treatment should be administered.

Rationale: The recommended changes are in compliance with CFR and current practices.

A comment was sent to applicant regarding dose extrapolation:

(b) (4)

Result: Since labeling had not been completed, changes were made to the label based on the Applicant's response were not reviewed.

The Applicant's proposed:

(b) (4)

FDA Recommends:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at daily doses of (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for u

p to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

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

Leuprolide may reduce male and female fertility. Administration of leuprolide acetate to male and female rats at dose of 0.024, 0.24, and 2.4 mg/kg monthly for 3 months (as low as 1/300 the estimated monthly human dose) caused atrophy of the reproductive organs, and suppression of reproductive function. These changes were reversible upon cessation of treatment. Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Rationale:

- The recommended changes are in compliance with CFR and current practices
- Human dose extrapolation values were updated based on monthly formulation
- Fertility information of leuprolide acetate was added

Comment was sent to Applicant regarding whether the mammalian test was to detect mutation and not chromosome aberration

(b) (4)

Result: Applicant has included information on chromosomal aberrations in the label.

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/s/

KIMBERLY R RINGGOLD
09/21/2010

HALEH SABER
09/21/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA/Serial Number:	20517/SE-030
Drug Name:	Lupron Depot® (Leuprolide Acetate)
Indication:	Palliative treatment of advanced prostate cancer
Applicant:	Abbott Laboratories
Date of Receipt:	December 17, 2010
PDUFA Goal Date:	June 17, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Drug Oncology Products
Clinical Team:	Katherine Delorenzo, M.D., Clinical Reviewer
	Virginia Maher, M.D., Clinical Team Leader
Project Manager:	Kim Robertson
Keywords:	Kaplan-Meier method; confidence interval; suppression rate

1. Conclusion and Recommendation

The applicant resubmitted the efficacy data and reanalysis results of leuprolide acetate 45-mg 6-month depot after receiving a Complete Response (CR) letter. The reanalysis result of the suppression rate 93.4% (95%CI: 89.2, 97.6) met the pre-specified criterion for a new formula of Lupron Depot® being successful that the lower bound of the one-sided 95% confidence interval of the suppression rate should be greater than 87%. The sensitivity analyses are consistent with the reanalysis of the primary endpoint. Whether the magnitude of suppression rate demonstrated in Study L-PC07-169 is clinically meaningful and sufficient to support the approval of leuprolide acetate 45-mg 6-month depot for the proposed indication is deferred to the clinical review team.

2. Introduction

This is an addendum to Dr. Xiaoping (Janet) Jiang's statistical review dated on September 2, 2010. The applicant originally submitted sNDA 20517/SE-030 on December 11, 2009. Efficacy data of leuprolide acetate 45-mg 6-month depot were collected from Study L-PC07-169 to support the proposed indication for the palliative treatment of advanced prostate cancer. For further details regarding the design, data analyses, and results of the study L-PC07-169, please refer to Dr. Jiang's statistical review (September 2, 2010).

During the FDA's review of December 11, 2009 submission, the Division of Scientific Investigations (DSI) conducted an audit of the Esoterix, the central laboratory for all laboratory analyses of the pivotal Study L-PC07-169. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from Study L-PC-07-169. As a result, FDA issued a Complete Response (CR) letter on the deficiencies that raised serious questions regarding the validity of the data needed to determine the efficacy and safety of Lupron Depot 45 mg 6-month. The Agency recommended that samples from the failed runs identified in the DSI audit of Esoterix should be reanalyzed such that efficacy and safety could be assessed based on adequate and reliable data. Based on the agreement reached between the Agency and the applicant during the December 6, 2010 Type A meeting, the applicant submitted the report of Reanalysis of Testosterone Concentrations from Study L-PC07-169 on December 17, 2010. For the simplicity, the submission dated on December 17, 2010 will be called resubmission through this addendum.

This addendum will be focused on review and evaluation of the results of the reanalysis and sensitivity analyses of the primary endpoint based on data from the testosterone reanalysis conducted by Abbott Bioanalysis in the resubmission.

3. Brief Overview of Study L-PC07-169

This section will provide a brief overview of the design and the original primary analysis results of Study L-PC07-169. For more details of review and evaluation of Study L-PC07-169, please refer to Dr. Xiaoping Jiang's statistical review of sNDA 20517/SE-030 (dated on September 2, 2010). The study L-PC07-169 was a phase 3, non-randomized, 48-week, multicenter clinical study conducted in men with prostate cancer. A total of 151 patients were enrolled to receive leuprolide acetate 45-mg 6-month depot. Patients participated in the study for approximately 14 months. The primary efficacy endpoint was the percentage of patients who had suppression of serum testosterone to, and maintenance at, medically castrate levels (≤ 50 ng/dL) from Week 4 to Week 48. Based on data from Study L-PC07-169 submitted

originally on December 11, 2009, the estimated percentage of the patients who had suppression of serum testosterone (≤ 50 ng/dL) (suppression rate) from Week 4 through Week 48 was 93.7 % (95% CI: 89.7; 97.7). Table 1 summarizes the original primary analysis.

Table 1. Original Primary Analysis

Total Number of Patients	150
Number of Patients Who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	141
Number of Patients Who Escaped Suppression (Failures)	9
Suppression Rate (two-sided 95% CI)	93.7 (89.7, 97.7)

Reviewer's Comments:

The applicant specified in the statistical analysis plan (SAP) that the formulation would be successful if the lower bound of a one-sided 95% confidence interval was greater than or equal to 87%. It was not clear if the Agency agreed with the pre-specified criterion for a formulation being successful before the completion of the study. The applicant used the two-sided 90% confidence interval to obtain the one-sided 95% confidence intervals in the submitted efficacy results including the reanalysis results. According to the Guidance ICH E9, the approach of setting Type I error rate for a one-sided test at an half of the conventional Type I error rate used in two-sided tests is preferable. Since the conventional Type I error rate used in two-sided tests is 5% in the regulatory settings, this reviewer has calculated and reported the two-sided of 95% confidence intervals for all analyses, including the applicant's Reanalysis of Primary Endpoint, in this addendum.

4. Reanalysis

Of the 3109 testosterone concentrations in the database from the original sNDA submission, there were a total of 403 (13.0% of 3109) samples that were identified from failed runs in pivotal Study L-PC07-169. Of those 403 identified samples, 369 had sufficient back-up samples available for reassay. For testosterone, only samples at or after Week 4 (window included data after Day 19) were applied to the primary efficacy endpoint of Study L-PC07-169. Per the Meeting Minutes dated on December 6, 2010, the Agency agreed with the applicant's approach of reanalyzing the primary endpoint using the new concentrations from the Abbott-validated Good Laboratory Practices (GLP) assay in place of the concentrations from the failed runs. Thus, the 403 new results of testosterone concentrations in the reanalysis of primary efficacy endpoint included 369 results from reassay by Abbott Bioanalysis and 34 missing results for the missing back-up samples.

Among 34 missing results, 29 samples corresponding to 22 patients were from Week 4 through Week 48. Of the 22 patients, only 4 patients had no available back-up sample at a key time point for assessment of testosterone suppression (Week 4, Week 24, or Week 48). Among the 4 patients, 2 patients did not have back-up samples at Week 4. Table 2 shows the submitted reanalysis of primary endpoint, percentage of patients who had suppression of serum testosterone <=50 ng/dL from Week 4 through Week 48.

Table 2. Applicant's Reanalysis of Primary Endpoint

Total Number of Patients	148
Number of Patients Who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	139
Number of Patients Who Escaped Suppression (Failures)	9
Suppression Rate (two-sided 90% CI)	93.6 (90.2, 97.0)
Suppression Rate (two-sided 95% CI)	93.6 (89.5, 97.6)

Reviewer's Comments:

FDA sent out a statistical request on February 09, 2011 to ask the applicant to 1) submit a list of 22 patients who were corresponding to a total of 29 samples with no back-up samples from Week 4 to Week 48, and 2) provide the details of handling the missing data when the back-up samples were not available in the primary efficacy analysis. In the response, the applicant clarified that a patient was excluded from the primary endpoint analysis if the data was missing at Week 4 (and the patient did not have a testosterone escape later) according to the original SAP, if the data was monotonically missing, then the patient would have been censored at the last available testosterone result if there were no escapes in testosterone suppression, and finally, if the data was in the midst of other non-missing testosterone results (but not at Week 4), the missing data would have been ignored. According to the submitted list of the 22 patients with no back-up samples, this reviewer found that 1) there were 2 patients who had no available back-up sample at Week 4 but did not have escapes (> 50 ng/dL) after Week 4, resulting in exclusion of the 2 patients from the reanalysis of the primary endpoint, 2) one patient had missing back-up sample at the Week 48, and 3) other 19 patients had missing back-up samples in the midst of other non-missing testosterone results (but not at Week 4). This reviewer has replicated the applicant's reanalysis results.

In the study, there were 4 patients who took megace, a concomitant medication which modulates serum testosterone, after Week 4. In addition, there was a patient who had a mix-up in samples with a non-study patient. The applicant did not justify the effect of megace in the submitted reanalysis of primary endpoint. Based on the data in the resubmission, this reviewer conducted the analysis by censoring the event days at the last available assessment of testosterone before the first days of using megace for the 4 patients (patient #281, 171, 187, and 118) and the last date of castrate testosterone prior to the mix-up for the patient (patient# 200) who had mix-up sample. Table 3 summarizes the analysis.

Table 3. Reanalysis of Primary Endpoint

Total Number of Patients	148
Number of Patients Who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	139
Number of Patients Who Escaped Suppression (Failures)	9
Suppression Rate (two-sided 90% CI)	93.4 (89.9, 96.9)
Suppression Rate (two-sided 95% CI)	93.4 (89.2, 97.6)

Reviewer's Comments:

FDA considers the analysis shown in Table 3 as the primary analysis of the suppression rate. As shown in Table 3, the primary re-analysis results of the suppression rate met the pre-specified criterion of being

successful for a new formula of Lupron Depot® that the lower bound of the 95% confidence interval (CI) of the suppression rate should be greater than 87%. Whether the magnitude of suppression rate demonstrated in Study L-PC07-169 is clinically meaningful is deferred to the clinical review team.

The applicant conducted 4 sensitivity analyses on the primary endpoint using different methods of imputing for missing back-up samples or treating 2 subjects with missing Week 4 back-up samples as failure at Week 4 or excluding 4 patients who took megace after Week 4 from the primary analysis population. Table 4 summaries the sensitivity analyses.

Table 4. Sensitivity Analyses

Approach to Sensitivity Analysis	N	Suppression Rate (%)	2-Sided 90% CI	2-Sided 95% CI
Treating 2 Subjects with Missing Week 4 Back-up Samples as Failure at Week 4	150	92.3	88.7, 96.0	88.0, 96.7
Excluding 4 subjects who took Megace	144	93.4	90.0, 96.9	89.3, 97.6
Data from missing back-up samples were imputed with the Esoterix data	150	93.7	90.3, 97.0	89.7, 97.7
Missing back-up samples were imputed with the average of the sample values immediately preceding and following the missing sample	150	93.7	90.3, 97.0	89.7, 97.7

Reviewer's Comments:

The sensitivity analyses shown in Table 4 are consistent with the primary analysis based on the resubmitted data. All sensitivity analyses conducted by both the applicant and this reviewer should be considered supportive or exploratory.

In the resubmission, the applicant also provided the reanalyzed results of two secondary efficacy endpoints: mean testosterone concentration at each visit and "acute-on-chronic" changes in testosterone from just prior to the second (Week 24) injection through the Visit 14 days after the second injection. Table 5 summaries the original and reanalyzed result of mean testosterone concentration at each visit.

Table 5. Mean Testosterone Concentration at Each Visit

	Serum Testosterone (ng/dL)					
	Original Analysis			Reanalysis		
Visit	N	Mean	SD	N	Mean	SD
Baseline[a]	151	432.9	176.29	151	434.6	175.06
Day 2	146	613.1	260.13	145	608.2	259.41
Day 8	146	468.2	200.01	145	467.5	200.13
Week 2	148	127.1	89.52	147	126.8	90.15
Week 4	150	16.0	8.54	148	15.9	8.48
Week 8	148	9.6	5.60	143	9.4	5.59
Week 14	148	9.2	5.60	139	9.1	5.39
Week 20	151	8.5	5.64	150	8.4	5.47
Week 24[b]	148	14.3	15.24	148	14.2	15.17
Week 26	138	9.0	5.50	135	9.1	5.52
Week 30	136	9.9	19.44	136	9.8	19.43
Week 34	133	13.0	47.70	131	13.0	48.06
Week 40	131	8.8	4.72	131	8.7	4.63
Week 46	129	8.8	5.27	129	8.7	5.20
Week 48	136	10.0	8.41	135	9.9	8.19
Final Visit	151	13.3	45.12	151	13.1	45.09

[Source: Reanalysis of Testosterone Concentrations from Study L-PC07169 Table 10]

Reviewer's Comments:

[1] *"Acute-on-chronic" changes in testosterone from just prior to the second (Week 24) injection through the Visit 14 days after the second injection was one of the secondary endpoints. However, the applicant did not define the level of luteinizing hormone (LH) or testosterone that represented an "acute-on-chronic" change in the levels. In addition, the applicant reiterated in the Meeting Minutes dated on December 6, 2010 that they did not intend to make labeling claims regarding LH (as part of the acute-on-chronic effect) and serum prostate-specific antigen (PSA) since the applicant did not plan to conduct repeat assays for LH and PSA concentrations. Therefore, this reviewer did not evaluate the reanalysis results of "acute-on-chronic" changes in testosterone.*

[2] *This reviewer has replicated the reanalysis results in Table 5.*

5. Conclusion

The reanalysis result of the suppression rate 93.4% (95%CI: 89.2, 97.6) met the pre-specified criterion for a new formula of Lupron Depot® being successful that the lower bound of the one-sided 95% confidence interval of the suppression rate should be greater than 87%. The sensitivity analyses are consistent with the reanalysis of the primary endpoint. Whether the magnitude of suppression rate demonstrated in Study L-PC07-169 is clinically meaningful is deferred to the clinical review team.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	20517/ SE-030
Drug Name:	Lupron Depot® (Leuprolide Acetate)
Indication:	Palliative treatment of advanced prostate cancer
Applicant:	Abbott Laboratories
Date(s):	Submission Date: December 11, 2009 PDUFA Date: October 10, 2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Drug Oncology Product
Clinical Team:	Gwynn Ison, M.D., Clinical Reviewer Virginia Maher, M.D., Team Leader
Project Managers:	CDR Dianne Hanner

Keywords: Kaplan-Meier method; Lower bound of confidence interval; Suppression rate

Table of Contents

Table of tables

Table of Figures

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The applicant submitted this supplement new drug application (sNDA) to seek an approval of the new formulation of Lupron Depot® (leuprolide acetate) for the palliative treatment of advanced prostate cancer. Based on the submitted efficacy data from Study L-PC07-169, the estimated percentage of the patients who had suppression of serum testosterone (≤ 50 ng/dL) (suppression rate) from Week 4 through Week 48 was 93.7 % (95% CI: 89.7; 97.7). The result of the suppression rate met the pre-specified criterion of being successful for a new formula of Lupron Depot® that the lower bound of the 95% confidence interval (CI) of the suppression rate should be greater than 87%. No statistical comparisons were conducted in the study and therefore no statistical inference can be drawn from the study. Whether the suppression rate demonstrated in Study L-PC07-169 is clinically meaningful and the inference regarding favorable benefit-risk profile for the use of the new formulation of Lupron Depot® (leuprolide acetate) for the palliative treatment of advanced prostate cancer are deferred to the clinical review team.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this sNDA submission, efficacy data were collected from Study L-PC07-169 to support a proposed formulation of Lupron Depot®, for the palliative treatment of advanced prostate cancer. Study L-PC07-169 was a phase 3, non-randomized, 48-week, multicenter clinical study conducted in men with prostate cancer. Based on in vitro testing and animal studies, two formulations (referred as Formulation A and Formulation B) were selected for evaluation in the study. The 2 formulations had different in vitro drug release characteristics over the dosing interval. The primary objective of the study was to evaluate the efficacy and safety of the 2 leuprolide acetate 45-mg 6-month depot formulations. Patients received a total of 2 injections of the same leuprolide acetate 45-mg 6-month depot formulation (Formulation A or Formulation B), administered 24 weeks apart. The first injection was administered on Day 1. The second injection was to be administered on Day 169 (i.e., Month 6 or Week 24). It was planned that the first 150 enrolled patients received leuprolide acetate 45 mg 6-month depot Formulation A and the next 150 enrolled patients received leuprolide acetate 45 mg 6-month depot Formulation B. A total of 151 patients were enrolled to receive Formulation A of leuprolide acetate 45-mg 6-month depot. Patients participated in the study for approximately 14 months. The submitted efficacy results were based on the 150 patients who received Formula A and had testosterone value at the visit of Week 4. The primary efficacy endpoint was the percentage of patients who had suppression of serum testosterone to, and maintenance at, medically castrate levels (≤ 50 ng/dL) from Week 4 to Week 48. The administration of Formulation B was stopped because of failures to adequately suppress testosterone to ≤ 50 ng/dL and escapes from testosterone suppression.

1.3 STATISTICAL ISSUES AND FINDINGS

Issues

- Per the statistical analysis plan (SAP), the lower bound of a one-sided 95% confidence interval must be greater than or equal to 87% in order for a formulation to be a success. The applicant obtained the lower bound of a one-sided 95% confidence interval through a two-sided 90% confidence interval. According to the ICH E9, the approach of setting Type I errors for one-sided tests at half the conventional Type I error used in two-sided tests is preferable. Since the conventional Type I error used in two-sided tests is 5% in the regulatory settings, this reviewer has calculated a two-sided of 95% confidence interval. The lower bounds of both confidence intervals were greater than 87%**.**

Findings

- A total of 151 patients were enrolled and received Formula A. The efficacy results were based on a total of 150 patients who received Formula A and had testosterone value at the visit of Week 4. As shown in Table A, the estimated percentage of patients who had testosterone suppression of serum testosterone (≤ 50 ng/dL) from Week 4 through Week 48 is 93.7 % with two-sided 95% confidence interval (89.7; 97.7). The lower bound of the two-sided 95% confidence interval of suppression rate was greater than 87% which was the pre-specified criterion of being successful for a new formula of Lupron Depot®. The results of sensitivity analyses of the primary endpoint were consistent with the results of the primary analysis.

Table A: Efficacy Results

Total Number of Patients	150
Number of Patients Who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	141
Number of Patients Who Escaped Suppression (Failures)	9
Percentage of Patients Who Had Suppression (two-sided 95% CI)	93.7 (89.7, 97.7)

2 INTRODUCTION

2.1 OVERVIEW

Lupron Depot® (leuprolide acetate) Injection is approved for the palliative treatment of advanced prostate cancer. In this supplement NDA submission; efficacy data were collected from Study L-PC07-169 to support a proposed new formulation of Lupron Depot®, for the palliative treatment of advanced prostate cancer. The proposed formulation provides for the administration of an injection of Lupron Depot®, containing 45 mg of leuprolide acetate, at six-monthly intervals.

2.2 DATA SOURCES

Data used for this review were from the electronic submission received in December 2009. The network path was "\\Cdsesub1\n020517\0038".

3 STATISTICAL EVALUATION

This review focuses on major efficacy results from 150 patients enrolled and received formula A in Study L-PC07-169.

3.1 EVALUATION OF EFFICACY

This section provides the brief description of Study L-PC07-169 based on the applicant's clinical study report, the protocol and statistical analysis plan. Any difference between the clinical study report and the protocol is also discussed in this section.

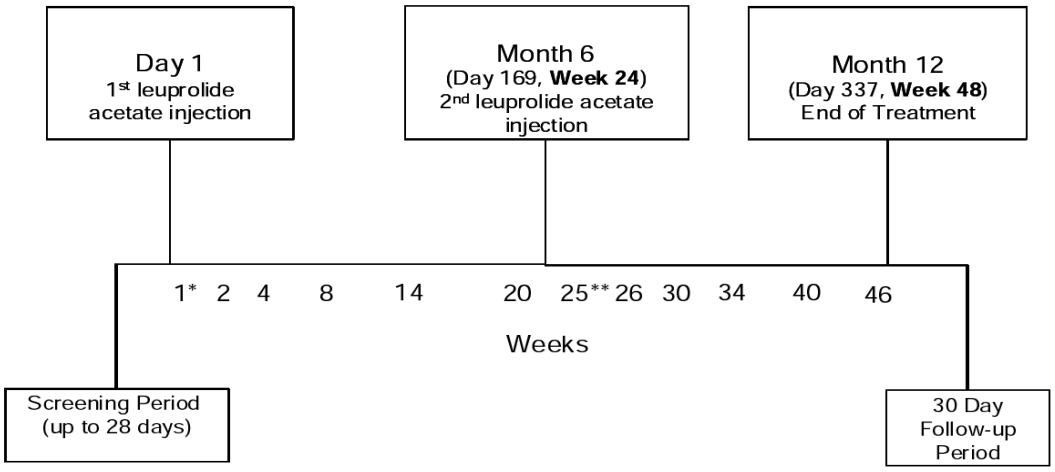
3.1.1 STUDY OBJECTIVES

The primary objective of study L-PC07-169 was to evaluate the efficacy and safety of 2 new leuprolide acetate 45-mg 6-month depot formulations over 48 weeks. Each formulation was to be delivered as 2 single injections 24 weeks apart, in patients with prostate cancer.

3.1.2 STUDY DESIGN

L-PC07-169 was designed as a Phase 3, non-randomized, 48-week, 2-arm sequential, multicenter clinical study conducted in patients with prostate cancer. With a total of 2 injections, administered 24 weeks apart, the first 150 enrolled patients received leuprolide acetate 45 mg 6-month depot Formulation A and the next 150 enrolled patients received leuprolide acetate 45 mg 6-month depot Formulation B. The first study drug injection cycle began on Day 1, the day of the first injection and ended on Day 169 (Week 24). The second study drug injection cycle began on Day 169, the day of the second study drug injection, and ended on Day 337 (Week 48). A total of 20 visits were planned for each subject (Screening Visit, 18 treatment period visits, and a post-treatment follow-up visit). The study schematic is shown in Figure 1.

Figure 1: Study Design Schematic



* During Week 1, visits to take place on Days 1, 2, and 8.

** During Week 25, visits to take place on Days 170, 171, and 176.

3.1.3 EFFICACY ENDPOINTS

3.1.3.1 Primary Efficacy Endpoint

The primary endpoint was the percentage of patients who had the suppression of serum testosterone (≤ 50 ng/dL) from Week 4 through Week 48. A patient was considered to have failed testosterone suppression if suppression did not occur by Day 32 (+4 days from scheduled Week 4 visit) or he "escapes" suppression (the escape was defined to have occurred on the day that the first testosterone value above 50 ng/mL occurred) by Week 48. Week 48 was defined as between Day 337 and Day 340 (+7 days from scheduled Week 48 visit), inclusive. Patients whose last testosterone value before Day 32 was > 50 ng/dL were to be defined as having failed testosterone suppression on Day 32.

3.1.3.2 Secondary Efficacy Endpoints

In Study L-PC07-169, the secondary efficacy endpoints were change from baseline in PSA levels at each treatment visit; mean testosterone concentrations at each treatment visit; and "acute-on-chronic" changes in testosterone and LH levels from just prior to the second (Week 24) injection through the Visit 14 days post-second injection.

3.1.4 SAMPLE SIZE CONSIDERATIONS

Assuming that the true percentage of patients suppressed testosterone through Week 48 was 93%, then a sample size of 150 patients would yield approximately 89% chance to achieve a one-sided 95% lower confidence bound greater than or equal to 87%, in order for a formulation to be a success. It was planned that the first 150 patients enrolled to receive Formulation A of leuprolide acetate 45 mg 6-month depot and the next 150 patients enrolled to receive Formulation B of leuprolide acetate 45 mg 6-month depot.

3.1.5 PRIMARY ANALYSES

The primary analysis was to estimate the percentage of patients suppressed testosterone from Week 4 through Week 48 was obtained by using the standard error from the Kaplan-Meier method for right censored observations. A patient who had onset of testosterone suppression by Day 32 and had no escapes from suppression was censored on the day that the final testosterone value was obtained (or on Day 337 if in the Week 48 window). For a patient who was suppressed by Day 32 and escapes from suppression by Week 48 (i.e., escape must occur between Day 33 and Day 340, inclusive), the escape (failure) was defined to have occurred on the day the first testosterone value above 50 ng/mL occurred. A patient was considered to have a failure on Day 32 if one of the followings occurred.

- suppression did not occur by Day 32 (+4 days from scheduled Week 4 visit)
- last testosterone on or before Day 32 was > 50 ng/dL was defined to have failed testosterone suppression on Day 32 (whether or not suppressed at a previous testosterone value)
- no Week 4 measurement of testosterone (between Day 20 and Day 32 per Section 4.2) and later had an escape

3.1.6 EFFICACY RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

This section summarizes the applicant's major efficacy results from a total of 150 patients who received Formula A and had testosterone value for Week 4 in Study L-PC07-169. In addition, this section provides the statistical reviewer's comments, including FDA analysis results performed by this reviewer.

Reviewer's Comments:

[1] Per the applicant, administration of Formulation B was stopped because of failures to adequately suppress testosterone to ≤ 50 ng/dL and escapes from testosterone suppression. Patients who had not yet received their second injection of Formulation B completed procedures through Week 24 and were discontinued. Patients who had received their second injection of Formulation B completed the study. Per the applicant, the results for Formulation B would be provided in a separate interim report that includes all data collected through 19 June 2009 and in a final report upon completion of all patients who received Formulation B.

[2] Per the statistical analysis plan, ITT population was defined as all patients who received at least 1 dose of study drug, had at least 1 post baseline measurement of the appropriate parameter, and who did not use prohibited treatment that lowered testosterone levels or blocked its action during the first 32 days following the initiation of study drug. All 151 enrolled patients who received Formula A were included ITT population. One patient was excluded from the primary efficacy analysis because the patient had no testosterone value for Week 4.

3.1.6.1 Disposition of Patients

Table 1 shows summary of patient disposition. Among 151 patients who enrolled and received at least 1 injection of leuprolide acetate 45-mg 6-month depot Formulation A, one hundred thirty-four Patients (88.7%) completed the study. Please see the discontinuation reasons for the 17 Patients who discontinued from Table 1.

Table 1: Summary of Patient Disposition

Final Status/Reason for Discontinuation	Number (%) of Patients (N=151)		
	All Patients	Received Only 1 Injection	Received 2 Injections
Completed	134 (88.7)	0	134 (88.7)
Discontinued	17 (11.3)	12 (7.9)	5 (3.3)
Primary reason for discontinuation			
Adverse event	7 (4.6)	7 (4.6)	
Withdrew consent	5 (3.3)	5 (3.3)	
Protocol violation	1 (0.7)	0	1 (0.7)
Serum testosterone not at therapeutic level	1 (0.7)	0	1 (0.7)
Disease progression	1 (0.7)	0	1 (0.7)
Other	2 (1.3)	0	2 (1.3)

3.1.6.2 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics of 151 patients are shown in Tables 2 and 3.

Table 2: Summary of Demographic

Characteristic		ITT Population for Primary Efficacy Endpoint N = 150	Safety Population N = 151
Race, n (%)	White	118 (78.7)	119 (78.8)
	Black or African American	30 (20.0)	30 (19.9)
	Asian	1 (0.7)	1 (0.7)
	Multi race[a]	1 (0.7)	1 (0.7)
Ethnicity, n (%)	Hispanic or Latino	7 (4.7)	7 (4.6)
	Not Hispanic or Latino	143 (95.3)	144 (95.4)
Age, n (%)	< 65 yrs	18 (12.0)	18 (11.9)
	≥ 65 yrs	132 (88.0)	133 (88.1)
Age, yrs	Mean (SD)	74.9 (8.44)	74.9 (8.42)
	Median	76.0	76.0
	Range	48.0 – 92.0	48.0 – 92.0
Weight, kg	Mean (SD)	84.9 (13.98)	85.0 (14.00)
	Median	84.0	84.0
	Range	49.0 – 129.4	49.0 – 129.4
Height, cm	Mean (SD)	175.2 (7.44)	175.1 (7.42)
	Median	175.3	175.3
	Range	149.9 – 193.0	149.9 – 193.0
BMI, kg/m^2	Mean (SD)	27.6 (4.18)	27.7 (4.21)
	Median	27.3	27.3
	Range	18.0 – 41.5	18.0 – 41.5

[Source: Clinical Study Report Table 14]

Table 3: Summary of Baseline Characteristics

Characteristic	ITT Population for Primary Efficacy Endpoint N = 150
Time since first histological diagnosis of prostate cancer, yrs	N = 149
Mean (SD)	4.6 (4.8)
Range	0.0 – 19.6
Time since first histological diagnosis of prostate cancer, n (%)	N = 149
< 1 year	56 (37.6)
1 to < 2 years	10 (6.7)
2 to < 3 years	8 (5.4)
3 to < 4 years	6 (4.0)
4 to < 5 years	9 (6.0)
5 to < 10 years	37 (24.8)
10 to < 20 years	23 (15.4)
Prostate cancer staging by NCI stage based on TNM classification,[a] n (%)	N = 144
II	103 (71.5)
III	20 (13.9)
IV	21 (14.6)
Testosterone, ng/dL	N = 150
Mean (SD)	433.1 (176.86)
Median	399.5
Range	67.0[b] – 1060.0
LH, mIU/mL	N = 150
Mean (SD)	7.2 (6.50)
Median	5.6
Range	0.1 – 45.0
PSA, ng/mL	N = 148
Mean (SD)	35.3 (137.33)
Median	9.8
Range	0.2 – 1517.3

[Source: Clinical Study Report Table 15]

Table 4: Summary of Baseline Characteristics (Continued)

Characteristic	ITT Population for Primary Efficacy Endpoint N = 150
PAP, ng/mL	N = 150
Mean (SD)	8.8 (42.29)
Median	1.9
Range	0.2 – 454.0
Gleason score category, n (%)	N = 144
4	3 (2.1)
5	1 (0.7)
6	46 (31.9)
7	53 (36.8)
8	28 (19.4)
9	13 (9.0)
ECOG score	N = 150
0	123 (82.0)
1	25 (16.7)
2	2 (1.3)

[Source: Clinical Study Report Table 16]

3.1.6.3 Primary Endpoints

The primary endpoint was the percentage of patients who had the suppression of serum testosterone (≤ 50 ng/dL) from Week 4 through Week 48. Table 5 shows the primary analysis results by using the standard error from the Kaplan-Meier method for right censored observations.

