

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203696Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets), co-packaged for intramuscular use and for oral use, respectively
Applicant	Abbott Laboratories, Inc.
Application/Supplement Number	NDA 203696 (Two different PI for 11.25 mg injection every 3 months and 3.75 mg injection every month, respectively)
Type of Application	Original
Indication(s)	For initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms
Established Pharmacologic Class ¹	Leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and, norethindrone acetate, a progestin
Office/Division	ODE III/DRUP
Division Project Manager	Kimberly Shiley
Date FDA Received Application	February 15, 2012
Goal Date	December 15, 2012
Date PI Received by SEALD	December 12, 2012
SEALD Review Date	December 13, 2012
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: Fix the horizontal lines for each heading in HL (they are too short) for both PI.

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

Selected Requirements of Prescribing Information

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: Delete “Revised” date at the end of the FPI. The revision date at the end of HL replaces the “revised” date at the end of the FPI and should not appear in both places.

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment: Insert a horizontal line between TOC and FPI for both PI.

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information

Comment:

- NO** 33. All subsection headings must be indented, not bolded, and in title case.

Comment: For the 3.75 mg every month PI, indent subsection heading 8.1 to align with the rest of the subsection headings in TOC. Also recommend moving the section heading 8 and subsection heading 8.1 to the top of the next column.

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION

Selected Requirements of Prescribing Information

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: For both PI change the following cross-reference presentations:

For subsection 1 and 2.1: Change “[see Warnings & Precautions (5.1)]” to [see Warnings and Precautions (5.1)]

For subsection 5.2: Change “[see Contraindications (4.3)]” to [see Contraindications (4)]

For subsection 8.1: Change “[see Warnings & Precautions (5.4)]” to [see Warnings and Precautions (5.4)]

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment: For both PI, delete the verbatim statement from “6 Adverse Reactions” and place it at the beginning of “6.1 Clinical Trials Experience.”

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ERIC R BRODSKY

12/14/2012

Eric Brodsky, SEALD labeling team leader, signing for Abimbola Adebawale, SEALD labeling reviewer, and Laurie Burke, SEALD division director

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

Memorandum

Date: December 7, 2012

To: Kim Shiley, RN, BSN, BSBA
Regulatory Health Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Division of Prescription Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD,
Acting Team Leader (DPDP)

CC: Jessica Cleck-Derenick, PhD,
Regulatory Review Officer (DPDP)

Subject: **NDA 203696**
LUPANETA PACK® (leuprolide acetate for depot suspension, for
intramuscular use and norethindrone acetate tablets for oral use)

Background

On April 18, 2012, DRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for LUPANETA PACK® (leuprolide acetate for depot suspension, for intramuscular use and norethindrone acetate tablets for oral use) (Lupaneta Pack).

DPDP reviewed the PI from the proposed substantially complete versions retrieved from the eRoom on November 27, 2012 and December 1, 2012. Our comments are provided below. DPDP also reviewed the carton/container labeling for 3 month administration retrieved from the December 6, 2012, submission to the electronic document room (EDR). Our comments are provided in the attachment.

DPDP notes that the Division of Consumer Drug Promotion (DCDP) provided comments on the PPI under a separate cover on December 3, 2012.

Thank you for your consult. If you have any questions on the PI or the carton/container labeling, please contact Melinda McLawhorn at 6-7559 or at melinda.mclawhorn@fda.hhs.gov.

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/s/

MELINDA W MCLAWHORN
12/07/2012

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

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

Memorandum

Date: December 3, 2012

To: Kimberly Shiley, R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

**Subject: NDA: 203696
LUPANETA PACK[®] (leuprolide acetate for depot suspension, for
intramuscular use and norethindrone acetate tablets for oral use)**

Background

On April 18, 2012, DRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for LUPANETA PACK[®] (leuprolide acetate for depot suspension, for intramuscular use and norethindrone acetate tablets for oral use) (LUPANETA PACK).