Table 5: Efficacy Results

Total Number of Patients	150
Number of Patients Who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	141
Number of Patients Who Escaped Suppression (Failures)	9
Applicant's Result: **Percentage of Patients Who Had Suppression (two-sided 90% CI)**	93.7 (90.3, 97.0)
FDA's Result (based on applicant data): **Percentage of Patients Who Had Suppression (two-sided 95% CI)**	93.7 (89.7, 97.7)

Reviewer's Comments:

[3] Per the statistical analysis plan (SAP), the lower bound of a one-sided 95% confidence interval must be greater than or equal to 87% in order for a formulation to be a success. The applicant obtained the lower bound of a one-sided 95% confidence interval through a two-sided 90% confidence interval. According to the ICH E9, the approach of setting Type I errors for one-sided tests at half the conventional Type I error used in two-sided tests is preferable. Since the conventional Type I error used in two-sided tests is 5% in the regulatory settings, this reviewer has calculated a two-sided of 95% confidence interval. As shown in Table 5, the lower bounds of both confidence intervals were greater than 87%.

[4] There were 15 patients who dropped out from the study. The applicant censored 14 of them at their drop-out dates in the primary analysis. Having discussed with FDA clinical review team, this reviewer conducted a sensitivity analysis by considering the 14 patients (see Appendix 1 for the patient IDs) as having a failure at the drop-out dates. As shown in Table 6, the estimated percentage of patients who had suppression of serum testosterone $\leq$ 50 ng/dL from week 4 through week 48 was less than 87%, so was the lower bound of its two-sided 95% confidence interval.

Table 6: Result of Sensitivity Analysis 1

Total Number of Patients	150
Number of Patients who had Suppression of Serum Testosterone $\leq$ 50 ng/dL from Week 4 through Week 48	127
Number of Patients Who Escaped Suppression (Failures)	23
Percentage of Patients Who Had Suppression (two-sided 95% CI)	84.7 (78.9, 90.4)

[5] Among the patients who received Formula A, there were 4 patients who received a protocol prohibited medicine which might affect their testosterone levels. This reviewer performed another sensitivity analysis by censoring the event dates of these 4 patients (see Appendix 2 for the patient IDs) on their dates of starting the prohibited medicine. As shown in Table 7, the result of this sensitivity analysis is consistent with the result of the primary analysis.

Table 7: Result of Sensitivity Analysis 2

Total Number of Patients	150
Number of Patients who had Suppression of Serum Testosterone $\leq$ 50 ng/dL from Week 4 through Week 48	141
Number of Patients Who Escaped Suppression (Failures)	9
Percentage of Patients Who Had Suppression (two-sided 95% CI)	93.6 (89.5, 97.6)

[6] This reviewer conducted a sensitivity analysis by using Clopper and Pearson Exact method and considering patients who had the suppression of serum testosterone ($\leq$ 50 ng/dL) from

Week 4 through Week 48 as responders. As shown in Table 8, the result of this sensitivity analysis is consistent with the result of the primary analysis.

Table 8: Result of Sensitivity Analysis 3

Total Number of Patients	150
Number of Patients who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	141
Number of Patients Who Escaped Suppression (Failures)	9
Percentage of Patients Who Had Suppression (two-sided 95% CI)	94.0 (89.0, 97.0)

3.1.6.4 Secondary Endpoints

The secondary endpoints in the study included mean testosterone concentration at each treatment visit and change from baseline in PSA levels at each treatment visit. The results of the secondary endpoints are shown in Table 9, Table 10 and Figure 1.

Table 9: Summary Testosterone Value at Each Visit

		Testosterone Value (ng/dL)		
Visit	**Number of Patients**	**Mean**	**SD**	**Range**
Baseline	151	432.9	176.3	67-1060
Day 2	146	613.1	260.1	57-1480
Day 8	146	468.2	200	68-1180
Week 2	148	127.1	89.5	16-652
Week 4	150	16	8.5	3-69
Week 8	148	9.6	5.6	3-42
Week 14	148	9.2	5.6	3-36
Week 20	151	8.5	5.6	3-39
Prior to 2nd Injection	136	10.8	11.7	3-105
2 hours After 2nd Injection	129	9.1	9.9	3-78
4 hours After 2nd Injection	126	9.8	11.6	3-98
8 hours After 2nd Injection	123	9.7	12.9	3-96
1 Day After 2nd Injection	138	10.8	10	3-74
2 Days After 2nd Injection	136	10.9	9.9	3-70
3-10 Days After 2nd Injection	137	10	7.9	3-53
11-17 Days After 2nd Injection	136	8.8	5.6	3-32
Week 24	148	14.3	15.2	3-105
Week 26	138	9	5.5	3-32
Week 30	136	9.9	19.4	3-227
Week 34	133	13	47.7	3-555
Week 40	131	8.8	4.7	3-23
Week 46	129	8.8	5.3	3-36
Week 48	136	10	8.4	3-58
Final Visit	151	13.3	45.1	3-555

Figure 2: Plot of Mean Testosterone vs. Visit

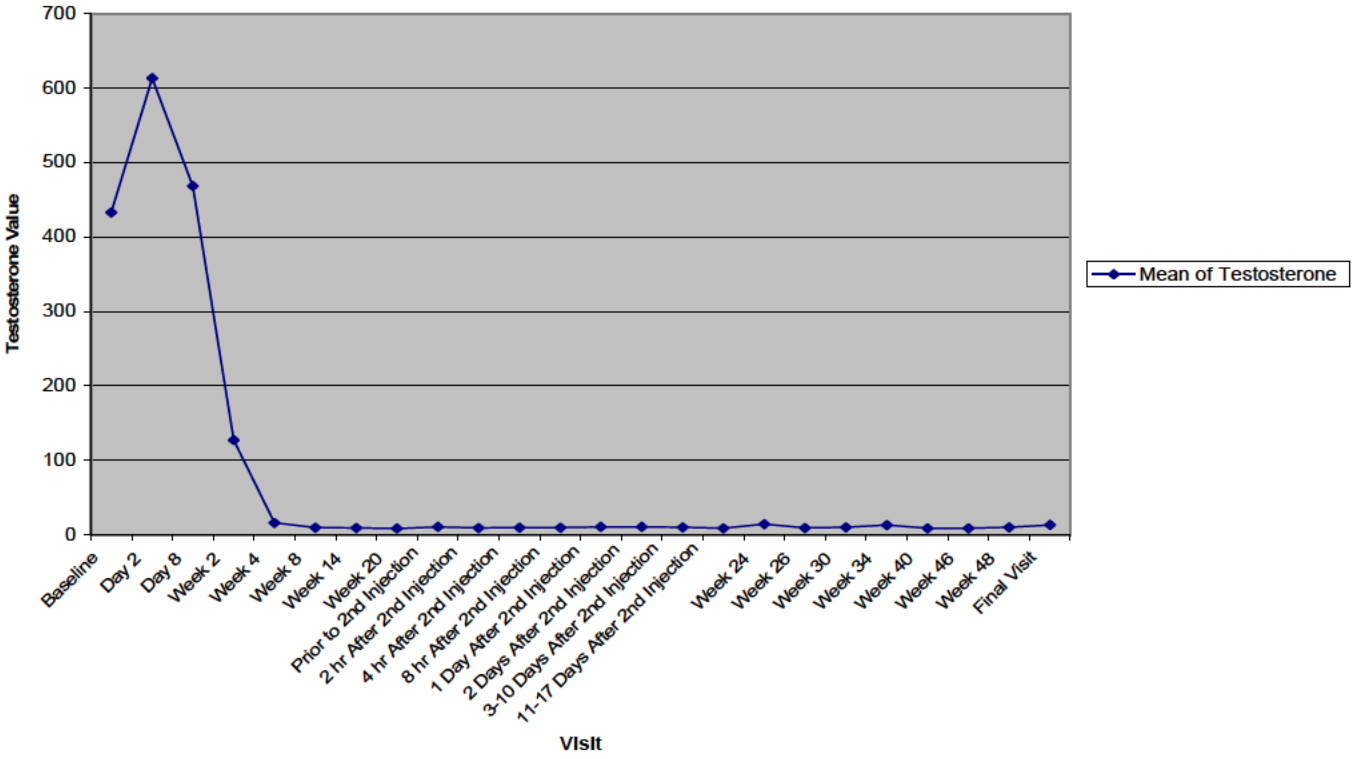


Table 10: PSA Categorical Changes from Baseline

		Number (%) of Subjects				
		Serum PSA Decrease from Baseline				Serum PSA
Visit	N	> 95%	90% to 95%	50% to < 90%	< 50%	Increase from Baseline
Baseline PSA > 4 ng/mL						
Day 8	110	0	0	1 (0.9)	33 (30.0)	76 (69.1)
Week 14	111	48 (43.2)	22 (19.8)	41 (36.9)	0	0
Week 24	109	63 (57.8)	15 (13.8)	29 (26.6)	1 (0.9)	1 (0.9)
Week 30	100	63 (63.0)	14 (14.0)	23 (23.0)	0	0
Week 40	98	65 (66.3)	13 (13.3)	17 (17.3)	1 (1.0)	2 (2.0)
Week 48	101	64 (63.4)	18 (17.8)	17 (16.8)	0	2 (2.0)
Final Visit	112	71 (63.4)	17 (15.2)	20 (17.9)	1 (0.9)	3 (2.7)
Baseline PSA 0 – 4 ng/mL						
Day 8	36	0	0	1 (2.8)	10 (27.8)	25 (69.4)
Week 14	37	21 (56.8)	6 (16.2)	8 (21.6)	2 (5.4)	0
Week 24	37	29 (78.4)	2 (5.4)	5 (13.5)	1 (2.7)	0
Week 30	34	23 (67.6)	5 (14.7)	5 (14.7)	1 (2.9)	0
Week 40	31	24 (77.4)	4 (12.9)	2 (6.5)	1 (3.2)	0
Week 48	32	24 (75.0)	3 (9.4)	4 (12.5)	1 (3.1)	0
Final Visit	37	28 (75.7)	3 (8.1)	5 (13.5)	1 (2.7)	0

[Source: Clinical Study Report Table 24]

Reviewer's Comment:

As shown in Table 9, there was a patient (subject Id 160) whose T-value in the final visit was 555 ng/dL. After excluding this patient, the range of final visit was 3.0-58.0.

3.2 EVALUATION OF SAFETY

Please refer to FDA clinical review for safety evaluation of leuprolide acetate 45-mg 6-month depot Formulation A.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section provides the reviewer's results of subgroup analyses.

4.1 AGE AND RACE

Since there were 18 (12%) patients who were less than 65 years old in the study, this reviewer performed the subgroup analysis by age for patients who were greater than 75 years old and less than or equal to 75 years old and patients who were greater than 75 years old. Table 11 shows the summary of subgroup analyses by age and race.

Table 11: Results of Subgroup Analyses

Subgroup	Age <75	Age >=75	Caucasian	Black
Total Number of Patients	67	83	118	30
Number of Patients who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	59	82	113	26
Number of Patients Who Escaped Suppression (Failures)	8	1	5	4
Percentage of Patients Who Had Suppression (Two-sided 95% CI)	87.6 (79.5,95.6)	98.8 (96.4, 100.0)	95.5 (91.6, 99.4)	86.5 (74.3, 98.8)

Reviewer's Comment:

The results of the subgroup analyses are consistent with the results of the overall population; especially the treatment effect in subgroup of patients who were older than 75 years seems more promising. However, the results of the subgroup analyses in Table 11 are considered as exploratory.

5 SUMMARY AND CONCLUSIONS

5.1 ISSUES AND FINDINGS

The applicant claimed that Formulation A of leuprolide acetate 45-mg 6-month depot met the pre-specified criterion for the formulation to be efficacious, i.e. the lower bound of the one-sided 95% confidence interval of the estimated percentage of patients who had serum testosterone suppression to values ≤ 50 ng/dL from Week 4 through Week 48 was greater than 87%. After complete review, this reviewer has identified some issues and has the following findings.

Issues

- Per the statistical analysis plan (SAP), the lower bound of a one-sided 95% confidence interval must be greater than or equal to 87% in order for a formulation to be a success. The applicant obtained the lower bound of a one-sided 95% confidence interval through a two-sided 90% confidence interval. According to the ICH E9, the approach of setting Type I errors for one-sided tests at half the conventional Type I error used in two-sided tests is preferable. Since the conventional Type I error used in two-sided tests is 5% in the regulatory settings, this reviewer has calculated a two-sided of 95% confidence interval. The lower bounds of both confidence intervals were greater than 87%.

Findings

- A total of 151 patients were enrolled and received Formula A. The efficacy results were based on a total of 150 patients who received Formula A and had testosterone value at the visit of Week 4. As shown in Table 12, the estimated percentage of patients who had testosterone suppression of serum testosterone (≤ 50 ng/dL) from Week 4 through Week 48 is 93.7 % with two-sided 95% confidence interval (89.7; 97.7). The lower bound of the two-sided 95% confidence interval of suppression rate was greater than 87% which met the pre-specified criterion of being successful for a new formula of Lupron Depot®. The results of sensitivity analyses of the primary endpoint were consistent with the results of the primary analysis.

Table 12: Efficacy Results

Total Number of Patients	150
Number of Patients Who had Suppression of Serum Testosterone ≤ 50 ng/dL from Week 4 through Week 48	141
Number of Patients Who Escaped Suppression (Failures)	9
Percentage of Patients Who Had Suppression (two-sided 95% CI)	93.7 (89.7, 97.7)

5.2 CONCLUSIONS AND RECOMMENDATIONS

Based on the efficacy data from Study L-PC07-169 submitted in this sNDA, the estimated percentage of the patients who had suppression of serum testosterone (≤ 50 ng/dL) (suppression rate) from Week 4 through Week 48 was 93.7 % (95% CI: 89.7; 97.7). The result of the suppression rate met the pre-specified criterion of being successful for a new formula of Lupron Depot® that the lower bound of the one-sided 95% confidence interval (CI) of the suppression rate should be greater than 87%. No statistical comparisons were conducted in the study and therefore no statistical inference can be drawn from the study. Whether the suppression rate demonstrated in Study L-PC07-169 is clinically meaningful and the inference regarding favorable benefit-risk profile for the use of the new formulation of Lupron Depot® (leuprolide acetate) for the palliative treatment of advanced prostate cancer are deferred to the clinical review team.

6 APPENDICES

Appendix 1: The list of patient IDs of the 14 patients who dropped out early from the study. In FDA sensitivity analysis 1, the 14 patients were considered as having failed treatment at the drop-out dates.

Subject ID
206
257
264
171
196
125
233
283
187
302
138
202
219
211

Appendix 2: The list of patient IDs of 4 patients who received a protocol prohibited medicine which might affect their testosterone levels. In FDA sensitivity analysis 2, these 4 patients were considered as having failed treatment at the drop-out dates.

Subject ID
118
171
187
281

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Xiaoping (Janet) Jiang, Ph.D.

Concurring Reviewer: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director

cc:
OODP/DDOP/ G. Ison
OODP/DDOP/ V. Maher
OB/DBV/S. Tang
OB/DBV/R. Sridhara
OB/L. Patrician

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

XIAOPING JANET J JIANG
09/02/2010

SHENGHUI TANG
09/02/2010

RAJESHWARI SRIDHARA
09/02/2010

STATISTICS FILING CHECKLIST FOR NDA20517S30

NDA Number: 20517S30 **Applicant: Abbott Laboratories**

Stamp Date: November 24, 2009 **Drug Name: Leuprolide Acetate**

NDA/BLA Type: Supplement NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			×	
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			×	
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			×	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

STATISTICS FILING CHECKLIST FOR NDA20517S30

Xiaoping (Janet) Jiang	02/12/2010
Reviewing Statistician	Date
Kun He	02/12/2010
Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

XIAOPING JANET J JIANG
02/12/2010

KUN HE
02/12/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

August 17, 2010

NDA: 20-517/S-030

Drug Product Name
Proprietary: Lupron Depot
Non-proprietary: leuprolide acetate for depot suspension
Drug Product Classification: N/A
Review Number: #3

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
Aug 11, 2010	Aug 11, 2010	n/a	Aug 17, 2010

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
Dec 11, 2009	1	April 6, 2010
Apr 2, 2010	1	April 6, 2010
June 3, 2010	2	July 2, 2010

Applicant/Sponsor
Name: Abbott Endocrine, Inc. (Abbott Laboratories)
Address: 200 Abbott Park Road; D-PA76/AP30-1NE; Abbott Park, IL 60064
Representative: Natalie Tolli, Director, GPRA
Telephone: 847-935-8099

Name of Reviewer: John Arigo, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA PAS amendment

2. SUBMISSION PROVIDES FOR: Change in formulation. Inclusion of a 45 mg 6 month injection. The only change relevant to microbiology is the addition of stearic acid as an excipient and a (b) (4) . These items ar (b) (4)).

3. MANUFACTURING SITE:

Site	Establishment Registration Number	Function(s)
(b) (4)		
Abbott Laboratories 100 and 200 Abbott Park Rd. Abbott Park, IL 60064-3500	1415939	Packaging

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 45 mg of sterile powder in a dual chamber syringe along with a sterile vehicle. IM injection – single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Palliative Treatment of Advanced Prostatic Cancer.

B. SUPPORTING/RELATED DOCUMENTS: none

C. REMARKS: Electronic submission. A telephone conference was held between J. Arigo and Lisa Marshall of Abbott Labs on July 27, 2010. The two deficiencies were faxed to Mrs. Marshall on July 27, 2010 for forwarding to Takeda. The deficiencies were also sent via official letter.

filename: N020517S030R1a2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Manufacturing processes are contained in DMF 9365. (b) (4)

B. Brief Description of Microbiology Deficiencies – none identified

C. Assessment of Risk Due to Microbiology Deficiencies –

No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / John Arigo, Ph.D.
Microbiology Team Leader/ CDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

The amendment is a response to the Agency's microbiology fax letter dated July 27, 2010. The original deficiencies are shown below in italics, followed by the applicant's response.

1. (b) (4)

2.

Note to reviewer: Abbott has provided an LOA authorizing access to DMF 9365 dated August 6, 2010. Abbott is responding to the above deficiencies through DMF 9365. This submission is reviewed in 9365mic2.doc, dated August 17, 2010 by J. Arigo. The response is found adequate.

Acceptable

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

JOHN T ARIGO
08/19/2010

KUN SHEN
08/19/2010

NEAL J SWEENEY
08/19/2010

PAUL L DEXTER
08/19/2010

Product Quality Microbiology Review

July 2, 2010

NDA: 20-517/S-030

Drug Product Name
Proprietary: Lupron Depot
Non-proprietary: leuprolide acetate for depot suspension
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
June 3, 2010	June 4, 2010	n/a	July 9, 2010

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
Dec 11, 2009	1	April 6, 2010
Apr 2, 2010	1	April 6, 2010

Applicant/Sponsor
Name: Abbott Endocrine, Inc. (Abbott Laboratories)
Address: 200 Abbott Park Road; D-PA76/AP30-1NE; Abbott Park, IL 60064
Representative: Natalie Tolli, Director, GPRA
Telephone: 847-935-8099

Name of Reviewer: John Arigo, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA PAS amendment

2. SUBMISSION PROVIDES FOR: Change in formulation. Inclusion of a 45 mg 6 month injection. The only change relevant to microbiology is the addition of stearic acid as an excipient (b) (4) (b) (4) . These items are .

3. MANUFACTURING SITE:

Site	Establishment Registration Number	Function(s)
(b) (4)		
Abbott Laboratories 100 and 200 Abbott Park Rd. Abbott Park, IL 60064-3500	1415939	Packaging

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 45 mg of sterile powder in a dual chamber syringe along with a sterile vehicle. IM injection – single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Palliative Treatment of Advanced Prostatic Cancer.

B. SUPPORTING/RELATED DOCUMENTS:
9365mic1a1.doc, dated July 2, 2010, by J. Arigo for review of DMF 9365.

C. REMARKS: Electronic submission.

filename: N020517S030R1a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Manufacturing processes are contained in DMF 9365. (b) (4)

B. Brief Description of Microbiology Deficiencies – (b) (4)

.

C. Assessment of Risk Due to Microbiology Deficiencies –

The safety risk associated with the microbiology deficiencies is considered low.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / John Arigo, Ph.D.
Microbiology Team Leader/ CDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

7 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

JOHN T ARIGO
07/27/2010

NEAL J SWEENEY
07/27/2010

PAUL L DEXTER
07/27/2010

Product Quality Microbiology Review

April 6, 2010

NDA: 20-517/S-030

Drug Product Name
Proprietary: Lupron Depot
Non-proprietary: leuprolide acetate for depot suspension
Drug Product Classification: N/A
Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
Dec 11, 2009	Dec 11, 2009	n/a	Feb 24, 2010
Apr 2, 2010	Apr 2, 2010	n/a	Apr 2, 2010

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
n/a		

Applicant/Sponsor
Name: Abbott Endocrine, Inc. (Abbott Laboratories)
Address: 200 Abbott Park Road; D-PA76/AP30-1NE; Abbott Park, IL 60064
Representative: Natalie Tolli, Director, GPRA
Telephone: 847-935-8099

Name of Reviewer: John Arigo, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA PAS and telephone amendment

2. SUBMISSION PROVIDES FOR: Change in formulation. Inclusion of a 45 mg 6 month injection. The only change relevant to microbiology is the addition of stearic acid as an excipient and (b) (4) (b) (4) . These items are .

3. MANUFACTURING SITE:

Site	Establishment Registration Number	Function(s)
(b) (4)		
Abbott Laboratories 100 and 200 Abbott Park Rd. Abbott Park, IL 60064-3500	1415939	Packaging

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 45 mg of sterile powder in a dual chamber syringe along with a sterile vehicle. IM injection – single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Palliative Treatment of Advanced Prostatic Cancer.

B. SUPPORTING/RELATED DOCUMENTS:
9365mic1.doc, dated April 6, 2010, by J. Arigo (b) (4) .

020517s30MicroTcon3-26-2010.doc, for the telephone conference between J. Arigo and L. Marshall of Abbott.

C. REMARKS: none.

filename: N020517S030R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Manufacturing processes are contained in DMF 9365. (b) (4)

B. Brief Description of Microbiology Deficiencies – (b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies –

The safety risk associated with the microbiology deficiencies is considered low.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / John Arigo, Ph.D.
Microbiology Team Leader/ CDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

6 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

JOHN T ARIGO
05/04/2010

KUN SHEN
05/04/2010

NEAL J SWEENEY
05/07/2010

PAUL L DEXTER
05/10/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	20-517/SDN# 190
Submission Date:	17 December, 2010
Brand Name:	Lupron Depot
Generic Name:	Leuprolide Acetate
Formulation:	45 mg injections
IND Number:	27,350
OCP Reviewer:	Young Jin Moon, Ph.D.
OCP Team Leader:	Julie M. Bullock, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	Abbott
Submission Type; Code:	Supplement-30; Class 2 response
Dosing regimen:	Lupron Depot-6 month: (45 mg) administered every six months as a single injection
Indication:	For the palliative treatment of advanced prostate cancer

Table of contents

1 EXECUTIVE SUMMARY

The current submission is a complete response to the Agency's Complete Response letter dated October 5, 2010.

A supplemental New Drug Application (20-517/S-030) for leuprolide acetate 45 mg 6-month depot (Formulation A) for the indication of advanced prostate cancer was submitted on December 11, 2009. As part of the review of the application, the Division of Scientific Investigation (DSI) conducted an inspection of Esoterix, Inc., the central laboratory for all laboratory analyses of pivotal Study L-PC07-169, which resulted in the issuance of a Form FDA-483 for findings associated with testosterone and other hormone testing performed at the Calabasas Hills, California site. Subsequently, on October 5, 2010, the applicant received a Complete Response Letter, outlining deficiencies that were identified by DSI and the Agency's recommendations for addressing them. In the Complete Response Letter, the Agency recommended that samples from the failed runs identified in the DSI audit of Esoterix should be reanalyzed such that efficacy and safety can be assessed based on adequate and reliable data.

Frozen back-up samples from the failed testosterone runs identified in the DSI audit of Esoterix were shipped from Esoterix to Abbott for reanalysis. Abbott Bioanalysis (Abbott Park, Illinois) measured testosterone concentration in 369 Formulation A back-up samples for reanalysis using a validated high performance liquid chromatography (HPLC) method with tandem mass spectrometric detection (MS/MS). The method validation and in-study assay appear generally acceptable. The method comparison for testosterone between Abbott Drug Analysis and Esoterix Endocrine Sciences suggests that methods at both sites produce data that is both reproducible and provide similar results between the two analytical sites.

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

Signatures:

Reviewer: Young Jin Moon, Ph.D. Division of Clinical Pharmacology 5	Team Leader: Julie Bullock, Pharm.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - K Robertson; MTL - E Maher; MO - K Delorenzo
DCP-5: Reviewer - Y Moon ; TL – J Bullock
DDD - B Booth ; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

The primary endpoint of the pivotal efficacy trial was suppression of serum testosterone to ≤ 50 ng/dL from Week 4 through Week 48. Serum testosterone was measured by liquid chromatography with mass spectrometry detection. A request for inspection of the bioanalytical site of the pivotal trial (L-PC-7-169), Esoterix, Inc. (Calabasas Hills, CA), was made to the DSI. Following the inspection, a Form 483 was issued to Esoterix. DSI identified that Esoterix violated stability, precision, accuracy, and calibration curve of an analytical method in measuring total testosterone. Therefore, at the time of the Original NDA review it was determined that the data generated from the pivotal trial were not reliable to determine efficacy and safety of Lupron Depot-6 month for approval.

Back-up samples from the failed testosterone runs identified in the DSI audit were shipped from Esoterix to Abbott for reanalysis. Abbott Bioanalysis (Abbott Park, Illinois) measured testosterone concentration in 369 Formulation A back-up samples for reanalysis using a validated high performance liquid chromatography (HPLC) method with tandem mass spectrometric detection (MS/MS). The Abbott method was shown to be accurate, precise, and specific for testosterone. In an ISR study, reproducibility of results from Abbott's GLP assay of testosterone was demonstrated by 95% of the reanalysis concentrations having repeated concentrations within 20% of the original concentrations, exceeding the Incurred Sample Reproducibility (ISR) (67%) requirement. Stability of the study samples was demonstrated over the entire storage time. In a comparability assessment study, concentrations from the Abbott and Esoterix methods were comparable, with differences between the mean concentrations (from Abbott and Esoterix) of all the samples within 15%. When the data were fit using linear regression, the coefficient of determination (r^2) was 0.999 and the slope of the line was 1.04.

2 QUESTION BASED REVIEW

For brevity only QBR questions referring to the current supplement are incorporated. Please refer to the original NDA 20-517 (Approval Date: 4/25/02) and the supplemental NDA 20-517/S-30 (DARRTS Communication Date: 9/10/10) for more information.

2.1 GENERAL ATTRIBUTES

2.1.3 What are the proposed dosage and route of administration?

The proposed formulation provides for the administration of an injection of Lupron Depot, containing 45 mg of leuprolide acetate, at six-monthly intervals.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Study L-PC07-169 is a phase 3, multi-center, open-label, non-randomized trial to evaluate the efficacy, safety and pharmacokinetics of two injections of a 6-month leuprolide formulation in subjects with prostatic adenocarcinoma. The primary efficacy endpoint was suppression of serum testosterone to ≤ 50 ng/dL from Week 4 through Week 48. The ITT population for the primary endpoint included 150 patients in the Original Analysis and 148 subjects in the Reanalysis. Serum testosterone was suppressed to ≤ 50 ng/dL from Week 4 through Week 48 in 93.7% of subjects in the Original Analysis and in 93.6% (Table 1) of subjects in the Reanalysis. The lower bound of the 2-sided 90% confidence interval (CI), using the Kaplan-Meier method, exceeded the prespecified minimum requirement of 87% for Formulation A to be considered successful for both the Original Analysis (90.3%) and the Reanalysis (90.2%).

Table 1. Suppression of Serum Testosterone from Week 4 Through Week 48 (ITT Population for the Primary Endpoint): Original Analysis Versus Reanalysis

Original Analysis				Reanalysis			
N	Percent Suppressed[a]	Standard Error	2-Sided 90% Confidence Interval	N	Percent Suppressed[a]	Standard Error	2-Sided 90% Confidence Interval
150	93.7	2.05	90.3, 97.0	148	93.6	2.08	90.2, 97.0

a. Suppression (testosterone ≤ 50 ng/dL) occurred by Day 32 and no escapes through Week 48. Percent suppressed was calculated using Kaplan-Meier method for right-censored observations. Subjects who had a visit between Day 337 and Day 340 and did not escape were considered as censored on Day 337. Subjects who escaped between Day 337 and Day 340 were considered as failed on Day 337.

Source: Study L-PC07-169 CSR Table 18 and Reanalysis Table 14.2__1.1.1

2.5 ANALYTICAL SECTION

2.5.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Testosterone

Due to extensive in-study failures of calibration curve and QC accuracy, Esoterix, Inc., the central laboratory for all laboratory analyses of pivotal Study L-PC07-169 received Form FDA-483 from the DSI. Back-up samples from the failed testosterone runs identified in the DSI audit of Esoterix were shipped from Esoterix to Abbott for reanalysis. Abbott Bioanalysis (Abbott Park, Illinois) measured testosterone concentration in 369 Formulation A back-up samples for reanalysis using a validated high performance liquid chromatography (HPLC) method with tandem mass spectrometric detection (MS/MS). The method validation and in-study assay appear generally acceptable. Details are as follows.

Method validation

Linearity of the Abbott GLP assay method (i.e., peak area ratio of the analyte to its internal standard versus concentration) was indicated by a coefficient of determination (r^2) ≥ 0.995885 for testosterone. The LLOQ was determined to be 2.50 ng/dL for testosterone.

The method was determined to be accurate, precise, and specific for testosterone. Inter-run precision (percent coefficient of variation; %CV) of the stripped QC levels for testosterone (concentration range: 6.41 to 2000 ng/dL) ranged from 3.5% to 4.7%, and the inter-run accuracy (percent Bias, % Bias) ranged from –1.3% to 4.7%. Inter-run precision (%CV) of the unstripped QC levels for testosterone (concentration range: 10.7 to 2030 ng/dL) ranged from 1.4% to 6.8%, and the inter-run accuracy (% Bias) ranged from –5.1% to 0.4%. Extraction recovery evaluation of stripped QC ranged from 71.5% to 76.0% for testosterone. Extraction recovery evaluation of the internal standard (testosterone-d3) was 74.6%.

Stability of Samples

Stability was demonstrated under various conditions, including freeze/thaw stability (3 freeze/thaw cycles), stability of thawed serum samples at room temperature (11 hours), reinjection reproducibility after storage in autosampler for up to 21 hours after initial injection, and post-preparative extract stability for up to 23 hours in a cool autosampler (set point of ~10°C). Frozen storage stability was evaluated at –70°C (17 days). Additional long-term storage stability at –70°C is ongoing at Abbott.

Abbott also demonstrated long-term frozen stability at –70°C from an ISR evaluation of 66 study samples with the longest storage time (939 to 973 days as of October 27, 2010) and valid results from Esoterix assay. In this study, 89.4% of the samples reanalyzed have concentrations within 20% of the original results, exceeding the ISR (67%) requirement. The reproducibility over the entire storage time demonstrated stability of the samples during the storage of the study samples.

Reproducibility of Concentrations

Reproducibility of the Abbott assay concentrations was demonstrated by Incurred Sample Reproducibility (ISR) study of 358 samples, with 95% of the reanalysis concentrations having repeated concentrations within 20% of the original concentrations, exceeding the FDA two-thirds (67%) requirement.

Cross-Validation of Testosterone Results from Esoterix and Abbott Methods

The concentrations between the Abbott and Esoterix methods demonstrated comparability, with the differences between the mean concentrations of 6 replicates of 4 levels of QC samples and 6 replicates of 12 serum samples (from Abbott and Esoterix) within 15% of the average of the Esoterix and Abbott mean values. Mean testosterone concentration data from Esoterix versus those from Abbott Bioanalysis were fit using linear regression (Figure 1). The coefficient of determination (r^2) is 0.999, and the slope of the line is 1.04.

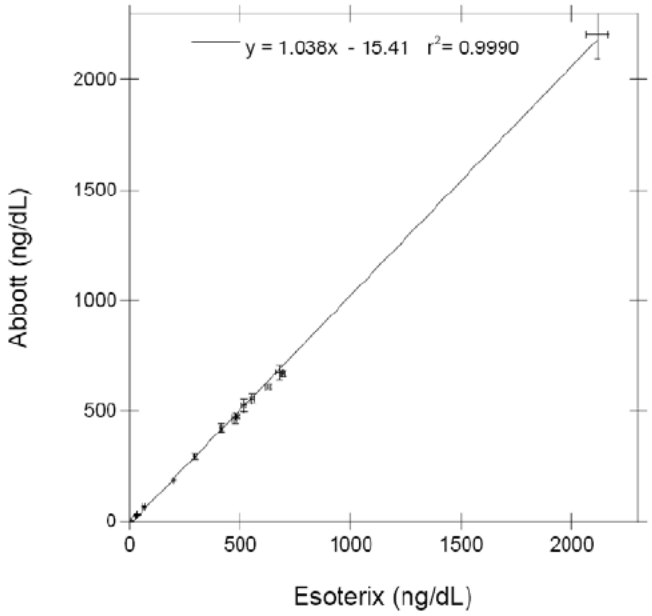

Figure 1. Correlation plots of mean (ng/dL ± SD) results from Esoterix and Abbott

Since too wide range of data was fitted in applicant's analysis, the reviewer plotted individual data with only near testosterone suppression threshold (50 ng/dL) level of the pivotal study (Figure 2). The data appear regressed linearly with coefficient of determination of 0.9889.

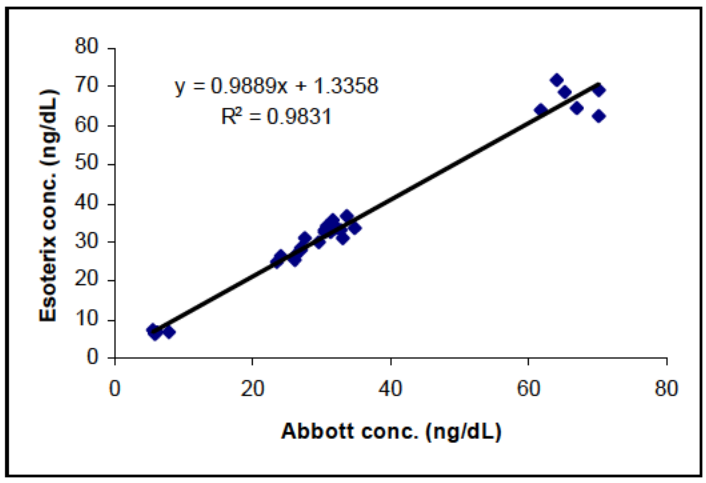

Figure 2. Correlation plots of mean (ng/dL ± SD) results (0-80 mg/dL) from Esoterix and Abbot

Individual data were plotted on a control chart to show an overlay of the data scatter from Esoterix and Abbott Drug Analysis (Figure 3). Replicate data from the two analytical sites overlay generally well.

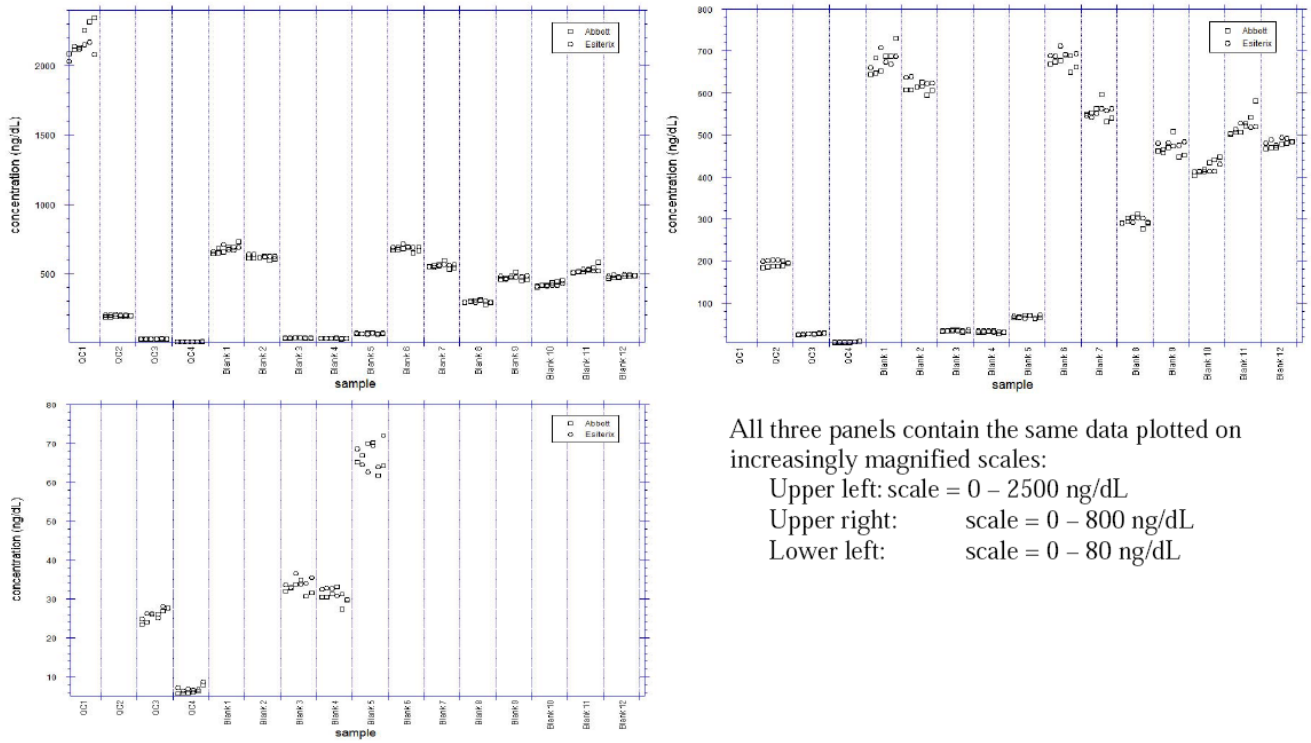

Figure 3. Control Chart Comparing Abbott and Esoterix Data

In conclusion, this method comparison for testosterone between Abbott Drug Analysis and Esoterix Endocrine Sciences suggests that methods at both sites produce data that is both reproducible and provide similar results between the two analytical sites.

3 DETAILED LABELING RECOMMENDATIONS

Labeling recommendations have been conveyed to the sponsor. The applicant accepted our recommendations.

WARNINGS AND PRECAUTIONS • Long-term androgen deprivation therapy prolongs the QT interval. Consider risks and benefits. (5.2)
5 WARNINGS AND PRECAUTIONS

5.2 Effect on QT/QTc Interval

Long-term androgen deprivation therapy prolongs the QT interval. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, stalol) antiarrhythmic medications.

APPEARS THIS WAY ON ORIGINAL

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

/s/

YOUNG J MOON
04/25/2011

JULIE M BULLOCK
04/28/2011

Clinical Pharmacology Review

NDA	20-517/S-030 SDN# 161
Submission Date:	11 December, 2009; 26 May, 2010
Brand Name:	Lupron Depot
Generic Name:	Leuprolide Acetate
Formulation:	45 mg injections
IND Number:	27,350
OCP Reviewer:	Young Jin Moon, Ph.D.
OCP Team Leader:	Julie M. Bullock, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	Abbott
Submission Type; Code:	SE-30
Dosing regimen:	Lupron Depot-6 month: (45 mg) administered every six month as a single injection
Indication:	For the palliative treatment of advanced prostate cancer

Table of contents

1 EXECUTIVE SUMMARY

This is a supplemental NDA for Lupron Depot® (leuprolide acetate for depot suspension) which provides safety and efficacy information to support a new 6-month formulation for the palliative treatment of advanced prostate cancer. The proposed formulation provides for the administration of an injection of Lupron Depot, containing 45 mg of leuprolide acetate, at six-month intervals. Currently, 3-month (22.5 mg) and 4-month (30 mg) Lupron Depot formulations are marketed.

To support approval, the sponsor submitted one phase 3 open-label, non-randomized trial in 150 subjects with prostatic adenocarcinoma (Study L-PC-7-169). This study evaluated the efficacy and safety of two doses of leuprolide acetate 45 mg, 6-month depot formulation. The primary endpoint was suppression of serum testosterone to ≤ 50 ng/dL from Week 4 through Week 48. In a subset of subjects, plasma leuprolide concentrations were determined to establish the pharmacokinetic profiles. After dosing, a rapid increase in plasma leuprolide concentrations was observed, followed by a rapid decline over the first 7 days after dosing. The maximum leuprolide concentration occurred approximately 2 hours after injection. The mean pharmacokinetic profile after the first dose was similar to that after the second dose.

The Division of Scientific Investigation (DSI) identified that the bioanalytical site, Esoterix, Inc. (Calabasas Hills, CA), violated stability, precision, accuracy, and calibration curve of the analytical method in measuring total testosterone. Therefore, the testosterone data generated from the pivotal trial are not reliable.

1.1 RECOMMENDATIONS

This application is not acceptable from a clinical pharmacology perspective based on the major deficiencies identified in the DSI Report. The Applicant should address and provide acceptable resolution of the deficiencies identified by the DSI's audit of the data from Study L-PC-7-169.

Signatures:

Reviewer: Young Jin Moon, Ph.D. Division of Clinical Pharmacology 5	Team Leader: Julie Bullock, Pharm.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - D Hanner; MTL - E Maher; MO - G Ison
DCP-5: Reviewer - Y Moon ; TL – J Bullock
DDD - B Booth ; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

The primary efficacy endpoint was suppression of serum testosterone to ≤ 50 ng/dL from Week 4 through Week 48. Serum testosterone was measured by liquid chromatography with mass spectrometry detection. A request for inspection of the bioanalytical site of the pivotal trial (L-PC-7-169), Esoterix, Inc. (Calabasas Hills, CA), was made to the Division of Scientific Investigations (DSI). Following the inspection, a Form 483 was issued to Esoterix for multiple violations. DSI identified the following issues- validation violation in stability, precision, accuracy, and calibration curve of an analytical method in measuring total testosterone, and extensive in-study failures of calibration curve and QC accuracy. Therefore, the data generated from the pivotal trial are not reliable to determine efficacy and safety of Lupron Depot-6 month for approval (see Section 2.5 Analytical Section for details).

The pharmacokinetics (PK) of a 45 mg, 6-month leuprolide acetate depot formulation was determined in a subset of subjects (N=26) in study L-PC07-169. Each subject received a total of two intramuscular injections that were administered 24 weeks (6 months) apart. Subjects received the first injection on Day 1, and the second injection on Day 169 (i.e., Week 24, Month 6). Pharmacokinetic parameters, including the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), the concentration at the end of the dosing period (C_{trough}) and the area under the plasma concentration-time curve (AUC) were determined using noncompartmental methods.

Pharmacokinetic profiles exhibited two phases. After dosing, an initial rapid increase of plasma leuprolide concentration was observed, followed by a rapid decline over the first 7 days post-dose. The maximum leuprolide concentration occurred at approximately 2 hours after injection. The mean C_{max} value was 6.7 ng/mL after first dose and the mean concentration then declined to 0.07 ng/mL at 24 weeks.

Leuprolide appeared to be released continuously by the third week after dosing with steady plasma concentrations through the 24-week dosing interval. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations. In this study, mean leuprolide plasma concentration-time profiles were similar after the first and second dose.

2 QUESTION BASED REVIEW

For brevity only QBR questions referring to the current supplement are incorporated. Please refer to the original NDA 20-517 (Approval Date: 4/25/02) for more information.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The 45 mg Lupron Depot 6M is a 6-month (b) (4) depot formulation containing 45 mg of leuprolide acetate as the active substance. The dosage form consists of a lyophilized microsphere (MC) powder, which contains leuprolide acetate, polylactic acid (PLA), stearic acid and mannitol, and an aqueous vehicle containing mannitol, carboxymethylcellulose sodium and polysorbate 80. The MC powder and the vehicle are filled in separate compartments of a dual-chamber syringe and are reconstituted in the syringe prior to administration. (b) (4) The quantitative composition of the proposed Lupron Depot 6M, 45 mg Formulation A (IP2) is listed in Table 1.

Table 1. Quantitative Composition of the Lupron Depot 6M, 45 mg Compared to the Marketed Products and Prototype Leuprolide Acetate 6M Development Formulations

(b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin/luteinizing–hormone-releasing hormone (GnRH or LH-RH). It blocks gonadal production of sex steroids by down-regulating the hypothalamic-pituitary-gonadal axis.

2.1.3 What are the proposed dosage and route of administration?

The proposed formulation provides for the administration of an injection of Lupron Depot, containing 45 mg of leuprolide acetate, at six-monthly intervals.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant conducted two clinical studies (Table 2) which used two different formulations (formulation A and B). The sponsor submitted only Formulation A for approval. Study C02-008 (Formulation B) was initiated in 2002, but did not meet the primary efficacy endpoint. Therefore only study L-PC07-169 for Formulation A was reviewed.

Table 2. Clinical studies

Study	Study design	Objectives (primary)	Dosage Regimens	Number of Subjects
L-PC07-169	Phase 3, open-label, uncontrolled	Efficacy, safety, and PK (suppression of serum testosterone ≤ 50 ng/dL from Week 4 through Week 48)	45 mg 6-month leuprolide acetate IM injections q 24 weeks for 48 weeks of treatment	Formulation A: 134 completed- Full report Formulation B: 31 completed - Interim
C02-008	Phase 3, open-label, uncontrolled	Efficacy, safety, and PK (suppression of serum testosterone)	45 mg 6-month leuprolide acetate IM injections q 26 weeks for 52 weeks of treatment	146 completed - Abbreviated

Study L-PC07-169 is a Phase 3, multi-center, open-label, non-randomized trial to evaluate the efficacy, safety and pharmacokinetics of two injections of a 6-month leuprolide formulation in subjects with prostatic adenocarcinoma. First, 150 subjects were enrolled to Formulation A, and the next 150 subjects were enrolled to Formulation B. The study design is shown in Figure 1.

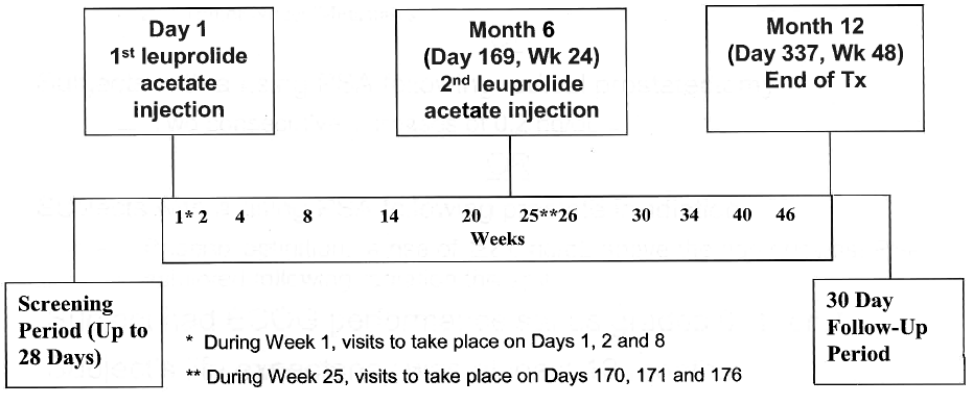

Figure 1. Study Design

The primary endpoint was the percentage of subjects who have:

- Onset of testosterone (T) suppression (≤ 50 ng/dL) by Day 32,
- No escapes (no T > 50 ng/dL at any visit), and
- Week 48 T result showing suppression.

Success criteria defined by Agency was lower bound of 2-sided 90% confidence interval of 87%. Results indicate that the percent of subjects with testosterone suppression from week 4 through week 48 was 93.7% (90% CI: 90.3, 97.0). There were 9 treatment failures (out of 150 patients). One subject failed to suppress by Day 32, and 8 subjects escaped from suppression after Week 4. None of the escapes were associated with increases in PSA.

The most common adverse events were hot flushes, injection site pain, and fatigue. The safety data are consistent with known safety profile of leuprolide acetate.

Reviewer's comment: Escape from suppression could not be explained by leuprolide PK, because PK data of leuprolide were not collected from subjects who escaped from suppression. DSI identified validation violation in stability, precision, accuracy, and calibration curve of an analytical method in measuring total testosterone, and extensive in-study failures of calibration curve and QC accuracy. Therefore, the testosterone concentrations from study L-PC07-169 are unreliable.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Leuprolide acetate is a GnRH agonist indicated for prostate cancer. It blocks gonadal production of sex steroids, hence, suppression of T is the primary biomarker. Achievement and maintenance of castration is the primary goal for clinical benefit. T was measured by LC-MS/MS after nonpolar solvent extraction.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

A pharmacokinetic and pharmacodynamic assessment of Formulation A was performed on plasma concentrations of leuprolide, and serum concentrations of testosterone. The testosterone data reported here were found to be unreliable based on the DSI report (see Section 2.5). The mean plasma concentration-time profiles of testosterone and leuprolide for both doses (Dose 1 was administered on Day 1 and Dose 2 was administered on Day 169 for most subjects) are presented in Figure 2.

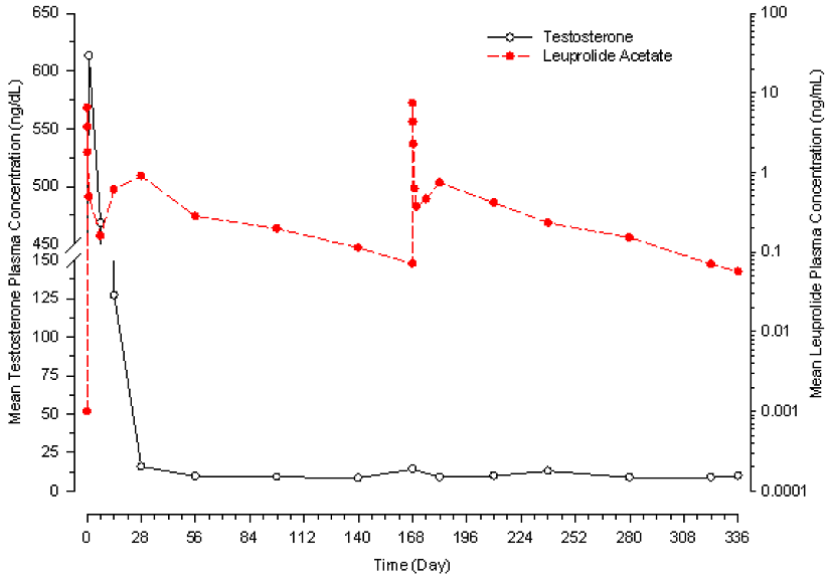

Figure 2. Mean Testosterone-Leuprolide Time course (Testosterone (N=150) - Linear, Leuprolide (N=26)-Log). The testosterone concentrations are unreliable based on the DSI report.

The observed initial rapid increase of leuprolide concentration was associated with rapid increases in serum testosterone and plasma concentrations. Mean serum testosterone concentration increased from a mean baseline value of 433 ng/dL to a peak of 613 ng/dL during this initial phase. With continuous plasma leuprolide exposure, the high mean serum testosterone concentration decreased over-time to reach a very low plateau concentration (approximately Week 4) that was maintained through the end of the study. At the end of each dosing period, 24 weeks after each injection, the majority of subjects had quantifiable leuprolide concentrations. The observed hormone responses coincide with the observed pharmacokinetic profile of leuprolide acetate 45 mg 6-month depot.

Since PK data are not available in patients who failed the primary endpoint, meaningful analysis for exposure-response could not be conducted.

2.2.4.3 Does this drug prolong the QT or QTc interval?

In the current submission, cardiovascular adverse events were reported for 27.8% of all subjects treated with Lupron. Seven subjects had acute cardiovascular or cerebrovascular events that were serious: 3 subjects had angina pectoris, or chest pain; 2 subjects had transient ischemic attacks; 1 subject had a cerebrovascular accident; and 1 subject had acute coronary syndrome. Six of these seven subjects had significant cardiac histories.

Since this drug was first approved in 1989, QT data have not been collected. Literature search suggests that androgen-deprivation therapy causes QT prolongations and it may be associated with an increased risk of cardiovascular morbidity and death. Although in the current submission the sponsor did not perform ECG monitoring, QT data for leuprolide could be found in another submission (NDA 22-201; Degarelix) where leuprolide 7.5 mg once every 28 days was used as a comparator drug to degarelix (approved) (refer to FIRMAGON® label): in

the randomized, active-controlled trial comparing degarelix to leuprolide, periodic ECGs were performed. Four (2%) patients in the leuprolide 7.5 mg group had a QTcF ≥ 500 msec. From base line to end of study, the median change for leprolide was 16.7 msec.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

The pharmacokinetics (PK) of 45 mg, 6-month leuprolide acetate depot (Formulation A only) was determined in the pivotal study L-PC07-169 in 26 prostate cancer patients. PK samples were collected at pre-dose and on days 1, 2, 8, 15, 29, 57, 99, 141, 169 (0, 2, 4, 8 hr after injection), 170, 171, 176, 183, 211, 239, 281, 323, and 337. The mean (± SD) pharmacokinetic parameters of leuprolide are shown in Table 3.

Table 3. Mean ± SD Leuprolide Pharmacokinetic Parameters in Plasma after the First and Second Injection of Formulation A

Pharmacokinetic Parameter	(units)	Study Drug Injection		
		First Dose	Second Dose	Overall
		Formulation A		
N		25	25	26
C_{max}	(ng/mL)	6.71 ± 2.00	7.40 ± 2.18	7.85 ± 1.65
T_{max}	(h)	2.1 ± 0.4	2.0 ± 0.2	2.1 ± 0.4
C_{trough}	(ng/mL)	0.073 ± 0.043[a]	0.057 ± 0.036	--
AUCt	(ng•h/mL)	1282 ± 551[b]	1142 ± 785	2483 ± 1311[c]

[a] N=22; [b] N=23; [c] N=22

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The mean PK profile was similar following the first dose and second dose (Figure 3).

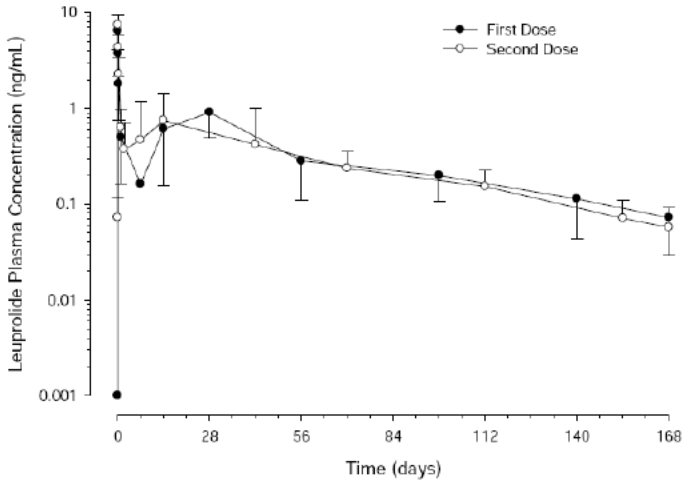

Figure 3. Concentration-time profile after first dose (N=25) and second dose (N=25)

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject variability ranged from 30 to 68% for C_{max}, C_{trough}, and AUC.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The relationship between Lupron exposure and demographic variables was examined (Figure 4). It appears that there was no effect of age, height, weight, and BMI. However, due to the small number of subjects (Figure 4 and Table 4), no conclusion can be made.

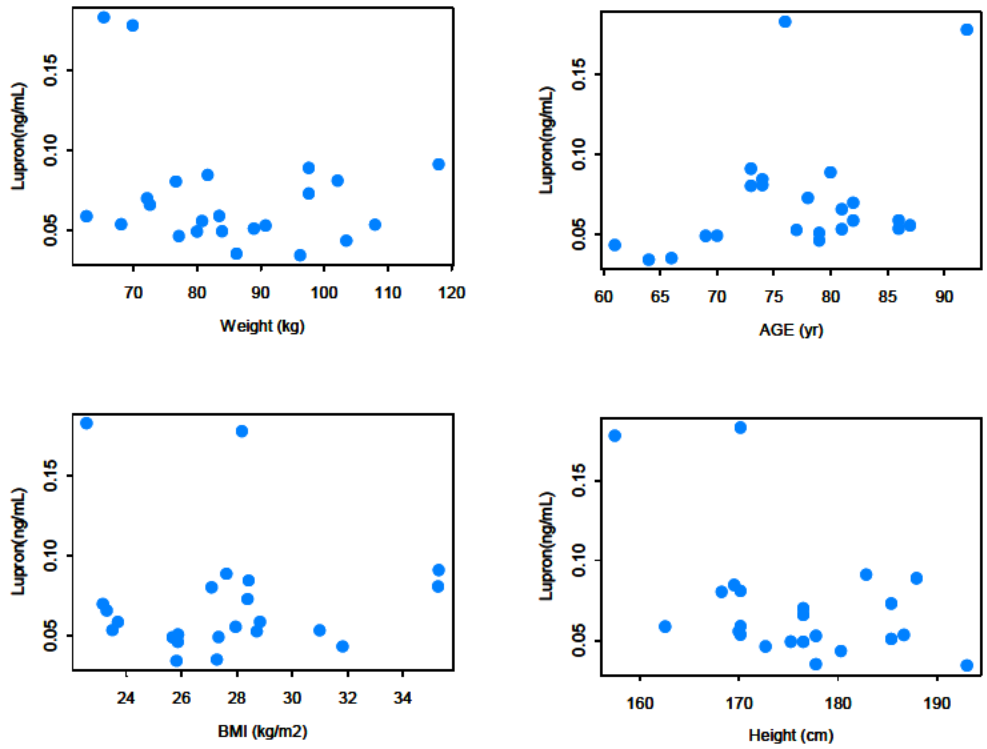

Figure 4. Effect of demographic variables (age, height, weight, and BMI) on trough concentrations of Lupron at Week 24.

Table 4. Demographic characteristics- Subject set included in the PK analysis dosed with Formulation A

VARIABLE	FORMULATION A (N=26) n (%)
SEX	
MALE	26 (100)
RACE	
WHITE	25 (96.2)
BLACK	1 (3.8)
ASIAN	0
ETHNICITY	
HISPANIC OR LATINO	1 (3.8)
NOT HISPANIC OR LATINO	25 (96.2)
AGE (YEARS)	
< 65	3 (11.5)
>= 65	23 (88.5)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Due to the limited PK data, meaningful analysis for exposure-response could not be conducted.

2.4 GENERAL BIOPHARMACEUTICS

2.4.2 What is the composition of the to-be-marketed formulation?

The components for Formulation A are identified in Table 5.

Table 5. Formulation Composition (Amount per Syringe)

Microsphere Powered Component[a]	
Leuprolide acetate[b]	45 mg
Poly lactic acid (PLA) (b) (4) (b) (4)	169.9 mg
Mannitol	39.7 mg
Stearic acid	10.1 mg
Total	265 mg
Vehicle	
Mannitol	75.0 mg
Carboxy methylcellulose sodium	7.5 mg
Polysorbate 80	1.5 mg
Glacial acetic acid[c]	q.s.
Water for injection	q.s.
Total	1.5 mL

q.s. = as much as needed

a. Amount of microcapsule (MC) powder does not include the (b) (4) overage in the syringe.

b. Total amount based on leuprolide acetate, which is calculated as leuprolide monoacetate

c. Addition of sufficient amount, if needed.