DCDP notes that the Division of Medical Policy Programs (DMPP) provided comments on the draft PPI on November 28, 2012. DCDP agrees with DMPP's comments and has provided additional comments directly on DMPP's review of the PPI (please see attached document).

Please note that DCDP comments are based on the substantially complete version of the draft PI retrieved from the eRoom on November 30, 2012. The Division of Professional Promotion/OPDP will provide comments on the proposed PI and carton/container labeling under separate cover.

Thank you for your consult. If you have any questions on the PPI, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
12/03/2012

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

PATIENT LABELING REVIEW

Date: November 28, 2012

To: Hylton Joffe, M.D., Director
Division of Reproductive and Urologic Products (DRUP)

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

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name and dosage form): Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets)

Application Type/Number: NDA 203696

Applicant: Abbott Endocrine, Inc.

1 INTRODUCTION

On February 15, 2012, Abbott submitted for the Agency's review an original new drug application (NDA) for Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets). Lupaneta Pack consists of two approved drug products, leuprolide acetate for depot suspension and norethindrone acetate tablets, indicated for the treatment of endometriosis [REDACTED] (b) (4). This NDA proposes to obtain marketing authorization for two new co-packaged kit configurations, a 1 month kit and a 3 month kit.

On November 19, 2012, the Division of Reproductive and Urologic Products (DRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for the Lupaneta Pack 3 month kit (leuprolide acetate for depot suspension and norethindrone acetate tablets). DRUP plans to apply similar revisions from the DMPP 3 month kit PPI review to the proposed 1 month kit PPI.

On November 26, 2012 Abbott requested input from the Agency regarding their desired removal of the PPI for this product. On November 27, 2012 the Agency advised Abbott that the PPI should not be removed because the patient will take home the norethindrone acetate tablets for self-administration.

This review is written in response to a request by the DRUP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for the Lupaneta Pack 3 month kit (leuprolide acetate for depot suspension and norethindrone acetate tablets).

2 MATERIAL REVIEWED

- Draft Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets) 3 month kit Patient Package Insert (PPI) received on February 15, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 19, 2012
- Draft Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets) Prescribing Information (PI) received on February 15, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 23, 2012
- Approved Lupron Depot (leuprolide acetate for depot suspension) comparator labeling dated June 14, 2011

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
11/28/2012

MELISSA I HULETT
11/28/2012

LASHAWN M GRIFFITHS
11/28/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review Addendum

Date: October 31, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Lupaneta Pack (Leupron Acetate for Depot Suspension and
Norethindrone Acetate Tablets)
3.75 mg/5 mg and 11.25 mg/5 mg

Application Type/Number: NDA 203696

Applicant/sponsor: Abbott Laboratories

OSE RCM #: 2012-904-1

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This addendum provides for update recommendations for the Lupaneta Pack labels and labeling after submission of labels and labeling presenting the most recent proposed proprietary name, (b) (4), and revised comments after discussion with ONDQA.

1.1 REGULATORY HISTORY

DMEPA previously completed a review (OSE Review #2012-904, dated July, 23, 2012) which provided recommendations for Lupaneta Pack labels and labeling to make the product line consistent with all Lupron products. However, after this review was finalized, Chemistry identified that required information (the inactive ingredients) did not appear on the labels and labeling. Therefore, DMEPA and Chemistry met to discuss possible revisions to include this information on the labels and labeling. This review is the recommend revisions that came from the Chemistry and DMEPA meeting.

2 METHODS AND MATERIALS REVIEWED

We reviewed the labels and labeling submitted by the Applicant on September 24, 2012.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted (Appendix B)
- Carton Labeling submitted (Appendix C)
- Insert Labeling submitted (no image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed multiple reviews on the Lupron products. OSE Review #2010-377, dated September 10, 2010, OSE Review #2011-1033, dated May 5, 2011, and OSE Review #2011-2437, dated August 1, 2011, evaluated medication errors that were identified in the AERS database, and recommended revisions to the labels and labeling of the entire line of Lupron products, however, they were only applied to NDA 020517 (Lupron Depot 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration) and NDA 020263 (only the Lupron Depot-Ped 11.25 mg and 30 mg for 3-month administration). The remaining formulations that are currently marketed (including NDA's 020011 and 020708; the presentations submitted by the Applicant for this Application) do not appear to have incorporated these labeling revisions because we gave the Applicant the option to include these revisions at the time of next printing. Additionally, DMEPA reviewed our previous

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

recommendations in OSE 2012-904, dated July 23, 2012, to revise the recommendations for this addendum based on our discussion with Chemistry.