2.5 ANALYTICAL SECTION

2.5.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

There are no relevant metabolites of leuprolide acetate formed in human plasma.

2.5.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Leuprolide plasma concentrations were determined by a liquid chromatography/tandem mass spectrometry (LC/MS/MS). The bioanalytical method (LCMSC 245) was developed by (b) (4) . This method is applicable to the quantitation of leuprolide within a range of 0.0250 to 25.0 ng/mL. Actual leuprolide concentrations in the pivotal trial (0.0257 ~ 11.7 ng/mL) were within the range. Intra or inter-assay precision (CV%) was less than 15%, and intra or inter-accuracy (%bias) was within ±15%. There were no significant chromatographic peaks detected at expected retention time of the analyte or its internal standard. Percent recovery at three concentrations of internal standard and leuprolide were 52-53-49% and 65-57-54%, respectively. Stability was tested after three freeze/thaw cycles, at room temperature for ~117 hours, and at -20°C for 15 days, and the samples appear stable at these conditions.

Reviewer's comment: It is not clear whether the long-term stability test covered the longest period time samples were stored. Therefore, the leuprolide concentrations from study L-PC07-169 are unreliable.

Testosterone

Serum testosterone was measured in singlet by liquid chromatography with mass spectrometry detection after nonpolar solvent extraction. The assay (report no.08-ESO-CAL-021v2, dated on Feb 20, 2009) was conducted by Esoterix, Inc. (Calabasas Hills, CA).

In past NDA submissions, DSI had detected substantial irregularities in laboratory practice and in the validation of the testosterone assay upon inspection of Esoterix, Inc (please refer to reviews in DARRTS on (b) (4)). Therefore, a DSI audit of this bioanalytical site of the clinical trial L-PC07-169 (pivotal trial) was requested (May 13, 2010). At the close of the DSI inspection, on August 17, 2010, a Form FDA 483 (Warning Letter, see Section 4.1) was issued to Esoterix. The deficiencies identified by the DSI's audit are as follows:

1. Many analytical runs had > 33.3% of the total QCs and/or > 50% at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations.
2. Failure to reject analytical runs when >25% of calibration standards in a standard curve failed to meet the acceptance criteria (< 15% or < 20% (LLOQ) deviation from nominal values or mean pooled QC concentrations).
3. Failure to use the appropriate QC values during analysis. For example, one testosterone QC for L-PC-7-169 used incorrect concentrations for some of the run acceptance criteria.

4. Failure to accurately demonstrate appropriate analyte stabilities. Room temperature serum and whole blood stabilities of testosterone concentrations below 200 ng/mL were not evaluated.
5. Audit trail of the 'Analyst' software version 1.41 was not enabled for all the validation and analytical runs. There are no audit trail records available for inspection and multiple samples were manually integrated without audit.

Reviewer's comments

- *#4 - The **stability** of analytes were not established based on Guidance for Industry – Bioanalytical Method Validation (May 2001, FDA).*
- *#5 - Without the audit trail, it is not possible for the inspector to verify the process of running the instruments for measuring analytes.*
- *#1 - The **precision** of analytes were not established based on FDA Guidance*
- *#1 – Many analytical runs were not rejected when the Quality Controls (QCs) failed (n = 47 runs)*
- *#1 – The operator failed to use an appropriate number of QCs (as described by the Guidance) to adequately monitor performance of the assay.*
- *#2 - The **accuracy** of analytes were not established based on FDA Guidance*
- *#2- The **calibration curve** was not generated based on FDA Guidance*
- *#2- Analytical runs were not rejected when the calibration curve failed (n = 14 runs)*
- *In conclusion, the testosterone data is unreliable since data was reported from failed runs.*

APPEARS THIS WAY ON ORIGINAL

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

YOUNG J MOON
09/08/2010

JULIE M BULLOCK
09/10/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**20-517/S-030**
Submission Date:	12/11/2009, 7/16/2010
Brand Name:	Lupron Depot
Generic Name:	leuprolide acetate for depot suspension
Formulation:	Injection
Strength:	45 mg
Sponsor:	Abbott Endocrine Inc
Reviewer:	John Duan, Ph.D.
Submission Type:	New formulation (6-month)

The purpose of this submission is to provide data to support a new formulation of Lupron Depot, for the palliative treatment of advanced prostatic cancer. The proposed formulation provides for the administration of an injection of Lupron Depot, containing 45 mg of leuprolide acetate, at six-monthly intervals. This formulation provides an alternative dosing regimen which results in fewer injections per year, compared to the currently-approved 3-month (22.5 mg) and 4-month (30 mg) Lupron Depot formulations. This review focuses on the in vitro release method and specifications.

RECOMMENDATION

The proposed specifications are not acceptable, which could not control the shape of the dissolution curve in (b) (4) Based on the data submitted, the in vitro release method and specifications are recommended as follows.

Methodology

(b) (4)

Specifications

(b) (4)

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 20517
Patrick Marroum, Angelica Dorantes, John Duan

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

JOHN Z DUAN
08/11/2010

PATRICK J MARROUM
08/12/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

OTHER REVIEW(S)

Division of Drug Marketing, Advertising, and Communications

Internal Consult

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

To: Kim Robertson, RPM, Division of Drug Oncology Products, (DDOP)

From: Adam George, Regulatory Reviewer Officer
Division of Drug Marketing, Advertising, and Communications, (DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC

Date: May 20, 2011

Re: Comments on draft labeling (Package Insert) for Lupron Depot (leuprolide acetate for depot suspension)

NDA 020517

In response to your consult request dated February 9, 2011, we have reviewed the draft version of the Package Insert (PI) for Lupron Depot (leuprolide acetate for depot suspension). DDMAC's concerns have been addressed during labeling meetings. We have no additional comments on the proposed draft version of the PI.

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/s/

ADAM GEORGE
05/20/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

Date:	May 11, 2011
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Melina Griffis, RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Prevention and Analysis
From:	Anne C. Tobenkin, Safety Evaluator Division of Medication Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name and Strengths:	Lupron Depot (Leuprolide Acetate for Depot Suspension), 22.5 mg, 30 mg, and 45 mg
Application Type/Number/Supplement:	NDA 020517/ S030
Applicant:	Abbott Laboratories
OSE RCM #:	2011-1033

1 INTRODUCTION

This review evaluates the Applicant's revised insert labeling for Lupron Depot (Leuprolide Acetate for Depot Suspension), 22.5 mg, 30 mg and 45 mg. The Applicant revised the insert labeling to incorporate instructions for use which were previously detailed in the 'Instructions on how to Mix and Administer' pamphlet. This pamphlet was previously included in the Lupron Kit but has now been eliminated. The Division of Medication Error Prevention and Analysis (DMEPA) provided container label, carton and insert labeling comments in OSE review # 2010-377 dated September 10, 2010, all of which were implemented by the Applicant. DMEPA provides comments for the insert labeling in Section 4.1 which have also been communicated to the Division during labeling meetings.

2 METHODS AND MATERIAL REVIEWED

An updated search of the Adverse Event Reporting System (AERS) from the previous OSE review was conducted using the following criteria: the Verbatim Term "Lupron Depot%" and limiting product selection to applicable strengths for this application (22.5 mg, 30 mg and 45 mg) and MedDRA reaction terms "Medication Errors" (HLGT), Product Quality Issues" (HLGT), and "Device Malfunction Events NEC" (HLT). The search date was limited to August 1, 2010 to April 20, 2011.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

Additionally, DMEPA evaluated the Applicant's revised insert labeling included in a submission dated February 3, 2011 as well as our comments included in OSE review # 2010-377.

3 RESULTS AND DISCUSSION

The following sections summarize our evaluation of the relevant AERS cases and insert labeling analysis for Lupron Depot.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The AERS search yielded 16 additional medication error reports involving Lupron Depot. Three of the 16 cases were eliminated because they involved adverse events not related to a medication error or an overdose unrelated to Lupron.

The remaining 13 cases involve medication errors associated with the use of Lupron Depot. All of the identified cases were of similar nature to those identified in our previous review, OSE # 2010-377. The identified categories were; wrong frequency,

wrong drug, wrong route, wrong storage, and device failure which were discussed in detail in OSE review # 2010-377.

- Seven of the medication error cases were associated with wrong frequency. Five of the seven suggest date calculation errors because there is no correlation between the wrong time it was administered and other formulations which may have resulted in confusion. However, one error, in which Lupron Depot three month formulation was administered once a month for 3 months suggests that the '3 month' component of the name may have been misinterpreted for the duration of therapy rather then the frequency of administration.
- Two of the 13 medication errors were associated with wrong route. In both cases, Lupron Depot was given subcutaneously rather then via the intramuscular route.
- Two of the 13 medication error cases involved wrong drug with the 22.5 mg and the 11.25 mg Lupron Depot strengths. Both of these Lupron Depot formulations are three month formulations, however one is specifically indicated for endometriosis (11.25 mg) and one is indicated for prostate cancer (22.5 mg). It is likely that because they both share the '3 month' time frame and both state this on the labeling that the strengths were overlooked and attention was paid to the '3 month statement'.
- The remaining errors involve device failure and wrong storage and did not describe why the errors occurred.

3.2 LABELING

The currently marketed Lupron Kit includes a separate 'Instructions on how to Mix and Administer' pamphlet in addition to the package insert. These instructions will now be incorporated into the *Dosage and Administration* Section of the package insert, thereby eliminating the need for the pamphlet. In a previous review, OSE # 2010-377, DMEPA made recommendations for the pamphlet in response to the medication errors identified in AERS. These recommendations were not forwarded to the Applicant. However, because the pamphlet has been eliminated, we have revised our recommendations accordingly so that there are no redundancies and they can more easily be incorporated into the insert labeling format.

Our analysis of the instructions determined that they do not provide adequate description of the proper method for intramuscular injection. Because multiple errors have been identified in AERS concerning wrong route of administration (primarily subcutaneously), a description of intramuscular injection, including proper angle and a picture can help mitigate future confusion regarding proper administration.

Currently, the insert labeling states 'Since Lupron Depot does not contain a preservative, the suspension should be discarded if not used immediately'. However, although this does provide some instruction, it is ambiguous and may cause unnecessary waste or exposure. Analysis of a similar product, Eligard, determined that an explicit time frame of ½ hour is instructed for time after preparation that the product must be discarded. Although no errors were identified in the AERS search, a clearly defined timeline for time from preparation to discard will be helpful.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA finds that the revised insert labeling, which includes the instructions for administration, lacks important instructions that can mitigate errors such as more detailed instructions for intramuscular instruction and more exact timeframes for when the product should be discarded after reconstitution. Our specific recommendations have been communicated to the Division during labeling meetings and are also detailed below.

Additionally, because no new types of medication errors were identified in our AERS search and all of our container label and carton labeling recommendations from OSE review # 2010-377 were implemented, we have no further recommendations with regards to the container labels and carton labeling

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

4.1 INSERT LABELING (SECTION 2.1 DOSAGE AND ADMINISTRATION)

1. Due to the identification of multiple cases which detailed subcutaneous injection, we recommend more detailed instruction, including a pictorial of a 90 degree intramuscular injection and where on the body to give the injections, to ensure that the importance of correct injection technique is conveyed in the insert.
2. Provide a more exact timeframe for discarding the reconstituted product if not used immediately (e.g. Eligard specifies 30 minutes after reconstitution).

REFERENCES

OSE review # 2010-377, Label and Labeling Review for Lupron Depot, 7.5 mg, 22.5 mg, 30 mg, and 45 mg, December 10, 2010, Crandall, A.

AERS Cases

ISRNUM	CK	CSENUM
6964374	X	7571946
6988367	1	7572062
7198607	4	7740482
7198613	X	7740487
7198628	1	7740498
7198722	5	7740567
7198741	9	7740585
7198742	0	7740586
7198745	6	7740589
7198746	8	7740590
7198776	6	7740620
7198779	1	7740623
7198785	7	7740629
7198789	4	7740632
7202700	7	7603659
7228041	X	7703842

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/s/

ANNE C TOBENKIN
05/11/2011

MELINA N GRIFFIS
05/11/2011

CAROL A HOLQUIST
05/12/2011

Summary and CDTL Review for Regulatory Action

Date	October 4, 2010
From	Anthony J. Murgo, M.D., M.S.
Subject	Acting Deputy Division Director CDTL/Summary Review
NDA # **Supplement #**	21-517 S-030
Applicant Name	Abbott
Date of Submission	11 December, 2009; 26 May, 2010
PDUFA Goal Date	11 October, 2010
Proprietary Name / **Established (USAN) Name**	Lupron Depot/ Leuprolide Acetate
Dosage Forms / Strength	Injection/45 mg
Proposed Indication(s)	For the palliative treatment of advanced prostate cancer
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	X
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X (Product Quality)
Clinical Pharmacology Review	X (including ONDQA Biopharmaceutics
DDMAC	
DSI	X
CDTL Review	
OSE/DMEPA	X
OSE/DDRE	
OSE/DRISK	
Other - Consults	Division of Reproductive and Urologic Products

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This is a supplemental NDA (20-517/S-030) for Lupron Depot® (leuprolide acetate for depot suspension) which provides safety and efficacy information to support a new 6-month formulation for the palliative treatment of advanced prostate cancer. The proposed formulation provides for the intramuscular administration of Lupron Depot, containing 45 mg of leuprolide acetate, at six-month intervals. Currently, 3-month (22.5 mg) and 4-month (30 mg) Lupron Depot formulations are marketed. To support approval, the sponsor submitted one phase 3 open-label, non-randomized trial in 150 subjects with prostatic adenocarcinoma (Study L-PC-7-169). This study evaluated the efficacy and safety of two doses of leuprolide acetate 45 mg, 6-month depot formulation. The primary endpoint was suppression of serum testosterone to ≤ 50 ng/dL from Week 4 through Week 48. The Division of Scientific Investigations (DSI) identified that the bioanalytical site, Esoterix, Inc. (Calabasas Hills, CA), violated stability, precision, accuracy, and calibration curve of the analytical method in measuring total testosterone. These deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of the new formulation. This is a major reason for a Complete Response action, which will also convey deficiencies in the carton and container (syringe) labels. Review of the remainder of the labeling will be completed during the next cycle or when the application is otherwise approvable. This Signatory Authority Review will focus on the salient aspects of the application and review, particularly those resulting in a CR action. The review contains sufficient information to also serve as a CDTL review.

2. Background

The purpose of this submission is to provide data to support a new formulation of Lupron Depot, for the palliative treatment of advanced prostatic cancer. The proposed formulation provides for the administration of an injection of Lupron Depot, containing 45 mg of leuprolide acetate, at six-monthly intervals. This formulation provides an alternative dosing regimen which results in fewer injections per year, compared to the currently-approved 3-month (22.5 mg) and 4-month (30 mg) Lupron Depot formulations.

Lupron is a synthetic nonapeptide agonist analog of naturally occurring gonadotropin releasing hormone, GnRH or LH-RH. It acts as an inhibitor of gonadotropin secretion (after an initial stimulation) with continuous exposure. The drug has the potential to retard the growth of hormone dependent tumors and can result in reproductive organ atrophy. In males, testosterone levels can be reduced to that of castration.

Lupron is the subject of an approved NDA and previous formulations have an approved package insert which summarizes information about the drug. The drug was first approved in 1985 for the treatment of advanced prostatic cancer. Since its initial approval, a larger strength dosage form has been approved so that the drug can currently be administered therapeutically as few as three times a year. The present supplement seeks approval of a depot dosage form at 45 mg that can be administered twice a year. The toxicity profile of the drug is fairly well established and includes hot flush, pain at the injection site, and fatigue.

The applicant submitted one pivotal study in support of this supplemental NDA: Protocol LPC07-169 (A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the

Efficacy, Safety and Pharmacokinetics of Two 6 Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma). This was an open label trial of Lupron 45 mg administered intramuscularly six months apart. Enrolled were 151 subjects at 30 sites. Only one of the formulations (Formulation A) met its efficacy endpoint while the other (Formulation B) did not. Efficacy and safety data has been submitted from patients who received Formulation A. Only safety data has been submitted from patients who received Formulation B. The sponsor reported that testosterone suppression was rapid and sustained throughout the 12 month testing period and that the suppression rate for testosterone levels (to less than or equal to 50 ng/dL after study Week 4) was 93.7%.

The Division of Scientific Investigation (DSI) identified that the bioanalytical site, Esoterix, Inc. (Calabasas Hills, CA), violated stability, precision, accuracy, and calibration curve of the analytical method in measuring total testosterone. Following DSI's inspection of Esoterix, Inc., (August 9-17, 2010) Form FDA-483 was issued and DSI's evaluation was sent to DDOP on September 9, 2010. DSI received responses to the inspection on September 8, 2010 from Esoterix and Abbott. DSI evaluated these responses, and found them to be inadequate (September 21, 2010 addendum to the DSI GLP and Bioequivalence Branch review). These deficiencies raised serious questions regarding the validity of the data needed to determine the efficacy and safety of the new formulation.

3. CMC

The initial CMC review was signed on August 26, 2010. That review recommended for Not Approval due to deficiencies in *in-vitro* release specification (noted in the original ONDQA Biopharmaceutics review signed August 12, 2010) and sterility assurance (noted in the original Microbiology Product Quality review signed July 2, 2010). A revised CMC review was signed by the primary reviewer and the branch chief on September 14 and September 15, 2010, respectively, noting that the sterility deficiencies were adequately addressed (see revised Microbiology Product review signed on August 19, 2010). I concur with the conclusions reached by these reviewers that there are no outstanding CMC or Microbiology Product Quality deficiencies. Please see Section 5, below, regarding ONDQA Biopharmaceutics deficiencies.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was signed September 21, 2010. In the present submission, the application included pharmacodynamic and local tolerance studies. *In vivo* pharmacokinetic and pharmacodynamic studies were completed in the rat and dog. After a single subcutaneous (rat) and intramuscular (dog) dose, leuprolide acetate levels were sustained for approximately 22 weeks in rats and 24 weeks in dogs. Testosterone levels were suppressed during the 24-week period post dosing. There were no release differences observed between the pilot lot and the clinical lot. Local tolerance studies were completed in rabbits. The results show that treatment did not increase local irritation effects. I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval of the proposed new dosage form.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was signed by the primary reviewer and team leader on September 8 and September 9, 2010, respectively. This review found the application not

acceptable from a clinical pharmacology perspective based on the major deficiencies identified in the DSI Report concerning the methodology for measuring testosterone levels from samples obtained in the Study L-PC-7-169 (see Section 7, below).

The ONDQA Biopharmaceutics review was signed by the primary reviewer and team leader on August 11 and August 12, 2010, respectively. That review, which focused on the *in vitro* release methodology and specifications, concluded that the data provided did not support the proposed acceptance criterion at 54 hours and that an additional time point at 72 hours is needed.

The following figure shows the release data for (b) (4) at 54 hours and 72 hours along with the proposed limits and recommended limits.

% Released at 54 hours

% Released at 72 hours

(b) (4)

Acceptance criteria

(b) (4)

I concur with the conclusions reached above by the clinical pharmacology/biopharmaceutics reviewers.

6. Clinical Microbiology

Not applicable to this application.

7. Clinical/Statistical-Efficacy

The final review by the DDOP Clinical Team was signed by the primary reviewer and team leader on October 1, 2010. The Response to the Request for Consultation by the Division of Reproductive and Urologic Products (DRUP) was signed September 30, 2010 and the Statistical review was signed September 2, 2010. Also, please refer to final review by DSI GLP and Bioequivalence Branch signed September 21, 2010. The design of the phase 3 protocol is summarized in Sections 1 and 5 above. The primary endpoint was the percentage of subjects with suppression of serum testosterone (T) to "medically castrate" levels (≤ 50 ng/dL) from week 4 through week 48. Success for this endpoint for an individual subject required:

- Onset of T suppression (≤ 50 ng/dL) by week 4 (day 32),
- No escapes (T > 50 ng/dL) at any visit, and
- Continued suppression at week 48.

Success for the entire study population was defined as the lower bound of 2-sided 90% confidence interval no less than 87%, reflecting a point estimate success rate of approximately 91%.

The primary endpoint was calculated using a Kaplan-Meier method for right-censored observations where failures counted at the first T > 50 ng/dL, success counted at the last T measurement, and premature terminations counted until the last T measurement. The 2-sided 90% lower confidence bound was also calculated using the standard error from the Kaplan-Meier method. In addition, seven supportive sensitivity analyses were performed to evaluate the effect of different assumptions on the primary endpoint analysis.

Based on the submitted efficacy data from Study L-PC07-169, the estimated percentage of the patients who had suppression of serum testosterone (≤ 50 ng/dL) (suppression rate) from Week 4 through Week 48 was 93.7 % (95% CI: 89.7; 97.7). The result of the suppression rate met the pre-specified criterion of being successful for a new formula of Lupron Depot® that the lower bound of the 95% confidence interval (CI) of the suppression rate should be greater than 87%. No statistical comparisons were conducted in the study and therefore no statistical inference can be drawn from the study. The Statistical team deferred to the clinical review team as to whether the suppression rate demonstrated in Study L-PC07-169 is clinically meaningful and whether the inference regarding favorable benefit-risk profile for the use of the new formulation of Lupron Depot® (leuprolide acetate) for the palliative treatment of advanced prostate cancer.

On August 17, 2010, DSI conducted an inspection of Esoterix, Inc. analytical laboratory in Calabasas, CA and issued a Form FDA-483. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from the single Phase 3 clinical study (Study L-PC-7-169). The deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of the drug product being considered for approval.

The deficiency of critical importance was that many analytical runs had > 33.3% of the total QCs and/or > 50% of the QCs at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations. The firm used the Westgard rules to accept or reject analytical runs, rather than the acceptance criteria listed in the 'FDA Guidance for Industry- Bioanalytical Method Validation'. During inspection, the firm was requested to recalculate the QC results in each run using criteria listed in the FDA guidance (i.e. reject a run when > 33.3 % of total # of QCs and/or > 50% of QCs at the same concentration with deviations > 15% (for MS based assays) or 20% (for ligand based assays) from the nominal concentrations. Many runs failed the run acceptance criteria used in the FDA guidance.

On September 7, 2010, Abbott Endocrine, Inc. provided a response to the Esoterix Form FDA-483 observations. The response addresses only the validation of the testosterone assay. The response does not address the extensive in-study failures of the testosterone calibration curve and QC accuracy. The results of the DSI inspection of laboratory methods used to measure testosterone have raised serious questions about the reliability of the phase 3 trial efficacy results. The FDA plans to advise Abbott that adequate and reliable data must be provided to assess the safety and efficacy of this drug product. The failed runs identified in the DSI audit should be re-analyzed. If these deficiencies cannot be adequately addressed, new Phase 3 data will be required.

DRUP was consulted on this application and the conclusions of the reviewers (in their September 30, 2010 review) are follows:

"If the DSI inspection of Esoterix Labs had not revealed significant deficiencies, then the results from study L-PC07-169 would have adequately supported the efficacy of the new product. This new preparation appeared to achieve the pre-specified efficacy requirements, resulted in no new safety signals, and showed a safety profile consistent with previously approved depot formulations. The occurrence of several "low-grade" escapes towards the end of each dosing cycle would not have jeopardized approval, but would have supported a dosing schedule of every 24 weeks (as per protocol), rather than every 6 months.

However, subsequent to our review, the results of the DSI inspection have called into question the validity of the reviewed data. Therefore, it appears that sponsor will need to present evidence that affirms the validity of the original data or will need to provide additional data for another review."

I concur with the with Clinical Review team and with the DRUP consultants that the QA deficiencies in the analytical methods used to measure testosterone raise serious questions regarding the validity of the data needed to adequately assess the efficacy and safety of the new formulation.

8. Safety

Please refer to the reviews of the DDOP Clinical Team and the DRUP consults cited above. I agree with the conclusions of the DDOP Clinical Team and the DRUP reviewers that the safety profile of the proposed formulation is consistent with the previously approved formulations and that there are no new safety signals.

The application was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). That review, signed September 10, 2010, identified the various areas related to the container, carton (clamshell labeling) and inserts labeling needing improvement which can be applied to both the currently marketed Lupron Depot products and the proposed 45 mg strength Lupron Depot. They request that these changes be implemented prior to approval. DMEPA also identified needed areas of improvement specifically related to the instructions for mixing and administering which were revised in the supplement submitted to the Agency in 2007. See Section 12 and 13 for more information.

9. Advisory Committee Meeting

For NMEs and BLAs- include rationale if product was not referred for review to an AC. For all other applications include salient discussions and votes/recommendations from the AC.

10. Pediatrics

Includes pediatrics exclusivity board review, PeRC review outcome, consults

11. Other Relevant Regulatory Issues

According to the DSI Good Clinical Practice Branch review signed September 14, 2010, two domestic clinical investigator sites were inspected in support of this sNDA. No significant deficiencies were identified and the data appeared acceptable in support of the pending application.

See Section 7 above regarding the DSI GLP and Bioequivalence Branch audit and related deficiencies.

There are no other unresolved relevant regulatory issues.

12. Labeling

Please see Section 8 above and Section 13 below regarding the container and carton labeling. Review of the remainder of the labeling will be completed during the next cycle or when the application is otherwise approvable.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Complete Response

Comments to be conveyed in the CR letter:

CLINICAL

The Division of Scientific Investigations (DSI) conducted an audit of the Esoterix, Incorporated analytical laboratory located in Calabasas, California. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from your single phase 3 clinical study (Study L-PC-7-169). These deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of your drug product. Specifically, the samples in the failed runs identified in Item 3 of the Form

FDA-483 come from 116 different subjects (77% of the total subject population) measured during the efficacy threshold window. Accuracy of all subject measurements during the threshold window must be established to evaluate if the primary endpoint was reached. In the absence of accurate data upon which an approval decision can be based, this NDA cannot be approved.

Information Needed to Address the Clinical Deficiency

Adequate and reliable data must be provided to assess the safety and efficacy of this drug product. Eliminating the subjects with failing samples from analysis provides too few subjects for proper evaluation. Therefore, the samples from the failed runs identified in the DSI audit should be re-analyzed. If these deficiencies cannot be adequately addressed, new Phase 3 data will be required.

PRODUCT QUALITY

The proposed in vitro release acceptance criteria do not control the shape of the release curve in (b) (4) therefore these criteria are not acceptable.

Information Needed to Address the Product Quality Deficiency

The following drug release acceptance criteria are recommended for Lupron Depot products using the proposed in vitro release methodology:

Acceptance criteria

(b) (4)

LABELING

1. Clam Shell Carton labeling for all strengths
    a. Box the strength statement that is located below the proprietary name with the same color band that is used for each strength at the top of the clamshell labeling to increase visual differentiation between the 7.5 mg. 22.5 mg, 30 mg and 45 mg strengths.
    b. Present the route of administration, “For intramuscular injection” so that the labeling is in compliance with CFR 201.100(b)(3).
    c. Relocate all the strength and frequency of administration statements on all principle display panels so that the strength appears first and then is followed by the frequency in which it is administered.

Lupron Depot
(Leuprolide Acetate for Depot Suspension)
45 mg
For 6-month administration

d. Post-marketing surveillance indicates that errors occur between the various formulations and strengths of Lupron. Provide an area on the front of the clamshell dedicated for the placement of the pharmacy label to decrease the risk that information, such as frequency of administration and pictures, intended to be read by patients and practitioners is not covered by a pharmacy label. This free space for a pharmacy label could be created by removing the "front chamber" contents and "second chamber" contents information and placing this in the prescriber information.

If revising the clamshell carton labeling in this manner is not feasible, revise the interior of the clam shell so that it includes a warning or statement that alerts practitioners to the correct patient population and frequency of administration on the inside of the clam shell. If a pharmacy label covers the population recommendations provided by the pictures on the principal display panel, the practitioner that is administering the drug may see this information when the clam shell is opened.

2. Syringe Label (all strengths)

a. Present the strength in the same color font as the color band used on the kit labeling. Alternatively, remove the color block currently used for the NDC number and product description and use it to present the strength.

b. Present the route of administration, "For intramuscular injection" so that the label is in compliance with CFR 201.100(b)(3).

3. Submit draft labeling that incorporates revisions from the FDA labeling document dated August 26, 2010. We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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/s/

ANTHONY J MURGO
10/04/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 14, 2010

TO: Diane Hammer, Regulatory Project Manager
Gwynn Ison, Medical Officer
Division of Drug Oncology Products

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20 517/SE2-030

APPLICANT: Abbott Laboratories

DRUG: Lupron Depot (leuprolide) injection

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Prostate Caner

CONSULTATION REQUEST DATE: January 27, 2010

DIVISION ACTION GOAL DATE: September 11, 2010

PDUFA DATE: October 11, 2010

I. BACKGROUND: Lupron is the subject of an approved NDA and has an approved package insert which summarizes information about the drug. The drug was first approved in 1985 for the treatment of advanced prostatic cancer. Since its initial approval, larger dosage forms of the drug have been approved so that the drug can currently be administered therapeutically as few as three times a year. The present supplement seeks approval of a depot dosage form at 45 mg that can be administered twice a year. The toxicity profile of the drug is well established and includes hot flush, pain at the injection site, and fatigue.

Lupron is a synthetic nonapeptide agonist analog of naturally occurring gonadotropin releasing hormone, GnRH or LH-RH. It acts as an inhibitor of gonadotropin secretion after an initial stimulation when given continuously. The growth of hormone dependent tumors is retarded and reproductive organs atrophy. In males testosterone levels are reduced to that of castrati.

The applicant submitted one pivotal study in support of this supplemental NDA: Protocol L-PC07-169 (Formulation A - A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety and Pharmacokinetics of Two 6 Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma). This was an open label trial of Lupron 45 mg given six months apart. Enrolled were 151 subjects at 30 sites. Testosterone suppression was rapid and sustained throughout the 12 month testing period. The suppression rate for testosterone levels was 93.7% less than or equal to 50 ng/dL after study Week 4.

Routine surveillance inspections were assigned for two of the larger sites that participated in the clinical trial.

II. RESULTS (by Site):

CI	Site#/ # of Subjects	Inspection Date	Final Classification
David Lipsitz, MD 1084 Vinehaven Drive Concord, NC 28025	50042/10	June 16-18, 2010	NAI
Daniel Saltzstein, MD Urology San Antonio Research, PA 7909 Fredericksburg Road, Ste 115 San Antonio, TX 78229	11706/8	June 2-8, 2010	NAI

Key to Classifications
NAI = No deviation from regulations.

1. David Lipsitz

a. **What was inspected**: The case histories of 11 subjects were audited for, but were not limited to, inclusion/exclusion criteria, drug accountably (receipt, storage, dispensing, and quantity returned), randomization process, screen failures, withdrawals, serious/adverse events, early discontinuation, monitoring, IRB approval, comparison of site CRF with data listings provided with the

assignment, primary and efficacy endpoint collection and overall protocol compliance. There were no limitations to the inspection.

b. **General observations/commentary**: The study appears to have been conducted adequately and there were no substantial problems identified. No Form FDA 483 was issued.

c. The data appears to be acceptable in support of the pending application.

2. **Daniel Saltzstein**

a. **What was inspected**: The records of 14 subjects enrolled into the study were reviewed. Specific items examined included, but were not limited to, inclusion/exclusion criteria, drug accountably (receipt, storage, dispensing, and quantity returned), randomization process, screen failures, withdrawals, serious/adverse events, early discontinuation, monitoring, IRB approval, comparison of site CRF with data listings provided with the assignment, primary and efficacy endpoint and overall protocol compliance. There were no limitations to the inspection.

b. **General observations/commentary**: The records were in order and no Form FDA 483 was issued.

c. Assessment of data integrity: The data appears to be acceptable in support of the pending application

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two domestic clinical investigator sites were inspected in support of this sNDA. No significant deficiencies were identified. The data appears to be acceptable in support of the pending application

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

ROBERT S K YOUNG
09/14/2010

TEJASHRI S PUROHIT-SHETH
09/14/2010

Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	September 10, 2010
To:	Robert Justice, MD Division of Drug Oncology Products
Through:	Melina Griffis RPh, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Anne Crandall, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Lupron Depot Labeling Review
Drug Name(s):	Lupron Depot (leuprolide acetate for depot suspension) 7.5 mg, 22.5 mg, 30 mg, and 45 mg
Application Type/Number:	NDA 20-517/ S025/S030 NDA 19-732/S032
Applicant/sponsor:	TAP Pharmaceutical Products, Inc
OSE RCM #:	2008-715 2008-1317 2010-377

CONTENTS

EXECUTIVE SUMMARY

This review responds to two seperate requests from the Division of Drug Oncology Products. The first request is to evaluate the revised Instruction for Mixing and Administering Pamphlet for Lupron Depot submitted as a prior approval labeling supplement to the Agency on December 10, 2007 for NDA 019732 (S-032) and NDA 020517 (S-025). The second request is to evaluate proposed labels and labeling for a new 45 mg strength of Lupron Depot submitted as part of an efficacy supplement dated December 11, 2009 for NDA 20517(S-030). Because all the Lupron Depot products contained in these supplements will be used for the same population and indication (palliative treatment of prostate cancer), the label and labeling reviews of the supplements were combined into one review.

The addition of the 45 mg strength to the Lupron product line is reasonable based on the Dosage and Administration of this product. However, DMEPA conducted an AERS search for medication error cases associated with the use of Lupron Depot and identified 74 medication error cases related to dispensing or administering the wrong formulation, administering Lupron products at the wrong frequency or issues with wrong technique or wrong site of administration. Most cases of wrong formulation occurred due to overlapping strengths between the different formulations of Lupron Depot or because practitioners used partial doses of a larger strength syringe or multiple smaller strength syringes to equal the specific syringe strength that was prescribed. The wrong frequency also occurred due to changes in strength during treatment and poor documentation in the patient's charts. In addition to these 74 cases, we identified 19 cases related to device malfunction.

Based on these post-marketing events and our evaluation of the proposed labeling submitted under these supplements, we provide recommendations for changes to the container label, carton, insert and pamphlet labeling in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to two consults from the Division of Drug Oncology Products to evaluate two supplements submitted by the Applicant and identify any outstanding areas of concern from a medication errors perspective. One supplement for two separate NDAs 019732 (S-032) and 020517 (S-025) consisted of revised pamphlet labeling and a subsequent efficacy supplement for NDA 020517 (S-030) contained proposed labels and labeling for new 45 mg strength of Lupron Depot.

1.2 PRODUCT INFORMATION

Lupron Depot (leuprolide acetate for depot suspension), is an LH-RH agonist, which acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Administration of leuprolide acetate has resulted in inhibition of growth of certain hormone dependent tumors as well as atrophy of the reproductive organs.

Lupron Depot is available as lyophilized micro spheres which are to be reconstituted and administered immediately after reconstitution under the supervision of a physician. Because Lupron must be administered by a health care professional, patients typically are prescribed the medication, the Lupron Depot is dispensed at the pharmacy and then returns to the physician office for administration by a health care professional. Lupron Depot is available in multiple strengths (3.75 mg, 7.5 mg, 11.25 mg, 22.5 mg, and 30 mg) and is used for a variety of indications across a very broad spectrum of patients. Lupron Depot Ped (NDA 020263) is used in

the treatment of children with central precocious puberty. Lupron Depot and Lupron Depot-3 (NDA 020011 and NDA 020708) are also used in women for the treatment of endometriosis and uterine fibroids.

Table 1 below describes the recommended dosing and coinciding frequencies for NDA 019732 and NDA 020517 (patients with prostate cancer), however for the purpose of fully understanding the Lupron product line, all Lupron products have been tabled according to the indication.

Table 1: Summary of Lupron Depot doses indicated in palliative treatment of prostate cancer that relate to this supplements under review (NDAs: 019732 and 020517)

Product Name	Patient Population	Dose (mg)	Frequency
Lupron Depot	Adult Male	7.5 mg	Once a month
Lupron Depot	Adult Male	22.5 mg	Once every 3 months
Lupron Depot	Adult Male	30 mg	Once every 4 months

Table 2: Summary of Lupron Depot-Ped Doses indicated for precocious Puberty (NDA 020263)

Product Name	Patient Population	Dose	Frequency
Lupron Depot-Ped	Children	7.5 mg	Once a month
Lupron Depot-Ped	Children	11.25 mg	Once a month
Lupron Depot-Ped	Children	15 mg	Once a month

Table 3: Summary of Lupron Depot and Lupron Depot doses indicated for endometriosis and anemia associated with leiomyoma uteri (NDAs: 20011 and 020708)

Product Name	Patient Population	Dose	Frequency
Lupron Depot	Adult Female	3.75 mg	Once a month
Lupron Depot	Adult Female	11.25 mg	Once every 3 months

Dosing can be chosen based on convenience, as Lupron Depot must be administered under the supervision of a Physician. Each Lupron Depot dose is packaged as a kit with a prefilled dual-chamber syringe, which is equipped with a LuproLoc safety device. To prepare for injection, the white plunger is screwed into end stopper of the syringe. The plunger is pushed slowly up into the syringe which mixes the diluent with the powder, which forms a milky white suspension. This suspension is gently mixed and then immediately injected into the patient via the intramuscular route.

1.3 Regulatory History

The applicant submitted labeling supplements on December 10, 2007. One for NDA 020517 and the second for NDA 019732, both approved for the palliative treatment of advanced prostate cancer. Subsequently, an efficacy supplement was submitted to the Agency on December 11, 2009 which proposed another strength, 45 mg, to the Lupron line which will be injected intramuscularly every 6 months.

Lupron Depot 7.5 mg/vial (NDA 19-732) was originally approved January 26, 1989 and is given intramuscularly on a monthly basis. Lupron Depot 22.5 mg and Lupron Depot-4 Month, a 30 mg, were approved December 22, 1995 (NDA 20-517). Various portraits of a face which represent the typical patient for the prostate cancer indication have been displayed on the principal display

panels of the clamshell, with the most recent revision of the picture occurring in 2007. The revision of labeling in 2007 also included a horizontal banner on the principal display panel which states "For Adult Use".

Additionally, during post-marketing surveillance, DMEPA evaluated a safety signal identified and error with Lupron Depot 11.25 mg and Lupron Depot Ped 11.25 mg. The safety signal states that Lupron Depot 11.25 mg was dispensed and administered every month for 11 months instead of the prescribed Lupron Depot Ped 11.25 mg. The patient experienced adverse events due to the error and had not fully recovered from the receiving the wrong drug. This signal prompted a review (OSE #2008-1317) which will be subsumed into this review.

Lupron Depot 3.75 mg was approved for use in females for the indication of endometriosis in October 1990. Subsequently, Lupron Depot-3 (11.25 mg) was approved for the same indication; however the frequency of administration was extended from once a month to every three months.

Lupron Depot-Ped was approved in the pediatric population for the indication of central precocious puberty in April 1993. No new formulations of this product have been approved since the initial product approval.

2 METHODS AND MATERIALS

2.1 MEDICATION ERROR CASES

2.1.1 Adverse Event Reporting System (AERS)

DMEPA conducted a search of the FDA Adverse Event Reporting (AERS) database to determine if any medication errors were associated with the product packaging and labeling. The timeframe of the AERS search was based on the most recent label revision which occurred in 2007. These labels added a "For Adult Use" and revised the picture on the principle panel to reflect a common patient with the prostate cancer indication. The search began with the date of January 1, 2007 and an end date of July 1, 2010 which was the date the AERS search was conducted. The search was conducted using the high level term (HLT) "device malfunction events NEC and the high level group terms (HLGT) "medication errors" and "product quality issues". The product was searched under the name "Lupron" and the active ingredient "leuprolide%".

The reports were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the reports to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors involving a different route of administration or dosage form) were excluded from further analysis. Duplicate reports were combined into cases. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. Additionally, the outcomes of the errors were categorized according to the National Coordinating Council for Medication Error Reporting Prevention (NCCMERP), which classifies the error according to the severity of the outcome (see Appendix C).[1]

[1] NCCMERP Index for Categorizing Medication Errors. http://www.nccmerp.org/pdf/indexColor2001-06-12.pdf

2.2 CARTON AND CONTAINER LABELS

The Applicant submitted two different supplements which pertained to different products.

On December 11, 2007 the Applicant submitted the following labels and labeling for our review (see Appendices A, B):

- Carton Labeling (Clamshell Kit): 7.5 mg, 22.5 mg, 30 mg,
- Syringe Label
- Instructions on How to Mix and Administer Pamphlet
- Prescriber information

On December 10, 2009 the Applicant submitted the following label and labeling for our review.

- Carton Labeling (Clamshell Kit): 45 mg
- Prescriber information

Using FMEA[2], the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling to identify aspects that may have contributed to the medication errors or could result in future errors.

3 RESULTS

3.1 AERS DATABASE

The AERS databases search conducted on July 1, 2010 returned 145 cases involving adverse events and medication errors associated with the use of Lupron Depot (see Appendix D for ISR listing of cases). Fifty two cases were eliminated from further review because they involved adverse events, missed doses, or practice related errors that were not relevant to this label and labeling review. The remaining 74 errors involving medication errors associated with the use of Lupron Depot are detailed below in Sections 3.1.1 (wrong formulation), 3.1.2 (wrong frequency), 3.1.3 (wrong route), 3.1.4 (miscellaneous errors), 3.1.5 (wrong drug), and 3.1.6 (storage errors). We also identified 19 cases of device malfunction and these are described in Section 3.1.7.

Although some of the cases retrieved involve strengths of Lupron Depot not associated with the proposed supplements under review, they were included in our analysis and noted as secondary findings. The reason we considered these cases as relevant to our analysis is that the same types of errors occurred through the Lupron product line and were not specific to strengths or indications.

3.1.1 Wrong Formulation (n=37)

The wrong formulation was dispensed or administered in 37 medication error cases (see Appendix D for narrative description of these cases). Twenty nine of these errors occurred between the same strengths (Lupron Depot 11.25 mg and Lupron Depot Ped 11.25 mg). Although the products contain the same amount of active drug, the formulations are different as well as the dosing intervals. This type of dispensing error occurred with both the pediatric formulation and the adult formulation.

[2] Institute for Healthcare Improvement (IHI). Failure Mode and Effect Analysis. Boston. IHI:2004.

- Fifteen cases (n=15) involved the pediatric formulation dispensed or administered instead of the prescribed adult formulation. In pediatric populations Lupron Depot Ped is administered once a month vs. every three months in adult women.
    - One case (n=1) involved dispensing the 7.5 mg strength, the outcome was not provided.
    - Three cases (n=3) merely stated that the pediatric formulation was dispensed to an adult, but did not include strength or outcome.
    - Eleven cases (n=11) involved the 11.25 mg strength. One of these cases was detected after administration and the woman had to come in every month for three months. In the other 10 cases, the error was reported, but the cases did not indicate how therapy was altered to correct the wrong formulation administration. Outcomes were not provided in the cases.
- Fourteen cases (n=14) involved the adult formulation dispensed or administered instead of the prescribed pediatric formulation.
    - One case (n=1) involved the 7.5 mg strength which was incorrectly dispensed by the pharmacist, no outcome was provided.
    - Four cases (n=4) did not cite state the strength (7.5 mg or 11.25mg) or the indication. One case clearly states that the pharmacist dispensed the wrong formulation. The other three cases state the patient was administered the wrong formulation, but no information was provided to describe whether it could be the physician's office error or pharmacist error.
    - Nine cases (n=9) involved the 11.25 mg strength. Three of these cases resulted in a child receiving more then one monthly dose of the adult formulation, which resulted in documented adverse events in one case. The other six cases involving the 11.25 mg strength were administered once and the wrong formulation was noticed after administration, however it indicates that the error was corrected and not repeated. One of these cases, the physician states that he thought the drug was the same because the strength was the same.

Some cases of medication errors also described the use of different strengths to achieve a dose. In these cases, health care practitioners erroneously combined Lupron Depot products that are formulated differently to achieve a dose.

- Eight errors occurred between different strengths and therefore different formulations were dispensed or administered or different strength syringes were used to obtain a dose.
    - Four cases (n=4) involved either the pharmacist or nurse using 3.75 mg, 7. 5 mg, 11.25 mg or 30 mg strength syringes to obtain the prescribed dose of 7.5 mg, or 22 mg.
    - One case (n=1) used three of the 3.75 mg syringes to equal a dose of 11.25 mg.
    - Three cases (n=3) involved dispensing the wrong strength of the adult formulation
        - Two cases involved erroneous dispensing with the one of the 3.75 mg syringes and one 7.5 mg syringe instead of the 11.25 mg syringe and the other case, the pharmacist dispensed two of the 11.25 mg syringes instead of the 22.5 mg strength.

3.1.2 Wrong Frequency (n=22)

The wrong frequency of administration was identified in 22 cases. These cases describe instances in which the correct strength and formulation were chosen, but the drug was administered either earlier or later then the recommended frequency.

- Two cases (n=2) involved the 7.5 mg strength. One patient received Lupron Depot 7.5 mg every three months, which should be given once a month. Another case involved a patient who received the 7.5 mg every month, but a nurse documented this as an error because she thought it should be every three months.
- Four cases (n=4) involved the 22.5 mg strength. In every case, the patient received the second dose one month after the first dose rather then 3 months later as recommended. One of these cases is attributed to poor documentation, as the patient received a 22.5 mg dose instead of 7.5 mg; however it was not documented in the chart as a change of dose. The three other cases, it is unclear whether the patient picked up the medication early and brought to the physician's office on his own, or whether he was instructed to pick it up in monthly intervals.
- Five cases (n=5) involved the 30 mg strength. Two of the cases, the patient received the dose every 2 months and one case he received it every month, rather then the recommended 4 month frequency. In all of these cases, it is unclear if the patient filled the medication early, or if they were told to return earlier then recommended. Two other cases, the 30 mg strength was administered once in the urologist office and another dose (22.5 mg) was given at the oncologist office a few weeks later.
- Four cases (n=4) involved early administration or refill; however the strength was not indicated. One case, the physician prescribed Lupron Depot once daily which the patient received for three days. The three other cases indicate that the patient either refilled the prescription early or was administered Lupron prior to the recommended frequency.
- Seven cases (n=7) involved the 11.25 mg strength. Six of the seven cases stated that Lupron Depot was administered every month, rather then the recommended frequency of every 3 months. The remaining case states that the patient received the dose every 3 months as prescribed, but received it for a year, which exceeds the recommended 6 months of therapy.

3.1.3 Wrong Route (n=6)

The wrong route of administration occurred in six cases.

- Four cases (n=4) involved Lupron Depot for prostate cancer being injected subcutaneously rather then the labeled intramuscular route.
- Two cases (n=2) were involved the subcutaneous route of administration for the endometriosis indication.

3.1.4 Miscellaneous Errors (n=3)

Three of the cases identified medication errors in which Lupron Depot was either administered in the wrong site or the healthcare practitioner used the wrong technique. These errors occurred in both hospital and clinics.

- One case, the Lupron Depot was administered in the forearm which is not a recommended site for IM injection.

- One case involved Lupron Depot administration with a syringe that was not the Lupron Depot syringe.
- One case complained that the needle provided was too long for a child and bruised the bone upon insertion into the muscle.

3.1.5 Wrong drug (n=4)

Four medication error cases identified the wrong drug being dispensed.

- One case involved a patient injected with Testosterone, but prescribed Lupron Depot.
- Three cases involved patients injected with Depo-Provera, but prescribed Lupron Depot for endometriosis.

3.1.6 Storage Errors (n=2)

Two cases identified incorrect storage of Lupron Depot for the endometriosis indication. The storage recommendations are on the container label, however the recommendation contain the ambiguous term, "excursion", which is used to define a time frame.

- Two cases stated that the drug was stored in a car that exceeded 100 degrees. In one of these cases the drug was administered and adverse events followed. In the other case, the patient did not inject the drug; however she missed her schedule dose due to the wrong storage.

3.1.7 Device Malfunction (n=19)

Nineteen cases identified some type of device malfunction.

- Six cases (n=6) occurred due to incomplete mixing of the powder and diluent or a clogged syringe.
- Six cases (n=6) reported that the syringe leaked.
- Seven cases (n=7) just reported "device malfunction" and no other details.

3.2 LABELS AND LABELING

The label and labeling review consisted of two evaluations for Lupron Depot products. The first evaluation focused on the revised "Instructions on how to mix and administer" pamphlet included in the 7.5 mg, 22 mg and 30 mg strength cartons which display a horizontal statement, "Adult Use Only" The second evaluation focused on the proposed container labels, instructions for reconstitution and administration and prescriber information for the 45 mg strength.

In both evaluations, DMEPA considered the medication error cases identified in AERS and the currently marketed container labels and carton labeling for the 7.5 mg, 22 mg and the 30 mg strengths. The results of our evaluation are provided below.

3.2.1 Syringe Label

The various strengths of Lupron use the same layout and are poorly differentiated.

3.2.2 Clam Shell Carton Labeling

The 7.5 mg strength Clamshell Kit container label does not state the frequency of administration on the principal display panel.

The strength is presented after the frequency of administration.

The storage recommendations contain the word “excursion” which is ambiguous and not clearly defined as a time-period.

The statement “Adult Use Only” and the images of faces may be inadvertently covered by a pharmacy label. The interior of the clam shell and container (syringe) label provide no indication of whether the formulation is for adults or pediatric patients.

3.2.3 Instructions on How to Mix and Administer

The statement, “For Adults Only” is printed vertically while the rest of the label is printed horizontally, which makes it less readable.

The instructions on how to mix and administer do not clearly state or provide pictorials to demonstrate how to properly administer an intramuscular injection (i.e. at a 90 degree angle).

The instructions do not recommend where to inject Lupron Depot.

3.2.4 Insert Labeling

The proprietary name, Lupron Depot, contains the frequency of administration throughout the insert labeling.

The Dosage and Administration section for the 7.5 mg strength lacks specificty with regards to frequency of administration (i.e. “once a month”, rather then “monthly”).

The Dosage and Administration section does not provide descriptive instructions to inject intramuscularly and to have the syringe enter the muscle “at a 90 degree angle”

It is unclear based on the Dosage and Administration section, whether therapy can be initiated at 22.5 mg every 3 months, the 30 mg every 4 months, or 45 mg every 6 months or whether the patient should be stabilized on the 7.5 mg and then begin therapy with the longer acting formulations.

4 DISCUSSION

Lupron Depot is available in many strengths and formulations and is indicated for a variety of disease states within the pediatric, adult and geriatric populations. Two pending labeling supplements contain revised pamphelt labeling and proposed label and labeling for a new strength of Lupron Depot.

An AERS search was conducted in order to evaluate post-marketing errors associated with the currently marketed Lupron products so that sugggestions could be made to the proposed label as well as the currently marketed labels in order to minimize ongoing and future confusion among the Lupron Depot products.

4.1 AERS FINDINGS

Lupron Depot has multiple indications for use and is used in a variety of patients including pediatrics and adult males and females. The safe use of Lupron Depot is further complicated by the fact that the various formulations share many overlapping strengths and achievable strengths and route of administration, but do not share the same frequency of administration. A large portion of the reported medication errors occurred because of the strength overlap between the adult and pediatric formulations which do not share the same frequency of administration. The varying frequency of administration across the Lupron product line was also a source of error

because Lupron Depot is recommended for different frequencies depending on the strength and/or indication.

Some of the cases retrieved involved a formulation of Lupron not associated with the proposed supplements under review for the specific indication of prostate cancer. However it was noted during the analysis that the medication errors that occurred with Lupron Depot were not driven or differentiated by formulation. The same errors occurred throughout the product line and are not specific to one strength or formulation. The total picture of the errors is better understood with the inclusion of all Lupron Depot products; therefore we included these errors in our overall analysis.

4.1.1 Wrong Formulation

Analysis of the 37 medication error cases that involved the wrong drug (Lupron Depot vs. Lupron Depot Ped) being administered or dispensed indicate that there is confusion between the pediatric and adult formulations because they are both available as 11.25 mg and the 7.5 mg strengths. Although the names differ; Lupron Depot and Lupron Depot-Ped, no cases explicitly stated that the "PED" modifier was used when prescribing or was overlooked by dispensing pharmacists. The contribution of the overlapping route name and strength to the confusion was confirmed in a number of reported errors. In some reports healthcare practitioner recognized that the patient they were caring for did not fit into the recommended and labeled population, however because the dose and drug were correct; the drug was administered. In one case, a nurse who was administering the drug questioned the physician about the product, however the physician said that the administration was acceptable because it was the right strength. In another case, the pharmacy dispensed Lupron Depot Ped 11.25 mg pediatric dose instead of Lupron Depot 11.25 mg. The pharmacist told the patient it was the same drug and dose, and the physician's office agreed with the pharmacy and administered the wrong drug.

The 7.5 mg strengths for both indications/populations are prescribed once a month, however the frequencies of administration for the 11.25 mg strength is three months for women vs. one month for pediatric patient. This type of error resulted in the under-dosing of women and overdosing of pediatric patients. One of the pediatric patients who received the adult formulation on a monthly basis experienced adverse events, such as pain and difficulty walking. These adverse events occurred while the patient received the wrong medication and persisted after the error was discovered.

Although the labels display faces of the representative age groups that would most likely be prescribed the coinciding drug and dose, the current label design does not have space to accommodate a pharmacy label. Because the front on the clam shell is the only large flat area, we are concerned that technicians (or pharmacists) could place the pharmacy label over the important information, thereby concealing the image and statements from the pharmacist that is verifying the medication or the nurse that is administering the medication after it has been picked up at the pharmacy. A designated area for the pharmacy label may help guide the appropriate placement of the pharmacy label away from the facial image or statement. Another option to help reduce the risk of wrong formulation errors is to place another graphic or statement regarding adult or pediatric use inside the clamshell. However, this type of revision to the inside of the clamshell will not prevent the dispensing error, but may help with detecting the error and prevent the administration of the wrong drug.

Eight medication error cases involving the wrong formulation (and strength) occurred because health care practitioners used a combination of smaller doses to equal a larger dose or only injected a partial of the higher dose to equal a smaller dose. The available formulations of Lupron are not equivalent and can not be interchanged. Although the prescriber information states, "Due to different release characteristics, a fractional dose of this 3-month depot formulation is not

equivalent to the same dose of the monthly formulation and should not be given", these types of error persist. The language used such as, fractional dose, could be more clearly described and we provide these recommendations under section 5.2.

The three remaining medication errors involve dispensing or administering the wrong formulation, however these errors were not related to overlapping strengths of adult and pediatric formulations, rather they were all adult male formulations but different strengths and therefore different frequencies of administration. Our analysis of the strengths that were involved in the errors revealed there is visual differentiation between the strengths, however it could be improved. The 7.5 mg, 22.5 mg, and 30 mg Lupron Depot strengths all utilize the same tan and white color scheme on the principal display and then use a band at the top each with a different color to designate the different strengths. It would be helpful to use the same color that designated the strength on the top to box in the strength that is located below the proprietary name and established name.

4.1.2 Wrong Frequency

Twenty-two medication error cases involve the wrong frequency of administration. Only the container labels for the 22.5 mg and the 30 mg Lupron Depot injections have the frequency of administration preceding the doses. Prominently including the frequency of administration after all the strengths may help mitigate confusion with regards to the frequency of administration for this specific strength. It will also provide consistency with presentation of the frequency for each strength on the principal display panel.

4.1.3 Wrong Route

Six medication error cases stated that Lupron Depot was given as a subcutaneous injection which in some cases resulted in tissue damage. Although it is unclear from the reports what lead to these errors, these adverse reactions may be avoided with explicit instructions on proper administration. Review of the instructions for administration noted that there were no clear instructions which describe proper injection technique. The instructions for mixing and administering should include explicit and include a pictorials demonstrating how to inject the syringe at a 90 degree angle. Additionally, the carton label does not include the route of administration following the established name. Relocating this statement to appear following the established name may make it more noticeable and help remind practitioners of the proper route of administration.

4.1.4 Device Malfunction

In our analysis we identified 19 cases of device malfunction. A number of cases reported that a partial dose was given and on some occasions was followed a subsequent injection during the same visit. The device malfunctions occurred primarily due to mixing problems and leaking. The Lupron Depot device does appear to leak when the plunger is pulled back after the powder and diluent have been mixed. Since there are no instructions that warn of leaking if the plunger is pulled back improved directions on how to mix and avoid leaking and inclusion of a warning about what to do if leakage occurs in the "Instruction on how to mix and administer" pamphlet should be considered.

Additionally, DMEPA would defer to ONDQA and CDRH for further assessment of this issue.

4.2 SUPPLEMENT FOR TWO SEPARATE NDAS 019732 (S-032) AND 020517 (S-025); REVISED PAMPHLET LABELING

The revised Lupron Depot clamshell label and the "Instructions on how to mix and administer" pamphlet display a statement "For Adult Use". The medication error cases encountered during the

AERS search indicate that adult patients have been dispensed and administered the pediatric formulation. Additionally, pediatric patients have been dispensed and administered the adult formulation. In one of these cases (ISR 5692740-1) the pediatric patient who received the adult formulation experienced adverse events which made her unable to walk. Although the case does not contain a medical professional explicitly indicating causality, there is a temporal relationship between when the wrong formulation was administered and the severity of the adverse events.

The horizontal banner on the principal display panel of the carton (clamshell) labeling displays the statement "For Adult Use". The Applicant may have used this banner and statement to help avoid administration errors with the wrong formulation. However, if the statement is covered with the pharmacy label so the practitioner administering the product cannot see the statement or not seen by practitioners, the wrong formulation could be administered. The horizontal statement "For Adult Use" on the mix and administer pamphlet also may help to deter the wrong formulation errors. However, practitioners may overlook the statement because the font of the statement is small and it is presented vertically, compared to the rest of the pamphlet which orients the text horizontally. Increasing the font size and therefore the prominence and orienting the statement horizontally may help communicate the statement to the practitioner and avoid administration of the wrong formulation.

4.3 EFFICACY SUPPLEMENT FOR NDA 020517 (S-0038); NEW STRENGTH OF LUPRON DEPOT (45 MG)

The proposed container label and clamshell labeling submitted in the efficacy supplement for the new 45 mg strength is visually well differentiated from the currently marketed Lupron products. The new strength uses a unique blue banner on the top of the clamshell labeling which provides adequate visual differentiation from the currently marketed strengths. However, similar to the currently marketed strengths, the clamshell labeling would benefit from increasing the use of the distinct color that is used to designate each strength. This can be accomplished by a color box around the strength located below the proprietary name, Lupron Depot which coordinates with the color band displayed at the top of the clamshell labeling. The color box around the strength would provide even greater differentiation among the various strengths of Lupron Depot.

4.3.1 45 Strength: 24 weeks versus 6 months

The entire Lupron product line expresses the frequency of administration in months. The proposed 24 week, although unique may contribute to wrong frequency of administration errors because of the established monthly dosing frequency for the product line. For these reasons DMEPA would prefer the frequency of administration to be expressed consistently throughout the labels and labeling (i.e. months). We acknowledge that there is likely clinical data to support patients improved outcomes with administration every 24 weeks versus 6 months. Thus, we defer to the clinical reviewer for analysis of the patient outcomes which will provide the basis for choosing the expression of frequency. However, if the weekly dosing is utilized DMEPA would recommend that adequate education to healthcare practitioners concerning this new frequency of administration be implemented at product launch.

4.3.2 Prescriber Information

Analysis of the insert labeling for the proposed new strength found that it is unclear if healthcare practitioners can initiate therapy with the longer acting formulations that are administered every 3, 4, or 6 months or if the patient treatment should be initiated with the 7.5 mg every month. Practitioners may believe that starting with the one month therapy may allow observation of any untoward effects however this may not be necessary or recommended. Practitioners would benefit

from explicit directions regarding sequential therapy in the Dosage and Administration section to avoid confusion.

5 CONCLUSIONS AND RECOMMENDATIONS

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis has identified the following areas of needed improvement related to the container labels, carton (clamshell labeling) and insert labeling which can be applied to both the currently marketed Lupron Depot products and the proposed 45 mg strength Lupron Depot. We request that these changes be implemented prior to approval. Additionally, as presented in the proposed label and labeling the introduction of the 45 mg strength of Lupron is reasonable.