3 CONCLUSIONS

The labels and labeling require revisions to ensure the safe use of the proposed product and bring consistency through out the Lupron product line.

4 RECOMMENDATIONS

DMEPA evaluated the container labels, carton, and insert labeling for each of the individual components of the co-packaged product. We have the following recommendation for the labels and labeling.

4.1 NORETHINDRONE ACETATE TABLETS CONTAINER LABELS

This product comes in a large carton and as such, pharmacists may label the carton and not open the carton to place a pharmacy label on the individual components contained in the pack. Additionally, patients may throw away this large carton after the Lupron component has been administered to save space in their home. Therefore, we request the usual dosage statement be revised to state the actual dose of the product (i.e. "Take 5 mg (1 tablet) by mouth once daily for 30 days" or "Take 5 mg (1 tablet) by mouth once daily for 90 days"). Revising the usual dose statement on the Norethindrone Acetate Tablets will ensure that the patients have directions for the tablets even if they discard the carton.

4.2 LUPRON COMPONENT

Based upon postmarketing errors with the Lupron product line and analysis of the proposed labels and labeling for Lupron Depot and Lupron Pack labeling, we recommend the following to be implemented prior to approval of this NDA. Additionally, we recommend that these changes also be carried across your entire Lupron product line at the time of next printing:

A. *Container Labels*

Lupron Depot syringe (3.75 mg and 11.25 mg)

- a. Relocate the established name to appear directly under the name, Lupron Depot, followed by the product strength, and frequency of administration on the Lupron Depot syringe. The revised presentation should appear as follows (note the use of title case lettering):

Lupron Depot

(leuprolide acetate for depot suspension)

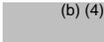
3.75 mg (or 11.25 mg)

For 1-month (or 3 month) administration

For intramuscular injection

- b. Remove the color block currently used for the NDC number and product description and use it to present the strength and the frequency of administration (see the presentation above). Additionally, use a lighter color

purple for the 3.75 mg strength to increase the visual contrast between the color block and the black font of the text.

- c. Include the route of administration, 'For intramuscular injection' on the principal display panel of the Lupron Depot syringe label (see the presentation above). This information can be placed under the color block containing the product strength and the frequency of administration, in bold letters.
- B. *Clam shell Carton Labeling (3.75 mg/5 mg and 11.25 mg/5 mg)*
1. Present the established name in parenthesis, followed by the product strength, the frequency of administration, and the route of administration (see the presentation in A1).
 2. Box the strength statement and the frequency of administration with the same color band that is used for each strength and frequency of administration at the top of the clam shell labeling to increase visual differentiation between the 3.75 mg and 11.25 mg strengths. The strength and frequency should statement should also be bolded. Although, the color differentiation between the two strengths of Lupron Depot kits placed inside of the proposed outer carton may not be as critical for the proposed product, for the purpose of consistency, the changes in the presentation of information should be implemented in all the available Lupron products.
 3. Revise the interior of the clam shell labeling 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 of the carton and clam shell labeling, the practitioner who is administering the drug may see this information when the clam shell is opened.
 4.  (b) (4).
 5. Retain the inactive ingredient statement on the principal display panel. We realize in previous communications you were instructed that the inactive ingredient statement could be deleted. However, this recommendation was not correct and this statement should remain on the carton labeling. This inactive ingredient information can be reformatted, made smaller, and relocated to the bottom right of the labeling where the  (b) (4) symbol, "Rx Only", and the Abbott symbol are currently located to help include the inactive ingredient information on the labeling of the principal display panel.
 6. Relocate the "Rx only" symbol and reduce its prominence to help make room for required labeling statements on the labeling.
 7. Relocate or delete the Abbott logo to help make room for the required labeling statements.
 8. If possible decrease the size of the bar code to help make room for required labeling statements.