DMEPA also identified needed areas of improvement specifically related to the instructions for mixing and administering which were revised in the supplement submitted to the Agency in 2007.

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy our division on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sue Kang, Project Manager, at 301-796-4216.

5.1 COMMENTS TO ONDQA

A number of AERS cases described errors with the storage of Lupron Depot. Patient's may find it helpful if the instructions for storage are revised to more clearly define the time period of "excursions" which permit the storage of Lupron Depot above or below the recommended temperature, e.g. up to 4 hours.

5.2 COMMENTS TO THE DIVISION

1. General Comment

   a. Our analysis of the AERS cases revealed a large number of device malfunctions that occurred during or prior to administration. DMEPA recommends ONDQA and CDRH be consulted to evaluate the significance of these events.

   b. DMEPA was involved with discussions involving ONDQA regarding the established and proprietary name. ONDQA has found the presentation of the established name to be inconsistent with USP and the regulations because it does not state the extended-release nature of the product and contains the word "depot". Despite the inconsistency with the standards and regulations, DMEPA understands that ONDQA has elected to retain the established name as is because the product is currently marketed. DMEPA agrees with this approach because it may avoid confusion that may result from such a change at this point in the product lifecycle.

   c. The proposed 24 week expression of frequency, although unique may contribute to wrong frequency of administration errors because of the established monthly dosing frequency for the product line. For these reasons DMEPA would prefer the frequency of administration to be expressed consistently throughout the labels and labeling (i.e. months). We acknowledge that there is likely clinical data to support patients improved outcomes with administration every 24 weeks versus 6 months. Thus, we defer to the clinical reviewer for analysis of the patient outcomes which will provide the basis for choosing the expression of frequency. However, if the weekly dosing is utilized DMEPA would recommend that adequate education to healthcare practitioners concerning this new frequency of administration be implemented at product launch.

d. The label and labeling recommendations as listed under 5.2 (section 2) should be implemented prior to approval of Lupron Depot 45 mg.

2. Analysis of the insert labeling identified the following areas of needed revision:

   a. The proprietary name should appear as "Lupron Depot". The proprietary name should not have the frequency of administration as a component of the proprietary name.

   b. Clarify in the Dosage and Administration section whether the patient can initiate therapy with the higher dose which allows for an extended time between administration or if the patient should start with 7.5 mg once monthly initially and then convert to the longer acting formulations. Most medications that are available as extended release and regular release recommend starting on the shorter duration product and then, provided there are no adverse events, switching to the extended duration product. However, if this type of dosing is not recommended or beneficial, this should be explicitly stated in the insert.

   c. Although the current prescriber information contains the statement, "Due to different release characteristics, a fractional dose of this 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given", these types of error persist. The language in the Dosage and Administration section (as well as highlight section) should be simplified to state, "Each strength and formulation has different release characteristics" "Do not use partial syringes or a combination of syringes to achieve a particular dose". These statements should also be written on the "Instructions on how to mix and administer" pamphlet to ensure that those who administer Lupron Depot, who may not read the prescriber information, have access to this pertinent information.

5.3 COMMENTS TO THE APPLICANT

Based upon our assessment of the Lupron Depot cases encountered during a search in the Adverse Event Reporting System (AERS) and analysis of the currently marketed and proposed labels and labeling for Lupron Depot, the Division of Medication Error Prevention and Analysis has identified the following areas of needed improvement.

1. Comments related to revised instructions pamphlet found in NDA 020517/S-025 and NDA 019732/S-032 submitted on December 11, 2007.

   A. Instructions on how to Mix and Administer

      1. Use larger font for the statement "adult use only" so that the statement has more prominence and revise the statement so that it read horizontally rather then vertically.

      2. Include the following statements so that providers administer the strength syringe that pertains to the exact prescribed dose and do not combine multiple syringes or give a partial dose of a syringe: "Check to make sure you have the correct formulation", "Each strength and formulation has different release characteristics", and "Do not use partial syringes or a combination of syringes to achieve a particular dose".

      3. A number of AERS cases stated that the syringe leaks when the plunger was pulled back. To prevent these errors, include a statement that instructs patients not to pull the plunger back once the drug is in suspension or instruct how far the plunger can be safely pulled back without causing the syringe to leak.

      4. A number of medication error cases submitted to the Agency stated that Lupron Depot was administered the subcutaneous route instead of the recommended intramuscular route. Some cases describe necrosis around the area of subcutaneous injection. Explicit instructions and pictorials showing where on the body (gluteal area, etc) and how to

properly inject intramuscularly (i.e. 90 degree angle) in the instructions pamphlet can provide a more complete guide for safe administration.

2. Comments specific to NDA 020517/S-030 submitted on December 11, 2009

A. Clam Shell Carton Labeling for all strengths

1. Box the strength statement that is located below the proprietary name with the same color band that is used for each strength at the top of the clamshell labeling to increase visual differentiation between the 7.5 mg. 22.5 mg, 30 mg and 45 mg strengths.

2. Present the route of administration, "For intramuscular injection" so that the labeling is in compliance with CFR 201.100(b)(3).

3. Relocate all the strength and frequency of administration statements on all principle display panels so that the strength appears first and then is followed by the frequency in which it is administered.

Lupron Depot

(Leuprolide Acetate for Depot Suspension)

45 mg

For 6-month administration

4. Post-marketing surveillance indicates that errors occur between with the various formulations and strengths of Lupron. Provide an area on the front of the clamshell dedicated for the placement of the pharmacy label to decrease the risk that information, such as frequency of administration and pictures, intended to be read by patients and practitioners is not covered by a pharmacy label. This free space for a pharmacy label could be created by removing the "front chamber" contents and "second chamber" contents information and placing this in the prescriber information.

a. If revising the clamshell carton labeling in this manner is not feasible, revise the interior of the clam shell so that it includes a warning or statement that alerts practitioners to the correct patient population and frequency of administration on the inside of the clam shell. If a pharmacy label covers the population recommendations provided by the pictures on the principal display panel, the practitioner that is administering the drug may see this information when the clam shell is opened.

B. Syringe Label (all strengths)

1. Present the strength in the same color font as the color band used on the kit labeling. Alternatively, remove the color block currently used for the NDC number and product description and use it to present the strength.

2. Present the route of administration, "For intramuscular injection" so that the label is in compliance with CFR 201.100(b)(3).

3. Based upon medication errors that were found in the Adverse Event Reporting System (AERS) throughout the Lupron product line, DMEPA recommends that the label and labeling revisions noted above be also applied to all the Lupron NDAs (019732, 019943, 020517, 020263, 020011, and 020708) via prior approval labeling supplements. These revisions should occur within one year or at next batch label printing, which ever occurs first.

1. See 1A1 (change to "Pediatric Use Only") through 1A4.

2. See 2A1 through 2A5.

3. See 2B1 and 2B2.

4. Increase the prominence of the “3 month” and “1 month” for Lupron Depot 11.25 mg and Lupron Depot Ped 11.25 mg by increasing the font to ensure that the different frequencies of administration are highlighted. In addition, ensure that the duration statement is located in the colored band of the principle display panel next to the strength designation.

APPEARS THIS WAY ON ORIGINAL

5 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

Appendix C: NCCMERP Index for Categorizing Medication Errors

Category	Definition
A	Circumstances of events that have the capacity to cause error
B	An error occurred by the error did not reach the patient
C	An error occurred that reached the patient but did not cause harm
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm and/or required intervention to preclude harm
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
G	An error occurred that may have contributed to or resulted in permanent patient harm
H	An error occurred that required intervention necessary to sustain life
I	An error occurred that may have contributed to or resulted in the patient's death

Appendix D: AERS Search Results

Wrong Formulation AERS Cases

ISR	CSE	FDA Receive date Date of Event	Narrative	Type of Error/Outcome
6515929	7228869	12/23/2009 N/A	Report from the USA of received the adult dose of LUPRON for one month straight coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. In 2008, the patient began LUPRON DEPOT therapy for precocious puberty. In Dec 2008, the patient, who is a five year old boy, received the adult dose of medication meant for a patient with prostate cancer. LUPRON DEPOT therapy was ongoing. The pharmacy that dispensed the medication was aware of the received the adult dose of LUPRON for one month straight. The nurse practitioner believed that the	Dispensing and administering error/ Outcome not reported, Category C

			received the adult dose of LUPRON for one month straight was not related to LUPRON DEPOT therapy.	
6626457-3	7314149	3/10/2010 2/1/2010	Spontaneous report from the USA of non-serious DISPENSED WRONG DOSAGE FORM and ADMINISTERED WRONG DOSE with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). In February 2010, the patient experienced ADMINISTERED WRONG DOSE. On 25 Feb 2010, the patient experienced DISPENSED WRONG DOSAGE FORM. The physician reported the pharmacy had dispensed the wrong dosage form of LUPRON DEPOT therapy. After the mother had administered the LUPRON DEPOT to her son, the mother noticed the package indicated LUPRON DEPOT ADULT. The patient is doing fine per the physican.	Dispensing and administering error/no adverse outcomes reported, Category C
6626468-8	7309250	3/10/2010 N/A	Spontaneous report from the USA of non-serious MEDICATION ERROR WRONG DOSE DISPENSED with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced MEDICATION ERROR WRONG DOSE DISPENSED. The pharmacist refused to be contacted. The patient was given the adult dose of LUPRON DEPOT therapy. CHANGE HISTORY On 09 Mar 2010, received updates to event information. 10 Mar 2010: follow up information received on 09 Mar 2010: Version created to correct MedDRA codes in database for electronic reporting. MAW	Dispensing and administering error/no outcomes reported, Category C
6687513-7	7359341	4/19/2010 4/5/2010	Spontaneous report from the USA of non-serious GIVEN WRONG DOSAGE and DISPENSED WRONG DOSAGE with LUPRON DEPOT-PED 11.25 MG (LEUPROLIDE ACETATE DEPOT). On 05 Apr 2010, the patient experienced GIVEN WRONG DOSAGE and DISPENSED WRONG DOSAGE. The physician ordered a three month supply of LUPRON DEPOT pediatric one month. The pharmacist read the prescription as the three month dosage. The nurse in the office questioned it with the	Dispensed and administering error/no outcomes reported, Category C

			doctor but the doctor said since it is the same amount it would be fine to give.	
6114001-9	6936297	3/12/2009 N/A	Report from the USA of incorrect dose coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT). On an unreported date, the patient began LUPRON DEPOT therapy for an unreported indication. On an unreported date, the patient received an incorrect dose of LUPRONDEPOT, described as being prescribed LUPRON DEPOT PED 11.25 mg one month and receiving LUPRON DEPOT 11.25 mg three month.	Dispensing and administering error/no outcomes reported, Category C
6113919-0	6936214	3/12/2009 9/19/2008	Report from the USA of an underdose coincident with LEUPROLIDE (LUPRON DEPOT) therapy. In Oct 2007 the patient began LUPRON DEPOT therapy for precocious puberty. In Jul 2008 the patient's dose was increased from 7.5 mg to 11.25 mg every month. On 19 Sep 2008 the patient went to the physician's office for a LUPRON DEPOT injection and instead of receiving the 11.25 mg pediatric dose the patient was given the 11.25 mg adult dose of LUPRON DEPOT, which is extended release over three months, resulting in an underdose. The LUPRON DEPOT 11.25 mg pediatric therapy was ongoing. The underdose resolved. The pharmacist stated the underdose was not related to the LUPRON DEPOT itself, but was due to human error.	Dispensing and administering error/no outcomes reported, Category C
6113889-5	6936184	3/12/2009 6/1/2008	Spontaneous report from the USA of wrong formulation coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date the patient began LUPRON DEPOT therapy in error for precocious puberty. In Jun 2008, the patient was dispensed and received a dose of LUPRON DEPOT 11.25mg three month formulation when he should have recieved LUPRON DEPO-PED as the physician had ordered. The physician ordered the medication to be on hold for two months. LUPRON DEPOT therapy was discontinued on an unreported	Dispensing and administering error/therapy held for two months, then therapy continued, Category C

			date. Follow-up information received from the healthcare professional on 25 Jul 2008: Reporter information, patient information and concomitant medication information have been added or revised. Follow-up information received from the healthcare professional on 28 Jul 2008: Reporter information and adverse event information were added or revised. The nurse believed that the event of wrong formulation was not related to LUPRON DEPO-PED therapy.	
6687499-5	7359328	4/19/2010 N/A	Consumer report from the USA of too much medication coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT-PED) therapy. In Feb 2008, the patient began LUPRON DEPOT-PED monthly. On an unreported date, the patient was going to change his medication to the 11.25 dose every 3 month. On an unreported date, the LUPRON DEPOT-PED prescription was refilled. The reporter stated she was not aware that the pharmacist had given her the 11.25 adult 3 month dose. On 05 Jun 2009, the reporter realized that the there were 3 LUPRON DEPOT 11.25 adult dose, missing from her supply, meaning she had inadvertently given the patient the 11.25 adult in place of the 11.25 ped which was every month. The mother had reported to the physician that the child had received 3 doses on unknown dates of the 3 month drug monthly resulting in too much medication being give. The mother declined physician contact. The mother reported no adverse events have been noticed with the increase dose. 16 Jun 2009: New version created for MedDRA correction.	Prescribing, dispensing and administering error/no adverse events reported, Category C
6687503-4	7359331	4/19/2010 3/2/2009	Report from the USA of wrong formulation given coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT PED) therapy. On 02 Mar 2009, the patient began LUPRON DEPOT PED for central precocious puberty. On 02 Mar 2009 and 06 Apr 2009, a mix-up occurred, and the patient was given two doses of the adult three month 11.25	Dispensing error/no outcomes reported, Category C

			milligrams formulation instead of 11.25 milligrams LUPRON DEPOT PED. The reporting pharmacist did not have any additional information.	
5692740-1		3/26/2008 4/2006	A 10-year-old Caucasian female experienced pain, weakness and a tingling sensation in both legs as well as difficulty walking approximately seven months after initiation of Lupron Depot-3 Month 11.25 mg therapy. The pediatric endocrinologist indicated that the patient had incorrectly received Lupron Depot-3 Month 11.25 mg instead of Lupron Depot-PED 11.25 mg due to a pharmacy dispensing error.	Dispensing and Administering error/Outcome Category H
6626368-3	7314052	3/10/2010 N/A	Report from the USA of a wrong dose given coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the patient began LUPRON DEPOT therapy for an unreported indication. On an unreported date, a pediatric patient received an adult dose of LUPRON DEPOT therapy.	Dispensing and administering error/no outcome reported, Category C
6687566-6	7359379	4/19/2010 N/A	Spontaneous report from the USA of non-serious USED WRONG FORMULATION with LUPRON DEPOT-PED (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced USED WRONG FORMULATION. The physician ordered pediatric LEUPROLIDE ACETATE (LUPRON DEPOT) but the patient received adult formulation of LUPRON DEPOT. CHANGE HISTORY On 11 Mar 2010, received updates to event information, reporter opinion of causality and narrative description. 11 Mar 2010: Version 1 created for MedDRA correction.	Dispensing and administering error/no outcomes reported, Category C
6113954-2	6936251	3/12/2009 12/1/2008	Report from the USA of a lack of effect and administered more than the prescribed dosage coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT-PED) therapy. On an unknown date, the patient began LUPRON DEPOT-PED therapy for an unknown indication. In Dec 2008, the physician increased the patient's dose of LUPRON DEPOT-PED therapy. The patient was given the adult three month dosage rather then the ped	Dispensing and administering error/Category E

			monthly dose. The patient rweceived the wrong dosage of medication in Dec 2008 and Jan 2009. In Jan 2009, the patient experienced a lack of effect.	
656582-9	7267941	2/1/2010 N/A	Report from the USA of adult formulation was dispensed instead of pediatric formulation coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the patient began LUPRON DEPOT therapy for an unknown indication. On an unreported date, the pharmacy dispensed the adult formulation instead of the pediatric formulation. The patient brought the medication back to the pharmacy and the adult formulation was exchanged for the pediatric formulation. The LUPRON DEPOT therapy was ongoing. There were no adverse events reported.	Dispensing error/was not administered, Category C
6687520-4	7359348	4/19/2010 9/8/2009	Report from the USA of a pediatric dose given coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT-PED) therapy. On 08 Sep 2009, the patient began the LUPRON DEPOT-PED therapy to suppress ovarian function prior to surgery. On 08 Sep 2009, the patient was administered a pediatric dose of LUPRON DEPOT-PED therapy instead of an adult dose. The reporter did not know if the LUPRON DEPOT therapy would be continued.	Dispensing and administering error/no outcomes reported, Category C
6113940-2	6936235	3/12/2009 N/A	Report from the USA of patient receiving one month dose of LUPRON instead of the three month dose of LUPRON coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the patient began LUPRON DEPOT therapy for pelvic pain. On an unreported date, the patient received one month dose of LUPRON DEPOT instead of the three month dose of LUPRON DEPOT. The physician believed that the event was not related to LUPRON DEPOT therapy.	Dispensing and administering error/no outcomes reported, Category C
6113979-7	6936276	3/12/2009 1/1/2005	Consumer report from the USA of worsening endometriosis, and received wrong medication coincident with LEUPROLIDE ACETATE	Dispensing and administering error/Category

			DEPOT (LUPRON DEPOT) therapy. In 2003, the patient began LUPRON DEPOT therapy for endometriosis. In 2003, six months later, LUPRON DEPOT therapy was completed. In 2005, the patient experienced worsening endometriosis. In 2005, LUPRON DEPOT therapy was restarted. In 2005, six months later, LUPRON DEPOT therapy was completed. On an unreported date, the worsening endometriosis resolved. In 2008, the patient experienced worsening endometriosis. In Sep 2008, LUPRON DEPOT therapy was restarted. In Sep 2008, the patient received the wrong medication described as LUPRON DEPOT PEDS 11.25mg instead of LUPRON DEPOT 11.25mg three month. In Sep 2008, the patient recovered from received the wrong medication. LUPRON DEPOT therapy was ongoing. The patient had not recovered from the worsening endometriosis. The patient declined physician contact.	E
6626306-3	7314010	3/10/2010 4/1/2009	Report from the USA of patient received 11.25mg ped monthly instead of 11.25mg 3 month coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT). In 2008, the patient began LUPRON DEPOT for endometriosis and pelvic pain. In Apr 2008, the patient received 11.25mg ped monthly instead of 11.25mg 3 month. LUPRON DEPOT was ongoing. The nurse did not report any adverse events.	Dispensing and administering error/no adverse events reported, Category C
6159518-6	6972281	4/20/2009 9/19/2008	Report from the USA of an overdose coincident with LEUPROLIDE (LUPRON DEPOT PED) therapy. On 19 Sep 2008 the patient was supposed to begin her LUPRON DEPOT 11.25mg every three month therapy for fibroids and menorrhagia. On 19 Sep 2008 the patient went to the physician's office to receive her first injection. The injection administered was the LUPRON DEPOT 11.25 mg pediatric dose, which is given every month, resulting in an overdose of medication. The patient was informed of the	Dispensing and administering error/Category C

			medication error and told to return to the doctor's office in one month to begin the LUPRON DEPOT 11.25mg every three month therapy. The overdose resolved and the LUPRON DEPOT therapy was ongoing. The physician believed the overdose was not related to LUPRON DEPOT PED therapy. The physician stated that the overdose was due to human error.	
6414947-8	7158778	10/26/2009 N/A	Report from the USA of a drug prescribing error coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the patient began LUPRON DEPOT therapy. On an unreported date, the patient experienced a drug prescribing error. On an unreported date, the physician wrote for "LUPRON DEPOT GYNE 11.25mg therapy." The pharmacist was interested in dispensing LUPRON DEPOT PED 3 month therapy. The LUPRON DEPOT 11.25 therapy was not equivalent to the LUPRON DEPOT PED 11.25 therapy. Therefore a potential medical error had occurred where the LUPRON DEPOT therapy and the LUPRON DEPOT PED therapy forms were not interchangeable.	Prescribing error/Potential error, Category A
6626367-1	7314051	3/10/2010 9/15/2009	Report from the USA of took wrong drug formulation coincident with LEUPROLIDE ACETATE (LUPRON DEPOT) therapy. On 15 Sep 2009, the patient began LUPRON DEPOT therapy for endometriosis. The physician wrote a prescription for 11.25 mg gynecological LUPRON DEPOT therapy. The pharmacy dispensed 11.25 mg pediatric dose of LUPRON DEPOT therapy. The pharmacist told the patient it was the same drug and dose, and the physician's office agreed with what the pharmacy had said. Therefore, on 15 Sep 2009, the patient was given the 11.25 mg pediatric dose. The patient did not suffer any adverse events. LUPRON DEPOT therapy was ongoing.	Dispensing and administering error/no adverse events, Category C
6626373-7	7314057	3/10/2010 N/A	Report from the USA of pharmacy dispensed wrong formulation coincident with LEUPROLIDE	Dispensing error/Category C

			ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the patient started LUPRON DEPOT therapy for an unknown indication. On an unreported date, the pharmacy dispensed the wrong formulation of LUPRON DEPOT therapy to the patient, described as the patient was given LUPRON DEPOT PED 11.25 milligrams instead of LUPRON DEPOT 3 month 11.25 milligrams . The patient brought the medication to the physicians office and the wrong formulation was identified by the registered nurse. The patient did not receive the incorrect medication. The pharmacy that dispensed the medication was not available.	
6626401-9	7314087	3/10/2010 8/7/2009	Report from the USA of wrong dose dispensed coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On 27 Aug 2009, while preparing to give the prescribed dose of LUPRON DEPOT, the nurse noted it was a pediatric dose and did not give the medication. This was to have been the intended patient's first dose for endometriosis.	Dispensing error/Category C
6626445-7	7314137	3/10/2010 12/1/2009	Report from the USA of dispensed wrong medication coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unknown date, the patient began LUPRON DEPOT-PED therapy for an unknown indication. In Dec 2009, the pharmacy dispensed the wrong medication to the patient. The pharmacy dispensed 11.25 milligrams pediatric dose instead of the 11.25 mg adult dose. The medical assistant sent the patient back to the pharmacy with the medication to get the correct dose. The patient did not receive the wrong dose of LUPRON DEPOT therapy dose of medication. On an unreported date, the dispensed the wrong medication resolved.	Dispensing error/Category C
6687495-8	7359324	4/19/2010 7/1/2009	Report from the USA of received wrong medication coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT-PED) therapy. On 08 Jan 2009, the patient began LUPRON DEPOT therapy for	Dispensing and administering error/Category C

			endometriosis. In Jul 2009, last week, the patient received LUPRON DEPOT-PED 11.25 mg, instead of the prescribed LUPRON DEPOT 11.25 mg every three month dosage. The patient experienced no known adverse event.	
6801674-8	7438573	6/29/2010 6/3/2010	Spontaneous report from the USA of non-serious WRONG DOSE GIVEN, WRONG DOSE ORDERED and DISPENSING ERROR with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT) and LUPRON DEPOT-PED 11.25 MG (LEUPROLIDE ACETATE DEPOT). On unknown dates, the patient experienced WRONG DOSE ORDERED and DISPENSING ERROR. On 03 Jun 2010, the patient experienced WRONG DOSE GIVEN. The patient was given the 11.25mg LUPRON DEPOT pediatric dose instead of the intended 11.25mg LUPRON DEPOT adult dose. CHANGE HISTORY On 28 Jun 2010, received updates to event information. Follow up information identified on 28 Jun 2010, Version created to correct MedDRA codes in database for electronic reporting.	Dispensing and administering error/ no outcomes reported, Category C
6687527-7	7359355	4/19/210 8/5/2009	Report from the USA of wrong formulation dispensed coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unknown date, the patient began LUPRON DEPOT therapy for prostate cancer. In 2008, the patient was administered the wrong dose. The patient had taken 7.5 mg LUPRON DEPOT PED, instead of taking 7.5 mg LUPRON DEPOT for prostate cancer. The pharmacist believed that the event was not related to LUPRON DEPOT therapy, but to an administration error due to label issues. The pharmacist stated that the medications sounded alike and looked alike, and that the label only had a small symbol to indicate the difference between the medications, and therefore the wrong dose was chosen. The event had not resolved. Additional information identified on 21	Dispensing and administering error/Category C

			Dec 2009: Version one created to update MedDRA coding.	
6626277-X	7313988	3/10/2010 Not reported	Report from the USA of a potential wrong dose coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the pharmacy dispensed the wrong dose of LUPRON DEPOT therapy to the patient for an unreported indication. On an unreported date, the patient experienced a potential wrong dose of LUPRON DEPOT therapy. LUPRON DEPOT PED therapy was dispensed for LUPRON DEPOT therapy. The patient did not administer the LUPRON DEPOT PED therapy. No adverse event occurred. 28 May 2009: Reversioned for MedDRA recodes. Potential wrong dose was coded to wrong drug dispensed. Intercepted drug administration error was added to the coding of potential wrong dose per MedDRA. MAW	Dispensing Error/Category C
6687501-0	7359329	4/19/2010 1/1/2008	Report from the USA of received pediatric dose and wrong dose dispensed coincident with LEUPROLIDE ACETATE DEPOT (LUPRON DEPOT) therapy. On an unreported date, the patient began the LUPRON DEPOT therapy for endometriosis. On 05 Aug 2009, the patient received a pediatric dose of LUPRON DEPOT therapy, instead of an adult dose of LUPRON DEPOT therapy. LUPRON DEPOT therapy was ongoing. The patient had not recovered from receiving the wrong dose. Follow-up information received from a licensed practical nurse (LPN) on 05 Aug 2009: Patient information, adverse event information, and suspect product information were added or revised. It was clarified that on 05 Aug 2009, the pharmacist dispensed a pediatric dose of LUPRON DEPOT therapy to the physician's office and told the office that it was the same as the adult dose. After the medication was administered to the patient, the pharmacist called back and indicated that the pediatric dose and adult dose were not the same. It was clarified that it was unknown if LUPRON	Dispensing and administering error/Category D

			DEPOT therapy was ongoing. The reporting LPN believed that the patient receiving the pediatric dose was not related to LUPRON DEPOT therapy.	

AERS Case Series for
Lupron Medication Errors

ISRNUM	CK		CSENUM
5477773		2	6441107
5493449	X		6456822
5499603		5	6452871
5506976		3	6459276
5523412		1	6476846
5610268		1	6547875
5636013		1	6568712
5661850		7	6579062
5683573		0	6691438
5692740		1	6255892
5712780		3	6627051
5808458		8	6706989
5816135		2	6704787
5930771		4	6796623
5977357		3	6838981
5978281		2	6818002
6025258		7	6874602
6027566		2	6872968
6052876		2	6892863
6052892		0	6892879
6052893		2	6892880
6052965		2	6892943
6052968		8	6892946
6052980		9	6892959
6052984		6	6892963
6052989		5	6892967
6052997		4	6892971
6059801		9	6897433
6059808		1	6897441
6059812		3	6897444
6059889		5	6897507
6082771		4	6907653
6091158	X		6931891
6113873		1	6936168
6113884		6	6936179
6113889		5	6936184
6113896		2	6936191
6113898		6	6936193
6113904		9	6936199
6113915		3	6936210
6113919		0	6936214
6113940		2	6936235

6113946		3	6936242
6113954		2	6936251
6113979		7	6936276
6114001		9	6936297
6114002		0	6936298
6114029		9	6936329
6141765		0	6959152
6141782		0	6959169
6141803		5	6959190
6159510		1	6972273
6159513		7	6972276
6159518		6	6972281
6207189		2	7005673
6221946		8	7030256
6263038		8	7051758
6270777		1	7052571
6310532		7	7082589
6331426		7	6710902
6355868		9	7125791
6414844		8	7158678
6414885		0	7158717
6414914		4	7158745
6414929		6	7158760
6414947		8	7158778
6414955		7	7158786
6414969		7	7158803
6414973		9	7158807
6415000	X		7158837
6415046		1	7158884
6416318		7	7159745
6440939		9	7180178
6515929		8	7228869
6516005		0	7228930
6516010		4	7228935
6516026		8	7228951
6516030	X		7228955
6516032		3	7228957
6516082		7	7229013
6516083		9	7229014
6516085		2	7229015
6530271		7	7239586
6565731		6	7267849
6565761		4	7267879
6565791		2	7267906
6565792		4	7267907
6565801		2	7267915
6565803		6	7267917
6565804		8	7267918
6565814		0	7267928
6565827		9	7267941

6565830		9	7267944
6565831		0	7267945
6565837		1	7267950
6565838		3	7267951
6568914		4	7269857
6582902		3	7273015
6607952	X		7250131
6609146		0	7302722
6626277	X		7313988
6626286		0	6936172
6626306		3	7314010
6626362		2	7314046
6626367		1	7314051
6626368		3	7314052
6626373		7	7314057
6626375		0	7314059
6626380		4	7314064
6626382		8	7314069
6626389		0	7314076
6626392		0	7314078
6626400		7	7314086
6626401		9	7314087
6626426		3	7314119
6626442		1	7314134
6626445		7	7314137
6626457		3	7314149
6626468		8	7309250
6635520		2	7320730
6662365	X		7340045
6679351		6	7134721
6682421	X		7222145
6687495		8	7359324
6687496	X		7359325
6687499		5	7359328
6687501		0	7359329
6687503		4	7359331
6687507		1	7359335
6687508		3	7359336
6687510		1	7359338
6687511		3	7359339
6687513		7	7359341
6687514		9	7359342
6687515		0	7359343
6687517		4	7359345
6687518		6	7359346
6687520		4	7359348
6687522		8	7359350
6687527		7	7359355
6687537	X		7359365
6687538		1	7359366

6687566	6	7359379
6713939	9	7371007
6756395	7	7363649
6801674	8	7438573

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-25	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT
NDA-19732	SUPPL-32	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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

/s/

MELINA N GRIFFIS
09/10/2010

CAROL A HOLQUIST
09/10/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 020517 BLA#	NDA Supplement #:S- 030 BLA STN #	Efficacy Supplement Type – New formulation
Proprietary Name: LUPRON DEPOT (3 month 22.5 mg, 4 month 30 mg and 6 month 45 mg) Established/Proper Name: leuprolide acetate for depot suspension Dosage Form: Sterile Depot Suspension for Injection Strengths: 3 month 22.5 mg, 4 month 30 mg and 6 month 45 mg		
Applicant: Abbott Endocrine Inc., Agent for Applicant (if applicable): N/A		
Date of Application: December 11, 2009 Date of Receipt: December 11, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: October 11, 2010	Action Goal Date (if different): October 11, 2010	
Filing Date: February 9, 2010	Date of Filing Meeting: February 2, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): New Formulation of Lupron Depot for Palliative Treatment of Advanced Prostatic Cancer		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): n/a	
List referenced IND Number(s): 027350	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			3 Years per submission in Module 1 of this supplement

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☒ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			DRUP consult

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? No Type C meeting conducted **Date(s):** 11-1-07 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 2, 2010

BLA/NDA/Supp #: 020517/S-030

PROPRIETARY NAME: Leuprolide Depot (3 Month 22.5 mg, 4 Month 30 mg, 5 Month 45 mg) acetate for depot suspension (LUPRON DEPOT 6 Month) 45 mg

ESTABLISHED/PROPER NAME: Leuprolide Acetate for depot suspension

DOSAGE FORM/STRENGTH: 6 month/45 mg

APPLICANT: Abbott Laboratories

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Prostate Cancer

BACKGROUND: The sponsor has submitted this supplement in support of a new formulation of Lupron Depot, for palliative treatment of advanced prostatic cancer.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	CDR Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer	Y
	CPMS/TL:	CAPT. Frank Cross Jr., M.A., MT (ASCP), Chief, Project Management Staff	Y
Cross-Discipline Team Leader (CDTL)	V. Ellen Maher, M.D., Clinical Team Leader		Y
Clinical	Reviewer:	Gwynn Ison, M.D., Medical Officer	Y
	TL:	V. Ellen Maher, M.D., Clinical Team Leader Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Young Jin Moon, Ph.D., Clinical Pharmacology Reviewer, DCP5	Y
	TL:	Jeanne Fourie, Pharm.D., Acting Team Leader, Office of Clinical Pharmacology, DCP5	Y
Biostatistics	Reviewer:	Xiaoping (Janet) Jiang, Ph.D., Math Statistician, DB 5	Y
	TL:	Kun He, Ph.D., Acting Team Leader, DB 5	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold, Ph.D., Pharmacologist/Toxicologist	Y
	TL:	Haleh Saber, Ph.D., Supervisory Pharmacologist	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Cheng Yi Liang, Ph.D.	
	TL:	Liang Zhou, Ph.D.	
Quality Microbiology *(for sterile products)*	Reviewer:	John Arigo	
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Cheng Yi Liang, Ph.D.	

	TL:	Liang Zhou, Ph.D.	
OSE/DMEPA (proprietary name)	Reviewer:	TBD (Consult sent 2-17-10)	
	TL:		
OSE/DRISK (REMS)	Reviewer:	(Consult sent 2-17-10) For PPI	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Robert Young, Ph.D.	
	TL:	Tejashri Purohit-Sheth, Ph.D.	
DRUP	Reviewer:	Harry Handelsman, M.D.	Y
	TL:	Mark Hirsch, M.D.	Y

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Acceptable electronic submission	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? • DSI ~ consult sent (2-2-10) **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert Justice, M.D., M.S. (Director DDOP) **21st Century Review Milestones**: YES **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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

/s/

DIANE C HANNER
06/17/2010

FRANK H Cross
06/17/2010

DSI CONSULT: Request for Biopharmaceutical Inspections

Date: May 4, 2010

To: Sam H. Haidar, Ph.D, Acting Branch Chief, GLP
Bioequivalence Branch, Division of Scientific Investigations
Martin K. Yau, Ph.D., Acting Team Leader, Bioequivalence

Through: Young Jin Moon, Ph.D., Clinical Pharmacology Reviewer, DCP5
Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5
Gwynn Ison, MD, Clinical Reviewer, DDOP
V. Ellen Maher, MD, Clinical Team Leader, DDOP
Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP
Robert Justice, MD, Division Director, DDOP

From: Diane Hanner, CSO, DDOP

Subject: **Request for Biopharmaceutical Inspections**

I. General Information

Application#: 20517 Amendment 38, received 12-11-09
Applicant: Abbott Laboratories
Drug: Lupron Depot (leuprolide acetate for depot suspension) 6 month 45 mg injection
NME: No
Study Population: Early and late stage prostate cancer
Proposed Indication: Prostate Cancer

PDUFA: Proposed October 11, 2010
Action Target Date: September 11, 2010
Inspection Summary Goal Date: August 11, 2010

II. Background Information

This is a formal request for DSI to conduct audits of the bioanalytical site of the clinical trial L-PC07-169.

The clinical pharmacology reviewer found that DSI detected substantial irregularities in laboratory practice and in the validation of the testosterone assay upon inspection of **Esoterix, Inc.** The primary endpoint of L-PC07-169 is based on testosterone levels (T). Esoterix performed the study L-PC07-169 assays during the same time period in which the irregularities, described below, were detected.

- **sNDAs (b) (4) (DMEP)**
    - The sponsor received a non-approvable letter on (b) (4) for both NDAs. Deficiencies were identified by DSI audit of the T data. The accuracy, specificity, and precision of the T assay were not validated.
- **IN (b) (4) (DRUP)**
    - All necessary validation experiments were not performed or were inadequately documented. Also, Esoterix did not adequately document deviations from their SOP or explain/document the criteria used to evaluate the runs.
- **ND (b) (4) (DRUP)**
    - Complete Response (b) (4) - "The DSI audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from your single phase III clinical study ((b) (4)). These deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of your drug product. In the absence of reliable data upon which an approval decision can be based, this NDA cannot be approved."

In the current submission, the time from blood collection to analysis was not adequately documented, and long term stability (especially with a QC near 50 ng/dL therapeutic limit) was not reported.

- Further, sample carry-over was reported, but strategies to minimize or correct the issue were not reported.. Finally, incurred sample reanalysis is not reported.

III. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Comments
Esoterix Inc. 4301 Lost Hills Road Calabasas Hills, CA 91301 Phone: (800) 444-9111 Fax#: (818) 880-8541	VR08-ESO-CAL-021v2	151	

IV. Site Selection/Rationale

Domestic Inspections:

We have requested inspections because (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
_X_ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
_ Other (specify): Large numbers of SAES and/or protocol violations at these sites.

International Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__ Other (specify):

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Should you require any additional information, please contact Diane Hanner (regulatory project manager) at 301-796-4058 or Dr. Young-Jin Moon (clinical pharmacology reviewer).

Concurrence: (as needed)

Young Jin Moon_____ Clinical Pharmacology Reviewer, DCP5
Julie Bullock,_____Team Leader, DCP5
Gwynn Ison_____ Medical Reviewer
Virginia E. Maher_____Medical Team Leader
Anthony Murgo, _____ Associate Director OODP IO, Acting Deputy Director DDOP
Robert Justice_____Division Director (for foreign inspection requests only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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

/s/

DIANE C HANNER
05/12/2010

VIRGINIA E MAHER
05/13/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-517/S030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 020517 SUPPL # 030 HFD # 150

Trade Name Lupron Depot

Generic Name (leuprolide acetate for depot suspension)

Applicant Name Abbott Endocrine Inc.

Approval Date, If Known June 17, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020263 leuprolide acetate

NDA#	020708	leuprolide acetate
NDA#	020517	leuprolide acetate
NDA#	020011	leuprolide acetate
NDA#	019732	leuprolide acetate
ANDA#	074728	leuprolide acetate
ANDA#	078885	leuprolide acetate
ANDA#	075471	leuprolide acetate
NDA#	021379	leuprolide acetate
NDA#	021488	leuprolide acetate
NDA#	021731	leuprolide acetate
NDA#	021343	leuprolide acetate

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)

IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety and Pharmacokinetics of Two 6-Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma (Formulation A)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety and Pharmacokinetics of Two 6-Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma (Formulation A)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 27,350	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Kim J. Robertson

Title: Regulatory Health Project Manager
Date: June 9, 2011

Name of Office/Division Director signing form: Anthony Murgo, MD, MS, FACP
Title: Acting Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

KIM J ROBERTSON
06/16/2011
Exclusivity Summary; N020517; Lupron Depot; Abbott Labs

ANTHONY J MURGO
06/16/2011

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#:020517 Supplement Number: 030 NDA Supplement Type (e.g. SE5): SE2

Division Name: Drug Oncology Products PDUFA Goal Date: June 17, 2011 Stamp Date: 12/17/10

Proprietary Name: Lupron Depot

Established/Generic Name: (leuprolide acetate for depot suspension)

Dosage Form: Injection

Applicant/Sponsor: Abbott Endocrine

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1)
(2)
(3)
(4)

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 5
(Attach a completed Pediatric Page for each indication in current application.)

Indication: The palliative treatment of advanced prostatic cancer

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); X dosage form; X dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☒ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

- Ineffective or unsafe:
  - ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
  - ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
  - ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Δ Formulation failed:
  - ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

ection C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_Kim J. Robertson_____
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

ıeck subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding ᵴtudy plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan ›mplate); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

ction F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

1.9.1 Request for a Full Waiver of Pediatric Studies

Product Name: Lupron Depot® (leuprolide acetate) 45 mg Injection

NDA Number: 020517

Applicant: Abbott Laboratories

Proposed Indication: Palliative treatment of advanced prostatic cancer

1. **What age ranges are included in your waiver request?**

   The applicant requests a full waiver for pediatric studies in patients aged 0-17 years inclusive.

2. **Justification for Waiving Pediatric Studies:**

   Reference is made to Abbott's January 22, 2009 submission to IND 27,350 of a Request for Advice regarding the planned sNDA submission to support the planned 45 mg depot formulation, which included a request for advice regarding the qualification of the proposed formulation for a disease-specific waiver of the pediatric study requirement. In the Agency's June 23, 2009 response to Abbott's Request for Advice the Agency stated that a waiver request should be submitted with the sNDA submission.

   Therefore, the applicant requests a waiver for pediatric studies for the proposed adult indications under Section 505B(a)(4)(A)(i) of the FD&C Act because studies are impossible or highly impractical. The proposed Lupron Depot 6-month formulation is intended to treat an indication that has extremely limited applicability to pediatric patients because the pathophysiology of these diseases occur for the most part in the adult population; that is, in older adult males. Furthermore, prostate cancer is included in the list of adult-related conditions that may qualify a drug product for a disease-specific waiver presented in

Attachment A of the September 2005 Draft Guidance for Industry, *How to Comply with the Pediatric Research Equity Act.*

3. Applicant Certification:

The applicant certifies that the above information is true and accurate.

APPEARS THIS WAY ON ORIGINAL

1.3.3 Debarment Certification

Certification Requirement for Approval of a Drug Product Concerning Using Services of Debarred Persons

Any applicant for approval of a new drug product submitted on or after June 1, 1992 per Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act must include:

(1) A certification that the applicant did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) and (b), in connection with such application.

Abbott Laboratories certifies that it did not, and will not use in any capacity the services of any person debarred under Section 306, subsection (a) and (b), in connection with this application.

Clinical Study L-PC07-169 (Pivotal Study)

No principal investigators or sub-investigators for Clinical Study L-PC07-169 were listed on the FDA Disqualified/Totally Restricted List for Clinical Investigators.

Clinical Study C02-008 (Supportive Study)

No principal investigators for Clinical Study C02-008 were listed on the FDA Disqualified/Totally Restricted List for Clinical Investigators.

One sub-investigator for Clinical Study (b) (4), (b) (4), was identified as being a probable match with the FDA Disqualified/Totally Restricted List for Clinical Investigators. A (b) (4) was added to the FDA Disqualified/Totally Restricted List for Clinical Investigators on (b) (4) He was also issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letter on (b) (4)

A (b) (4) M.D. was listed as a sub-investigator for Clinical Study (b) (4) at principal investigator (b) (4) MD's site in (b) (4). The site details are listed below:

(b) (4)

(b) (4) patients were enrolled in this study at Dr. (b) (4) site during the time period of (b) (4) It is noted that the study activities at this site pre-date the time when (b) (4) M.D. was issued a NIDPOE Letter and was added to the FDA Disqualified/Totally Restricted List for Clinical Investigators.

Abbott believes that the probable match of "FDA Disqualified/Restricted List" for Clinical Investigators and issuance of a NIDPOE letter for subinvestigator, (b) (4) (b) (4), M.D., should not negatively impact the data quality of the current submission.

[See attached electronic signature]

Natalie Tolli, B.Pharm, M.S.
Director, Global Pharmaceutical Regulatory Affairs
Abbott Laboratories

Document Approval

Debarment Certification - 2009-dec-02

Version: 1.0 **Date:** 02-Dec-2009 08:32:09 PM **Abbott ID:** 12022009-00AB619FB342D9-00001-en

Signed by:	Date:	Meaning Of Signature:
Tolli_Natalie_J	02-Dec-2009 08:32:09 PM	Approver

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 20517 BLA #	NDA Supplement # 030 BLA STN #	If NDA, Efficacy Supplement Type: SE2
Proprietary Name: LUPRON DEPOT (3 month 22.5 mg, 4 month 30 mg and 6 month 45 mg) Established/Proper Name: leuprolide acetate for depot suspension Dosage Form: Sterile Depot Suspension for Injection		Applicant: Abbott Endocrine Inc., Agent for Applicant (if applicable): N/A
RPM: Kim J. Robertson		Division: Drug Oncology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 17, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Complete Response; October 05, 2010

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	June 15, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) October 05, 2010; June ??, 2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	December 11, 2009; December 17, 2010
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	December 11, 2009; December 17, 2010
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA September 10, 2010; May 12, 2011 ☐ DRISK ☒ DDMAC May 20, 2011 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	June 17, 2010
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC June 30, 2010 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Refer to Outgoing Communications tab in Action Package
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg November 1, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None Deputy Director; June 13, 2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None May 20, 2011
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A
• Clinical review(s) *(indicate date for each review)*	September 29, 2010; May 18, 2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 10 of the September 29, 2010 Clinical Review; Page 11 of the May 18, 2011 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DRUP Review: September 30, 2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A ☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested September 14, 2010

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None September 2, 2010; May 20, 2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None September 10, 2010; April 28, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None September 9, 2010
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None September 21, 2010; May 23, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None August 12 and 26, 2010; September 15, 2010; May 20, 2011; June 15, 2011
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed May 10, 2010; July 27, 2010; August 19, 2010
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharmaceutical Review; August 12, 2010

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC Review; June 15, 2011
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: May 16, 2011 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

From: Robertson, Kim
Sent: Tuesday, May 17, 2011 5:34 PM
To: 'Jean M Conaway'
Cc: Kevin M Fitzpatrick
Subject: RE: NDA 20517/S-030 Lupron

Hello Jean/Kevin:

Thank you for the updates. You are correct in that we appear to have the latest agreed upon carton/container information in house. I will reference the December 17, 2010 submission for the information I need.

With regard to the "deletion of the stand alone mixing insert and stand alone patient information brochure at this time.", it is perfectly acceptable for Abbott to delete this information. I thought that I conveyed this in a telephone conversation that took place between Kevin and myself, but if it was not made perfectly clear in the phone conversation, I will reiterate that the division agreed with Abbott in that the removal of the mixing insert and stand alone patient brochure/pamphlet is acceptable.

Kim

From: Jean M Conaway [mailto:jean.conaway@abbott.com]
Sent: Tuesday, May 17, 2011 11:14 AM
To: Jean M Conaway
Cc: Kevin M Fitzpatrick; Robertson, Kim
Subject: Re: NDA 20517/S-030 Lupron

Hi Kim:
Slight correction to the email below. We will submit on 5/19 instead of 5/18 as noted below.

Thanks Jean

Jean Conaway, RPh, RAC, MBA
Associate Director
Global Pharmaceutical Regulatory Affairs
Dept PA76, Bldg AP30-1NE

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jean.conaway@abbott.com

From:	Jean M Conaway/LAKE/GPRA/ABBOTT
To:	"Robertson, Kim" <Kim.Robertson@fda hhs.gov>
Cc:	Kevin M Fitzpatrick <Kevin.Fitzpatrick@abbott.com>
Date:	05/17/2011 09:56 AM
Subject:	NDA 20517/S-030 Lupron

Hi Kim:

I left you a voicemail this morning, however I am not certain if your VM is functioning as it appears to only have a phone number recorded. I will recap here as well just in case:

Thank you for your email.

The USPI labeling looks fine and we will submit a clean copy as you requested. Please note that we previously submitted the revised container/carton labeling for the 3mo, 4mo and 6mo Lupron products on December 17, 2010; (eCTD sequence 0067). This submission contained the container/ carton labels (3mo, 4mo and 6mo) with changes as FDA requested. In the submission tomorrow, we will provide reference to the eCTD location Seq 0067 for ease of FDA review.
Please clarify whether this addresses your request (in the email below) for inclusion of carton and container labels in our submission tomorrow.

We previously proposed to FDA that the stand alone mixing insert and stand along patient information brochure be deleted . The amendments with the proposed deletions are as follows:

- stand alone mixing insert (March 21, 2011; amendment 023; eCTD Seq 0078) and
- stand alone patient information brochure (May 17, 2010; amendment 012; eCTD Seq 0053).

It would be helpful if FDA could confirm the acceptability of deletion of the stand alone mixing insert and stand alone patient information brochure at this time.

Thanks in advance,

Best Regards,
Jean

Jean Conaway, RPh, RAC, MBA
Associate Director
Global Pharmaceutical Regulatory Affairs
Dept PA76, Bldg AP30-1NE

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From:	"Robertson, Kim" <Kim.Robertson@fda hhs.gov>
To:	'Jean M Conaway' <jean.conaway@abbott.com>
Cc:	Kevin M Fitzpatrick <Kevin.Fitzpatrick@abbott.com>
Date:	05/16/2011 03:07 PM
Subject:	NDA 20517/S-030 Lupron

Hello Jean/Kevin:

Please see the attached document, as it is the Lupron label that contains what we believe should are final remarks from the division. If Abbott concurs, please submit finalized labeling; inclusive of any carton and container, by Thursday, May 19, 2011.

Thank you,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845

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

/s/

KIM J ROBERTSON
06/16/2011
May 17 Correspondence to Abbott

From: Robertson, Kim
Sent: Monday, May 16, 2011 4:08 PM
To: 'Jean M Conaway'
Cc: Kevin M Fitzpatrick
Subject: NDA 20517/S-030 Lupron
Importance: High

Hello Jean/Kevin:

Please see the attached document, as it is the Lupron label that contains what we believe should are final remarks from the division. If Abbott concurs, please submit finalized labeling; inclusive of any carton and container, by Thursday, May 19, 2011.

Thank you,
Kim

APPEARS THIS WAY ON ORIGINAL

25 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

KIM J ROBERTSON
06/16/2011
May 16 Lupron IR/PI

From: Robertson, Kim
Sent: Wednesday, May 11, 2011 11:39 AM
To: 'Jean M Conaway'
Cc: Kevin M Fitzpatrick
Subject: RE: NDA 20517/S-030; Lupron

By "alignment" in the case of 4.1 and 4.2 in the HL Section of the PI, we *literally* mean to please ensure that the **text** itself is properly aligned with the remaining sub-headings. To us, it appears that the words 'HYPERSENSITIVITY' and 'PREGNANCY' are not lining up with other sub-headings (i.e. 'Tumor Flare'; Section 5.1, or 'Administration of Injection'; Section 2.4. These are just two examples chosen for comparison only. Notice that the words 'HYPERSENSITIVITY' and 'PREGNANCY' are a little too far over to the left. Their alignment is slightly off. We attempted to do it during the labeling meeting given that it is a minor request; however, during a few meetings, it has proven to be a little challenging for us to manipulate text within those text boxes. Otherwise, we would've simply taken care of it ourselves.

With regard to your second question, you may just add vertical lines in the left hand margin next to: Option B (1&2). For now, we would like to see the vertical lines.

Kim

From: Jean M Conaway [mailto:jean.conaway@abbott.com]
Sent: Wednesday, May 11, 2011 12:03 AM
To: Robertson, Kim
Cc: Kevin M Fitzpatrick
Subject: NDA 20517/S-030; Lupron

Hi Kim:

We are planning on sending you the labeling on Wednesday as you requested. However, we have two questions for you:

1. In terms of FDA comment: "To Abbott: Please align text for 4.1 and 4.2 in the HL section" - We have interpreted this to mean that we should align the abbreviated text in the two bullets within the HL section under CONTRAINDICATIONS with the text within Sections 4.1 and 4.2 within the body of the labeling. Please advise.

So for example:
Highlight Section:
Hypersensitivity to GnRH, GnRH agonist or any of the excipients in LUPRON DEPOT (4.1) (Note: We corrected

the section number)
Pregnancy: LUPRON DEPOT may cause fetal harm when administered to a pregnant woman (4.2, 8.1) (Note: We aligned this text with the text within Section 4.2)

2. Also please advise if we should add vertical lines in the left hand margin only next to

A. those sections that we have revised compared to the labeling you sent us on May 6, 2011. Or
B. 1) those sections that we have revised compared to the labeling you sent us on May 6, 2011 **as well as** B2) those sections in the body of the labeling that are listed in the Highlight Section entitled "recent major changes"

Please advise which option is accurate. Thanks in advance.

Best Regards,
Jean

Jean Conaway, RPh, RAC, MBA
Associate Director
Global Pharmaceutical Regulatory Affairs
Dept PA76, Bldg AP30-1NE

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jean.conaway@abbott.com

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

/s/

KIM J ROBERTSON
06/16/2011
May 11 Correspondence to Abbott

From: Robertson, Kim
Sent: Friday, May 06, 2011 6:34 PM
To: 'Jean M Conaway'
Cc: Kevin M Fitzpatrick
Subject: N 20517/S-030; Lupron
Importance: High

Hello Jean/Kevin:

Please find the attached label, as it is Abbott's Lupron label containing FDA May 6, 2011 comments to Abbott's May 2, 2011 label.

Please review with your Abbott colleagues and provide labeling back to us with either your concurrence, or objections no later than **Wednesday, May 11, 2011.**

Regards,
Kim

APPEARS THIS WAY ON ORIGINAL

25 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

KIM J ROBERTSON
06/16/2011
May 6 Lupron IR/PI

From: Robertson, Kim
Sent: Tuesday, April 26, 2011 2:16 PM
To: 'Kevin M Fitzpatrick'
Subject: RE: Lupron 20-517
Importance: High

Hi Kevin:

Please find the attached Word .doc, that is Abbott's Lupron label with FDA comments/suggestions. Please review and provide us with a return label with either Abbott's concurrence or objections, as well as any formatting **by Tuesday, May 3, 2011, 12Noon.**

Thanks,
Kim

From: Kevin M Fitzpatrick [mailto:Kevin.Fitzpatrick@abbott.com]
Sent: Thursday, April 21, 2011 6:55 PM
To: Robertson, Kim
Subject: RE: Lupron 20-517

Thanks Kim. I appreciate the open communication. I look forward to hearing from you further on this supplement, if you do anticipate a delay I would be appreciative if you would inform me so that we can help resolve any issues.

Thanks,
Kevin

Kevin M Fitzpatrick
Director, Antiviral & Renal
US & Canada Regulatory Affairs
Pharmaceutical Products Group

Abbott
200 Abbott Park Rd.
PA76, AP30-1E
Abbott Park, IL 60064-6157

Office 847 935-6696
Fax 847 937-8068
Kevin.Fitzpatrick@abbott.com

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/s/

KIM J ROBERTSON
06/16/2011
April 26 Lupron IR/PI

From: Robertson, Kim
Sent: Thursday, March 24, 2011 5:08 PM
To: Kevin M Fitzpatrick
Subject: RE: Lupron Mixing Instructions
Importance: High

Hi Kevin:

Upon reviewing Abbott's updated March 21, 2011 PI, a few of us on the Lupron team were wondering why quite a few of Abbott's proposals that were clearly accepted by the division have made their way back into the label? If we have to once again re-accept the information during another team meeting, this would cause for repetitive work on our parts and we would loose valuable review/discussion time necessary for other topics concerning the Lupron PI.

At this time we ask that Abbott please refer to the label that was attached in the March 16, 2011 e-mail from the division, taking note of the sections of the PI that Abbott proposed **and** that the Agency accepted, as well as sections where we may have added our tracked changed insertions. In updated labeling, we only need to see all "new" proposals/insertions by Abbott, (i.e. any corrections to formatting we suggested, our comment regarding insertion of the 'Instructions On How To Mix And Administer' information, any new data (if any), and any rejections (if any) by Abbott of the Agency's insertions; all clearly shown by tracked changes of course. All other previous proposals that were found acceptable by the division (i.e. LUPRON DEPOT 22.5 mg for 3–month administration, given– 3 Month: (22.5 mg) as a single intramuscular injection every 12 weeks (2.1); 30 mg for 4–month administration, given – 4 Month: (30 mg) as a single intramuscular injection every 16 weeks (2.2); and 45 mg for 6–month administration, given as a single intramuscular injection every 24 weeks (2.3)) need not be reflected again as tracked changes in **updated** labeling. As you can guess, seeing those proposals again still in tracked changes automatically draws our attention to them, thereby taking away valuable time from the more recent proposals. Again, these are areas of the Lupron PI that we have already reviewed, discussed, and accepted and we do not need to re-visit them again.

Please re-submit new labeling to us no later than **Friday, April 1, 2011.**

Thanks,
Kim

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/s/

KIM J ROBERTSON
06/16/2011
March 24 Lupron IR/PI

From: Robertson, Kim
Sent: Wednesday, March 16, 2011 4:31 PM
To: Kevin M Fitzpatrick
Subject: RE: Lupron Mixing Instructions
Importance: High

Hi again Kevin:

Please see the attached, as it is Abbott's PI for Lupron. Within you will find an Agency request re: Section 2.4 of the PI. Please review and provide labeling back to us no later than **Monday, March 21, 2011.**

Regards,
Kim

From: Robertson, Kim
Sent: Wednesday, March 16, 2011 12:02 PM
To: 'Kevin M Fitzpatrick'
Subject: RE: Lupron Mixing Instructions

Hi Kevin:

I'm sure I'm going to have an IR (Information Request) for Abbott shortly; one that shouldn't be too taxing. As soon as I receive word from a couple of my Lupron reviewers, I will send forth the IR.

Kim

From: Kevin M Fitzpatrick [mailto:Kevin.Fitzpatrick@abbott.com]
Sent: Wednesday, March 16, 2011 11:43 AM
To: Robertson, Kim
Subject: RE: Lupron Mixing Instructions

Hello Kim,

Was there anything that came out of your internal meeting on Friday that I need to follow up on? This product is made in Japan and the site did not get damaged and all of our Abbott manufacturing and R&D sites remain operational. However, as you can imagine there are a great number of issues that make "normal" life difficult so if you could provide us any heads up on when we could be expecting requests for information or even an action letter I would appreciate it.

Thanks,
Kevin

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/s/

KIM J ROBERTSON
06/16/2011
March 16 Lupron IR/PI

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, September 07, 2010 1:41 PM
To: 'Kevin.Fitzpatrick@abbott.com'
Subject: Preliminary responses regarding NDA 20517/S-030 Lupron

Importance: High

Hi,
I have been instructed to inform you that below are the preliminary responses regarding (NDA 20517/S-030) the adverse events questions.

AE Table Term	Preferred Terms Used	TEAE	TRAE
Injection site pain/discomfort	Injection site pain, injection site discomfort	29 (19.2%)	16 (10.6%)
URI	Influenza, nasal congestion, nasopharyngitis, rhinorrhea, upper respiratory tract injection, viral upper respiratory tract infection.	32 (21.2%)	0
Fatigue/lethargy	Fatigue, lethargy	20 (13.2%)	18 (11.9%)
Hypertension/BP increased	Hypertension, BP increased	10 (6.6%)	3 (2.0%)
Anemia/hemoglobin decreased	Anemia, hemoglobin decreased	10 (6.6%)	2 (1.3%)
Coronary artery disease/angina	Coronary artery disease, angina pectoris	8 (5.3%)	1 (0.7%)
Urinary incontinence	Urinary incontinence	7 (4.6%)	2 (1.3%)
Second primary neoplasm	Basal cell carcinoma, bladder transitional cell carcinoma, lung neoplasm, malignant melanoma, non-Hodgkin's lymphoma, squamous cell carcinoma	11 (7.3%)	0
Pneumonia	Lobar pneumonia, pneumonia, pneumonia aspiration	3 (1.98675%) serious	0
Heart failure	Heart failure congestive	2 serious	0

Regards,

Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
09/07/2010

Lambert, Tu-Van

From: Lambert, Tu-Van
Sent: Friday, August 20, 2010 11:02 AM
To: 'natalie.tolli@abbott.com'; 'Kevin M Fitzpatrick'
Subject: NDA 20-517/S-030 CMC information request

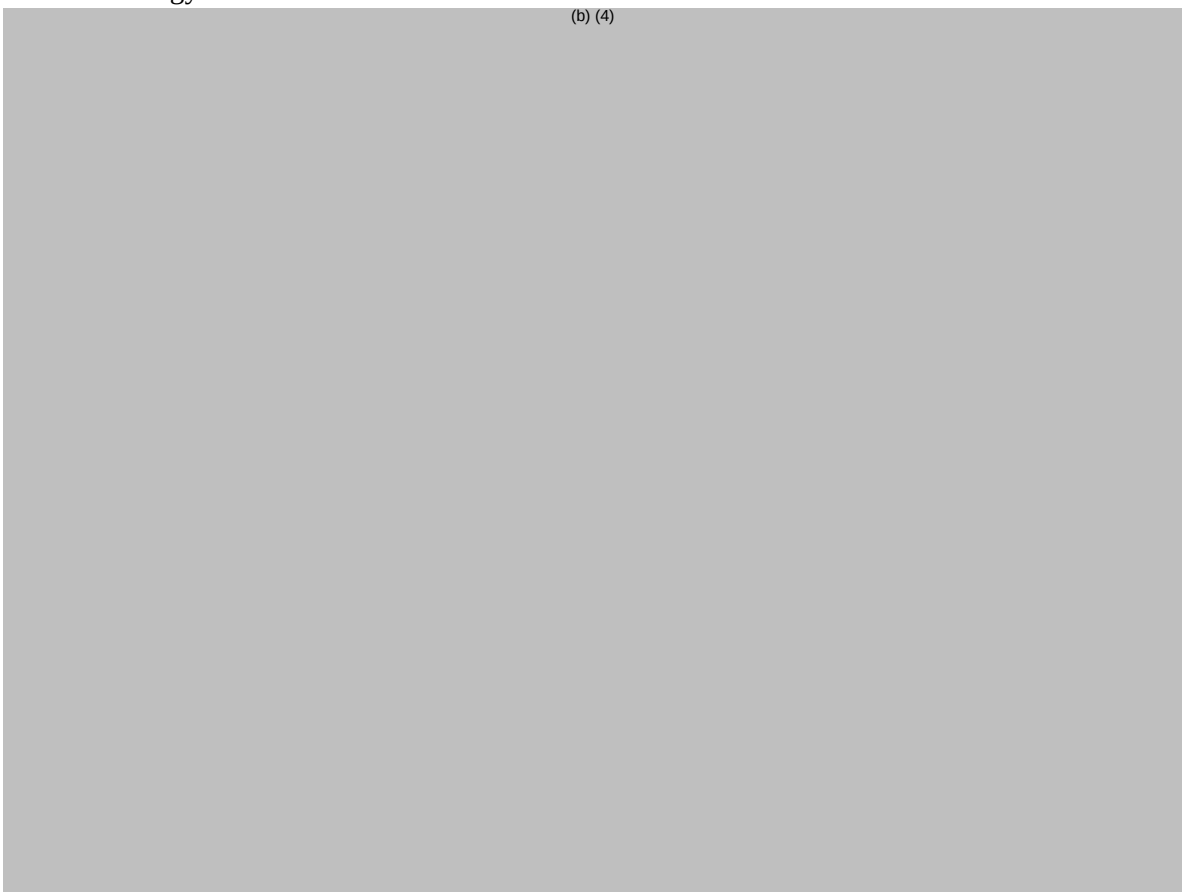
Dear Mr. Fitzpatrick,

In reference to the Chemistry, Manufacturing, and Control section of NDA 20-517/S-030 please provide responses to the following:

The proposed specifications are not acceptable, which could not control the shape of the dissolution curve in (b) (4) Based on the data submitted, the in vitro release method and specifications are recommended as follows.