Due to the complicated nature of revisions we have included a crude draft of the revisions. We have used the Adult 22.5 mg for 3 month administration NDA 020517 as the beginning template to show the revisions since this version previously incorporated the previous recommendations from the Agency. This draft should only be used to guide the placement of information and not the content. Although we are providing this draft layout, alternate proposals can be made provided they include all of the same information.

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

4.3 LUPANETA OUTER CARTON LABELING

1. Revise the presentation of the proposed proprietary name to “Lupaneta Pack” and present the entire proposed proprietary name as title case (i.e. Lupaneta Pack) and in a single color font size, and type. The use of all capital letters for the word “PACK” and the use of two different colors is a form of tall man lettering. We reserve tall man lettering for established names with known name confusion. Additionally, presenting the name in one color, font size, and font type will help reinforce the entire proprietary name as “Lupaneta Pack”.
2. Revise the established name to have a prominence commensurate with the prominence of the proprietary name, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
3. Revise the established name presentation to include the strength of each component of Lupaneta Pack following the dosage form statement. Additionally, ensure the strength of the Leuprolide Acetate component (i.e. 3.75mg and 11.25 mg) is prominent (i.e. using a larger font size). Incorporating the strength statement can provide another tool (in addition to the frequency of administration; ‘1-month’ and ‘3-month’) to help differentiate the two different Lupaneta Pack products and may help mitigate the risk of medication errors due to product selection. The revised presentation may appear as follows:

‘Lupaneta Pack

leuprolide acetate for depot suspension,
3.75 mg for intramuscular injection only
and Norethindrone Acetate Tablets, 5 mg for oral administration

Lupaneta Pack

leuprolide acetate for depot suspension, 11.25 mg for intramuscular injection only and
Norethindrone Acetate Tablets, 5 mg for oral administration’

4. Replace the ‘plus sign’ within the established name with the word ‘and’.
5. Remove the large plus sign that appears on the left hand side of the proprietary and the established names, as well as the lower right hand side of all the side panels where it appears. As currently presented, the large plus sign can distract from the proprietary name and the frequency of administration.
6. Remove the two-toned color band that contains the proprietary and the established names, as well as the frequency of administration. The color band should be used only for the frequency of administration, consistent with DMEPA’s recommendations for the Lupron Depot products.

7. Increase the prominence of the frequency of administration statement on the top right hand side of the display panel by increasing the font size, bolding, and using dark ink against a light purple color block, to increase contrast. It is important to provide visual differentiation between the 1-month and the 3-month frequency of administrations of Lupaneta Pack to minimize medication errors due to selection errors in the pharmacy.
8. Include the Usual Dose for Norethindrone Acetate on the principal display panel. As currently presented, this information does not appear under the second bullet point. The statement may appear as:

‘Usual Dose: Take 5 mg (one tablet) orally once daily for 1 month (or 3 months). See package insert for full prescribing information.’
9. Reduce the prominence of the company name and logo on the principal display panel. As currently presented, this information competes in prominence with the proprietary name and the frequency of administration statement.
10. Expiration date and Lot number for the co-packaged product should be displayed on the carton label. The expiration date should be the same as the product whichever expires earlier.
11. Storage condition should be displayed for the co-packaged product in addition to the storage condition of individual product. The storage condition for the co-packaged product should be displayed as “Store at 25°C (77°F), excursion permitted to 15°C- 30°C (59-86°F) [See USP Controlled Room Temperature].”
12. ^{(b) (4)} “ Not made with natural rubber latex”.