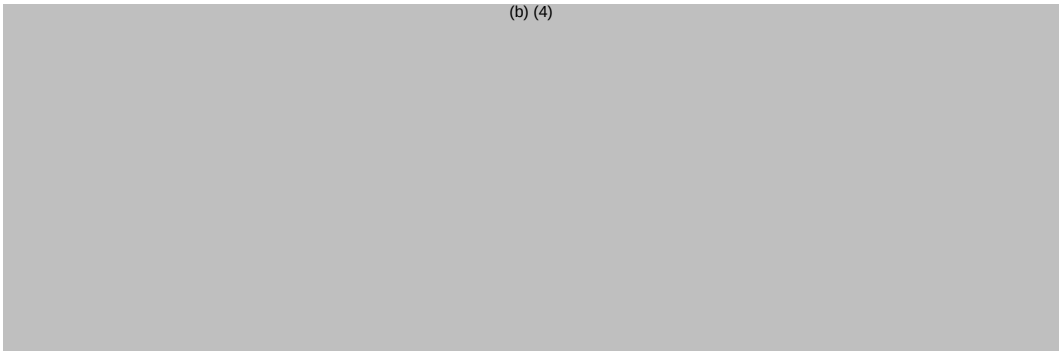
Methodology

(b) (4)



Specifications

(b) (4)



(b) (4)

Please provide a response to this inquiry as soon as feasible. Please also confirm that you have received this information request.

Warm Regards,

Tu-Van Le Lambert
Product Quality Regulatory Health Project Manager
ONDQA/OPS/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 21, Room 2625
Silver Spring, MD 20993
Phone: (301) 796-4246
Fax: (301) 796-9748

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

TU-VAN L LAMBERT
08/20/2010

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, July 13, 2010 2:53 PM
To: 'Natalie J Tolli'
Subject: FW: Lupron Depot sNDA 20-517/S-030 - ISR information requests
Importance: High

Hi,
I have been instructed to request the following:

Please submit the ISR results regarding sNDA 020517/S-030.

- In our May 11, 2010, information request we requested that you "Please submit the ISR results."
- According to your reply (dated May 26, 2010) the ISR results were supposed to be located in Appendix B (pages 124-127) of the (b) (4) analytical report provided in Module 5, Section 5.3.1.4.

However, the ISR information is not located there. Therefore, we request that this information be sent in again. Thank you in advance for your cooperation regarding this matter.
Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
07/13/2010

From:	Lambert, Tu-Van
To:	"natalie.tolli@abbott.com";
CC:	
Subject:	CMC Information Request for NDA 20-517/S-030 (Lupron)
Date:	Monday, June 28, 2010 10:45:06 AM
Attachments:	

Dear Ms. Tolli,

We have reviewed the Chemistry, Manufacturing and Control sections of the above NDA supplement for Lupron and request the following information.

1. (b) (4) lease provide the raw data including the conditions used and the data for each individual unit.
2. When setting the release specifications please refer to the IVIVC guidance entitled: *"Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations"* at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239.pdf*
3. Please provide the plasma concentration data for formulations (b) (4) did not meet the clinical protocol primary endpoint. Please specify what the endpoint is and provide the data.

Please respond as quickly as possible with a formal submission to the supplement. If possible please let me know when you formally submit your response. Please also confirm that you have received this information request.

Kindly,

Tu-Van Le Lambert
Product Quality Regulatory Health Project Manager
ONDQA/OPS/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 21, Room 2625
Silver Spring, MD 20993
Phone: (301) 796-4246
Fax: (301) 796-9748

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

TU-VAN L LAMBERT
06/28/2010

Hanner, Diane

From: Hanner, Diane
Sent: Friday, May 28, 2010 2:21 PM
To: 'Natalie J Tolli'
Subject: Information request (5-28-10) regarding NDA 20517/S-030

Importance: High

Hi,
I have been instructed to request that you address the following regarding NDA 20517/S-030:

In the discontinuation Table 10 in the CSR for Formulation A, 5 patients discontinued due to "withdrawal of consent". One of these patients, #164, is listed in the Table as being homebound after an SAE. In the AE dataset, the only AE patient #164 experienced were mild hot flashes.

In the DS data tabulation set, patient #264 (not 164) is listed as one of the patients who discontinued prematurely d/t "withdrawal of consent", but the explanation listed in another column says that this patient (264) was homebound after an SAE. Please clarify which patient, 264 or 164 discontinued prematurely, and then explain why the reason for D/C is not listed as an SAE, rather than withdrawal of consent. In addition, provide details as to what the SAE was.

Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
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Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
05/28/2010

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, May 20, 2010 12:05 PM
To: 'Natalie J Tolli'
Subject: FW: patient narrative request regarding sNDA 20517

Hi Natalie,

Please provide narratives for the following 3 patients listed below, regarding liver function abnormalities that occurred while they were on the study:

The patient ID numbers (Formulation A) are: 136, 179, and 295.
Please send this information to me by C.O.B. Wed. May 26.
Thank you.
Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
05/20/2010

Hanner, Diane

From: Hanner, Diane
Sent: Friday, May 14, 2010 3:20 PM
To: 'Nashi_Kenji@takeda.co.jp'
Subject: FW: NDA 20517/S-030 DMF Holder Microbiology Deficiencies

Importance: High

Hi Mr. Nashi,

Please confirm that you're the official contact for DMF: 9365 at Takeda Pharmaceutical Company.

I have been instructed to convey the following (DMF Holder) Microbiology deficiencies regarding NDA 20517/S-030:

DMF: 9365
DMF HOLDER: Takeda Pharmaceutical Company, Ltd.
Title: Lupron Depot 6 month 45 mg

Microbiology Deficiencies:

1. (b) (4)
2. (b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.
Thank you.
Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
05/14/2010

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, May 11, 2010 2:07 PM
To: Natalie J Tolli
Subject: Microbiology Deficiencies regarding NDA 20517/S-030

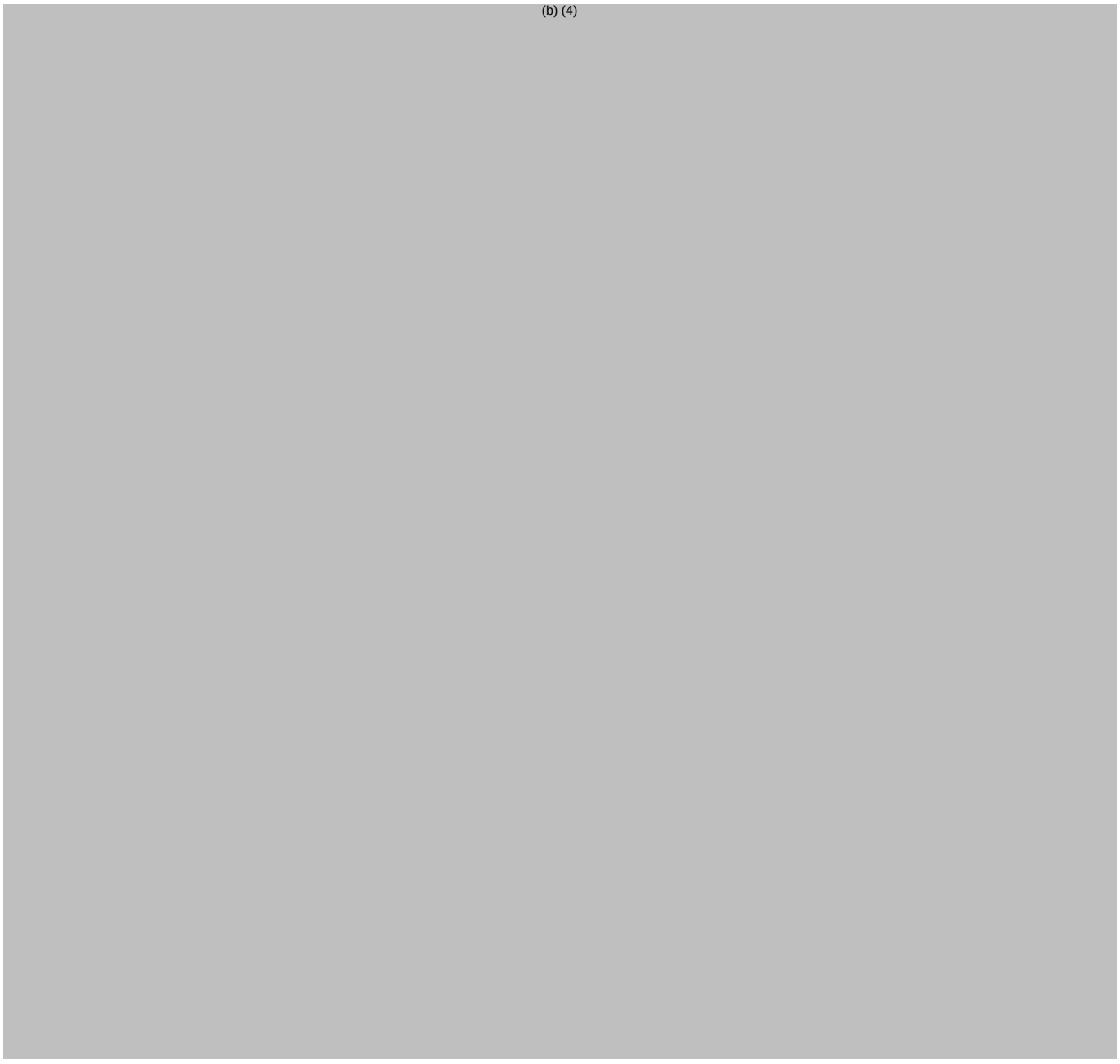
Importance: High

Hi,
I have been instructed to convey the following Microbiology deficiencies regarding NDA 20517/S-030:

A. Microbiology Deficiencies:

1. DMF 9365 is deficient. The DMF holder has been notified.

(b) (4)



2.
   a.
   b.
   c.
   d.
   e.
3.
   a.
   b.
   c.
4.
   a.
   b.
   c.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. (b) (4)

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
05/11/2010

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, May 11, 2010 3:45 PM
To: Natalie J Tolli
Subject: FW: Lupron NDA 20517/S-030 Information request
Importance: High
Follow Up Flag: Follow up
Flag Status: Red

Hi,
I have been instructed to request that the following data be sent to me ASAP:

1. Please submit the longest period of time samples were stored, and under what conditions (e.g. -20, -80 deg C).

2. Please submit the long term stability data for the testosterone samples. We are especially interested in data near the 50 ng/dL therapeutic level cut-off. Ideally you can provide data for 30 ng/dL.

3. Since you have determined that sample carryover could occur, which could lead to false negatives, please provide your strategy for eliminating the carryover. If the carryover could not be eliminated, how was it detected/corrected for during the analysis?

4. Please submit the ISR results.

Thank you.

Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
05/11/2010

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, May 04, 2010 3:12 PM
To: Natalie J Tolli
Subject: FW: Lupron-6 mo (NDA 20517/S030) Information request

Importance: High

Hi,
I have been instructed to request that you please provide the composition of the study drug used in study C02-008.
Thank you.
Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
05/04/2010

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, April 22, 2010 10:22 AM
To: 'Natalie J Tolli'
Subject: FW: Iinformation request regarding sNDA 20517

Hi,
I have the following information request regarding the Lupron supplement sNDA 20517:

Please provide us with a define file or dataset (if not present in the datasets that have been provided) so that we may be able to confirm your calculation of the following parameter for each patient:

Time since 1st histological diagnosis of prostate cancer in years.

Based on the data available in the submitted datasets, we have been unable to reproduce this baseline disease characteristic (in Table 2 of Module 2.7.3), particularly with respect to the actual dates that the Sponsor used to determine this for each patient (for instance, was this number calculated from date of diagnosis to date of randomization, and if so, where are these dates located in the datasets?)

Please respond to this request by April 28, 2010. Thank you.
Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
04/22/2010

Hanner, Diane

From: Hanner, Diane
Sent: Monday, March 01, 2010 2:16 PM
To: 'Natalie J Tolli'
Subject: FW: FW: Lupron NDA 20517 S-030 Patient Labeling Question

Hi Natalie,

We need further clarification from you regarding what you mean by "caregiver" because this will make a difference in the way we treat the "instructions on how to mix and administer".

Additionally, you should be made aware that the brochure, if it is meant to be part of the approved labeling (and not a promotional piece) will not be approved as is, and will need to be revised. It is recommended that you follow the format and content for Medication Guides as specified in 21 CFR208.20 for consistency across patient labeling.

Regards,

Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
03/01/2010

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, February 02, 2010 5:44 PM
To: 'Natalie.tolli@Abbott.com'
Subject: FW: sNDA 20-517 Lupron L-PC07-169 protocol milestones.doc

Attachments: Lupron protocol milestones.doc

Hi Natalie,
I have another information request…please complete the attached table.

Lupron protocol milestones.doc...

If you have any questions please let me know.
Regards,
Diane

Milestone	Dates	# Patients Enrolled	
		Formulation A	**Formulation B**
Original Protocol Version 1 (L-PC07-169)	December 7, 2007	0	0
Protocol Version 2 (Amendment #1)	March 31, 2008		
Administrative Letter #1	July 31, 2008		
Protocol Version 3 (Amendment #2)	October 31, 2008		
Changes from Last Protocol Amendment to Final SAP			

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
02/03/2010

Hanner, Diane

From: Hanner, Diane
Sent: Wednesday, February 03, 2010 1:35 PM
To: 'Natalie.tolli@Abbott.com'
Subject: Information Request regarding NDA 20517/S-030

Attachments: Information request 2-3-10.doc

Hi Natalie,
Please click on the attached, and view another information request regarding NDA 20517/S-030.
Please let me know if you have any questions.
Thanks,
Regards,
Diane

Information request 2-3-10.doc...

DRUP Requests for Information
NDA 20-517 Serial 030

1. For Subject #282, please explain why there are 4 testosterone (T) concentrations listed for Day 167, but only one T concentration listed for Day 169. Did this patient receive his second dose administration on Day 167, rather than on Day 169? If so, which T concentrations on Day 167 are pre-dose administration and which are after dose administration?

2. For Subject #167, please explain why no T concentrations are listed for Day 169, but six T concentrations are listed for Day 170. Did this patient receive his second dose administration on Day 170, rather than on Day 169? If so, which T concentrations on Day 170 are pre-dose administration and which are after dose administration?

3. For Subjects #159, #153 and #318, please explain which T concentrations on Day 169 are pre-dose administration, and which are post-dose administration.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
02/03/2010

Hanner, Diane

From: Hanner, Diane
Sent: Wednesday, January 27, 2010 4:25 PM
To: 'Natalie.tolli@Abbott.com'
Subject: FW: Additional Investigator information needed

Hi Natalie,

Please provide the following information regarding the respective investigators listed below:

1) David Lipsitz (Inv # 50042)- I need phone and fax numbers.
2) Gary Karlin (Inv # 14898)- I need fax number and email address.
3) Daniel Saltzstein (Inv # 11706)- I need all three- phone, fax, and email.
4) James Cochran (Inv # 22915)- I need fax # and email address.

Thanks.
Regards,
Diane

CDR Diane Hanner
Senior Program Management Officer
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20517	SUPPL-30	ABBOTT ENDOCRINE INC SUB ABBOTT LABORATORIES	LUPRON DEPOT

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/s/

DIANE C HANNER
01/27/2010

Hanner, Diane

From: Hanner, Diane
Sent: Friday, January 15, 2010 10:12 AM
To: 'Natalie.tolli@Abbott.com'
Subject: FW: Re: Lupron 6-month sNDA 20571 Revised table to be completed and Information Request

Hi Natalie,
I have been instructed to have you complete the revised table below instead of the table that was previously requested:

Investigator (name and site #, and address)	# subjects randomized	# Discontinuations	# AEs	# SAEs	# protocol violations

Also, I need a word copy of your complete proposed labeling as well as your highlight strikeout copy of the labeling showing the changes. In addition, please also provide the patient counseling information. Finally, please also submit all of the above officially. As a reminder all labeling should be included with the product and should be submitted with the original NDA or supplement. For this supplement is there going to be new carton container labeling? If so, also please submit this new carton container labeling. Thank you.

Regards,
Diane

CDR Diane Hanner
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/s/

DIANE C HANNER
01/15/2010

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DRUP (Attn.Olga Salis)

FROM: HFD-150/Diane Hanner

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT :	DATE OF DOCUMENT:
1-13-10	27350 (for reference only)	20517/S030	review consult	12-11-09

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lupron	Standard		5-4-10 (per GRMP)

NAME OF FIRM: Abbott

REASON FOR REQUEST

I. GENERAL

- ☐ 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
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x 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:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY/PK 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: See the Attachment concerning our consult rationale which is from the DDOP Medical Officer regarding sNDA 20517
Also the following link has been provided for your convenience:

\\Cdsesub1\evsprod\NDA020517\0038

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one):
Diane Hanner	MAIL X DARRTS
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

Attachment to the DRUP Consult on sNDA 20-517

We have received the supplemental New Drug Application (sNDA 20-571) for Lupron Depot (leuprolide acetate for depot suspension)- 6-month, 45 mg injection, submitted on 12/11/09 by Abbott Endocrine Inc. (subsidiary of Abbott Laboratories). The revised for proposed indication in the Lupron Depot label will be: Lupron Depot -3 month (22.5 mg), -4 month (30 mg), and -6 month (45 mg) (leuprolide acetate) are indicated in the palliative treatment of advanced prostate cancer.

The pivotal study in support of the new labeling is L-PC07-169, "A Phase 3, multicenter, open-label trial to evaluate the efficacy, safety, and pharmacokinetics of two 6-month leuprolide formulations in subjects with prostatic adenocarcinoma". This nonrandomized trial included subjects with any stage prostate cancer who had a rising PSA after radical prostatectomy on 2 consecutive assessments, or a rising PSA after XRT, as per the Phoenix definition.

The study evaluated the efficacy and safety of 2 new leuprolide depot formulations, Formulation A and Formulation B. The study design was such that the first 150 patients enrolled received Formulation A, and the second 150 patients received Formulation B. Subjects received a total of two 45-mg IM injections, administered 24 weeks apart, both of the same formulation.

The study primary endpoint was to assess the efficacy and safety of the 2 new leuprolide acetate 45-mg 6-month depot formulations over 48 weeks. This was based on the suppression of serum Testosterone level ($\leq$ 50 ng/dL) from week 4 through 48.

At the time of this sNDA submission, only the final results for the patients receiving Formulation A have been finalized. An interim report for the Formulation B portion of the study is also included in the submission, and the final results will be provided when available. It is notable that the Sponsor is only seeking approval for Formulation A.

We request brief DRUP input on the adequacy of the results from study L-PC07-169. A Type C meeting occurred between the Sponsor and DDOP and DRUP on 11/7/07 (the meeting minutes are provided by the Sponsor in Module 1.6.3). A subsequent meeting with the Agency occurred on 6/23/09 (minutes provided in Module 1.12.4). The Clinical Overview for the application is contained in Module 2.5 of the sNDA. Module 2.7.3 contains the Summary of Clinical Efficacy and 2.7.4 contains the Summary of Clinical Safety.

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/s/

DIANE C HANNER
01/14/2010

TELECON MINUTES

MEETING DATE: 11-1-07 **TIME:** 10AM **LOCATION:** room 2201

Drug Name: Lupron **IND:** 27,350 **Type of meeting:** EOP2

Sponsor: TAP **Meeting Request Submission Date:** 7-27-07
Briefing Document Submission Date: 9-28-07

FDA Invitees, titles and offices:
Robert Justice, M.D., Division Director
Ann Farrell, M.D., Deputy Division Director
Nancy Scher, M.D., Medical Officer
Rajeshwari Sridhara, Ph.D., Deputy Director, Division of Biometrics V
Somesh Chattopadhyay, Ph.D., Statistical Reviewer
Margaret Brower, Ph.D., Pharmacology Reviewer
John Leighton, Ph.D., Pharmacology Team Leader
Brian Booth, Ph.D., Deputy Director, Division of Clinical Pharmacology 5
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer
Sarah Pope, Ph.D., Pharmaceutical Assessment Lead
Ravi Harapanhalli, Ph.D., Branch Chief, DPAMS
Mark Hirsch, M.D., Deputy Director, DRUDP
Harry Handelsman, M.D., Medical Officer, DRUDP
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices
Stuart Atkinson, M.D., Senior Scientific Director, Head of Therapeutic Areas
Anthony Edmonds, MS; Associate Director, Project Management
Donna Helms, Director, Regulatory Affairs
Robert Jackson, M.D.; Head, Clinical Development, Outcomes and External Research
Lois Larsen, Ph.D.; Manager, Statistics
Darcy Mulford, Ph.D.; Director, Drug Disposition, Efficacy and Safety
Ronald Walls, M.D.; Medical Director, Men's Health, Women's Health and Clinical Pharmacology
Majid Vakilynejad, Ph.D.; Senior Research Investigator, Drug Metabolism & Pharmacokinetics
Allison Villinski; Senior Regulatory Product Manager, Regulatory Affairs

Meeting Objective(s):
TAP plans to initiate a Phase 3 study for the palliative treatment of advanced prostate cancer in the first quarter of 2008. This teleconference/meeting will focus on the study design of the proposed Phase 3 study examining two new six month formulations of Lupron Depot.

Background:
TAP is proposing a new Phase 3 study to evaluate the safety and efficacy of two new formulations of leuprolide acetate for depot suspension 45 mg administered every 6 months. In the planned study, testosterone (T) control in prostate cancer with a longer-acting 6 month formulation will be assessed. Minimizing escapes from T suppression is also a goal of treatment as they can have a serious impact on the patient's quality of life and be associated with a temporary increase in tumor symptoms such as bone pain and spinal cord compression.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. TAP plans to evaluate two, 45 mg 6 month depot formulations in the proposed Phase 3 study. This study will not be randomized. A total of 300 subjects will be enrolled (150/formulation). The first 150 subjects enrolled will receive the first formulation and the next 150 subjects will receive the second formulation.

   Is the proposed Phase 3 study design as outlined in the protocol acceptable, specifically:

a. *Number of subjects*

b. *Study duration (i.e. 2 injections, 48 weeks total)*

c. *Inclusion/exclusion criteria*

d. *Visit schedule (to assess onset of suppression and maintenance of suppression)*

e. *Statistical analyses*

f. *Proposed formulation discontinuation criteria?*

FDA response:

a. Please clarify how you determined the proposed number of subjects, taking into account the interim analysis and acceptable range of percentage of subjects with testosterone suppression from Week 4 to Week 48.

Discussion: TAP stated that there will be no interim analysis.

b. Yes.

c. Yes.

d. Although we agree with assessments at weeks 46 and week 48, we would like you to increase the assessments in cycle 2 to conform more closely to the pattern of assessments in cycle 1.

Discussion: TAP stated that there will be the same number of visits for both cycles. They will add one visit to cycle 2. The intervals between visits will be no longer than 6 weeks. The sponsor stated that they will retain assessments for weeks 46 and 48.

e. No. See the reasons below.

1. **Although the estimate of the primary endpoint based on Kaplan-Meier methodology may be satisfactory, it will be biased if censoring (drop-out) is not independent of testosterone suppression. This will be a review issue.**

Discussion: TAP stated that all patients while going off study for any reason will have the final assessments performed at that time.

2. **You should use a two-sided 95% confidence interval or a one-sided 97.5% confidence interval for the primary endpoint.**

Discussion: See question 5.

3. **The confidence level for the final analysis should be adjusted for the interim analysis. Clarify the procedures for the interim analysis.**

Discussion: TAP stated that there will be no interim analysis.

4. **If a subject has onset of testosterone suppression by Day 32, has no escapes from suppression, and has a final testosterone value of less than or equal to 50 ng/dL before Week 48, the subject should be censored at the day of their final testosterone value. The amount of premature discontinuation will be a review issue.**

Discussion: The Agency reiterated that the censoring of the time of observation should be the exact date of the measurement. The Agency suggested that the sponsor could consider obtaining measurements at or beyond week 48 (Day 337) for all patients in order to obtain a KM estimate at week 48.

5. **To make any efficacy claim based on** (b) (4)

Discussion: TAP does not intend to file the NDA if the primary endpoint is not successful. If an NDA is submitted then the sponsor intends to include (b) (4) ***in the proposed label. The FDA stated that it is premature to discuss labeling at this time.***

6. (b) (4) **).**

Discussion: The FDA stated that it is premature to discuss labeling at this time. If the sponsor wishes, this issue can be discussed in the future.

f. Yes.

2. TAP plans to enroll early stage (Clinical Stage A and B) prostate cancer patients as well as those with locally-advanced and metastatic disease (Clinical Stage C and D including patients with biochemical failure after curative therapy) in this study. TAP does not plan on having a minimum number of Stage C and D patients in this study.
Is this plan acceptable for the proposed indication?

FDA response: Yes. The proposal to enhance enrollment by inclusion of subjects with earlier stages of cancer is acceptable in the context of the pharmacodynamic primary endpoint and the understanding that the indication will remain: "*…the palliative treatment of advanced prostate cancer*."

3. With the proposed study design, results for the first formulation will be available prior to results for the second formulation. If results for the first formulation are successful, TAP

plans to file an NDA only for the first formulation. (b) (4) .
Is this acceptable?

FDA response: Yes

4. The NDA will include safety, efficacy and pharmacokinetic data on all subjects through Treatment Month 8 (32 weeks) for the chosen formulation, and available safety data from subjects treated with the other formulation. (b) (4)

Is this acceptable?

FDA response: No. (b) (4)

5. The proposed primary endpoint is the percentage of subjects with testosterone (T) suppression ≤50 ng/dL on or before Week 4 and no "escapes" from suppression (T value >50 ng/dL) through Week 32 (interim analysis for NDA)/Week 48 (final analysis for 4 Month Safety Update). For the study to be a success, 90% of subjects will have to achieve both of these criteria for the interim analysis and 90% for the final analysis.
Is the proposed primary efficacy endpoint acceptable?

FDA response: Please provide a point estimate such that the lower bound of the 2-sided 95% confidence interval is not less than 87%.

Discussion: The Agency agreed that 1-sided 95% confidence interval with a lower bound not less than 87% is acceptable for this particular product and this circumstance.

6. *Does the Agency have any additional comments on the proposed Phase 3 study protocol?*

FDA response: Please submit a detailed statistical analysis plan.

Discussion: TAP will submit a detailed SAP at least 30 days prior to enrollment of the first subject.

7. *Does the proposed study design in addition to the literature support an indication for the* (b) (4) *If not, what additional data would be required to support this claim?*

FDA response: No. Clinical benefit would need to be shown in clinical trials.

Additional Clinical Pharmacology Comment

Please provide information on the composition of the two formulations that will be used in the proposed Phase 3 Study L-PC07-169.

Discussion: TAP will submit the compositions of the 2 formulations.

ADDITIONAL COMMENTS

FINAL PROTOCOLS:

If you plan on submitting a request for Special Protocol Assessment, please refer to the May 2002 "*Guidance for Industry – Special Protocol Assessment"* (posted on the Internet 5//2002) and submit final protocol(s) to the IND for FDA review as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF), the statistical analysis plan, the independent radiologic review charter (if applicable), and the independent data monitoring committee charter should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we may use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs until 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE:

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or

Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system by will be made available to the public on the Internet at http://clinicaltrials.gov.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE:

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

PEDIATRIC RESEARCH EQUITY ACT (PREA):

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY:

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DEMOGRAPHICS:

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by

gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-≤1 Mo.		>1 Mo.-≤ 2Year		>2-<12	
	12-16		17-64		≥65	
Race:	White		Black		Asian	
	Other					

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/s/

Ann Farrell

11/6/2007 09:53:03 AM