4.4 INSERT LABELING (1-MONTH AND 3-MONTH)

1. 1-month administration only: The Dosage and Administration Sections of Highlights of Lupaneta Pack for 1-month administration insert labeling refers to the frequency of administration of Lupron Depot and Norethindrone Acetate as ‘every 4 weeks’ and ‘for 4 weeks’ respectively, which is inconsistent with the phrase used in the Dosage and Administration Section of the Full Prescribing Information (i.e. ‘monthly’ and ‘for one month’) as well as the Dosage and Administration Sections of the Highlights and Full Prescribing Information of Lupaneta Pack for 3-month administration (i.e. ‘every 3 months’ and ‘for 3 months’). Additionally, the proposed 30-count bottle of Norethindrone Acetate tablets is also inconsistent with the proposed ‘4-week’ (i.e. 28 days) frequency of administration. Revise the Dosage and Administration Section of the Highlights of Lupaneta Pack for 1-month administration insert labeling to refer to the frequency of administration as ‘every one month’ (or ‘monthly’) and ‘for 1 month’ for Lupron Depot and Norethindrone Acetate respectively. The revised statements would appear as follow:

‘Lupron Depot 3.75 mg for 1-month administration given as a single intramuscular injection every one month (or monthly). Norethindrone Acetate 5 mg tablets should be taken orally once per day for one month.’

2. Delete the parenthesis around the Lupron Depot’s strength and frequency of administration in some areas of the package insert. The use of parenthesis is unnecessary and is inconsistent. The parenthesis presentation appears in the Dosage and Administration Sections of the highlights and the Full Prescribing Information, Reconstitution and Administration, Dosage Forms and Strengths, and Description sections.
3. Replace the abbreviation ‘IM’ with ‘intramuscular’ in the Dosage and Administration, as well as the How Supplied/Storage and handling sections.
4. 3-month only: Dosage and Administration Section of the Full Prescribing Information states: ‘Lupron Depot (11.25 mg for 3-month administration) is supplied in a prefilled dual chamber syringe and administered by IM injection monthly used in combination with’. The use of the word ‘monthly’ for the 3-month administration kit is confusing and misleading because the injection is given every 3-month. Revise the sentence to appear as follows:

‘Lupron Depot 11.25 mg for 3-month administration is supplied in a prefilled dual chamber syringe and is given as a single intramuscular injection every 3 months.’

5. Reconstitution and Administration for Injection for Lupron Depot: for clarity, include the statement ‘Discard if not used within 2 hours’ to the end of the sentence in #8.
6. Norethindrone Acetate Administration: The dosing information provided for Norethindrone Acetate in this section differs from the recommended once daily dosing for 1 month (or 3 months) for the proposed indication, and may be confusing for healthcare providers or patients. We defer to the Division regarding the different dosing recommendations provided in this section.
7. Description, Lupron Depot 11.25 for 3-month administration: Remove the trailing zero from ‘D-mannitol (75.0 mg)’. The revised format should appear as ‘D-mannitol (75 mg)’. The use of trailing zeros is error-prone and can result in ten-fold dosing error if the Decimal is not seen. As part of a national campaign to prevent the use of error-prone dose designations such as trailing zeros in prescribing, FDA agreed not to approve error-prone dose designations in labeling because they are carried on to the prescribing practice.

If you have further questions or need clarifications, please contact Marcus Cato, project manager, at 301-796-3904.

REFERENCES

1. OSE Review 2011-2437, Lupron Depot-Ped Label and Labeling Review, McMillan, T. August 11, 2011.
2. OSE Review 2012-904, (b) (4) (Lupron Depot and Norethindrone Acetate) Label and Labeling Review, Siahpoushan, M.

APPENDICES

Appendix A: Container Labels



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

/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: July 20, 2012

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Division of Medication Error Prevention and Analysis

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Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Tradename (Leupron Acetate for Depot Suspension and
Norethindrone Acetate Tablets)
3.75 mg/5 mg and 11.25 mg/5 mg

Application Type/Number: NDA 203696

Applicant/sponsor: Abbott Laboratories

OSE RCM #: 2012-904

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container closure system, container labels, carton and insert labeling for Tradename NDA 203696 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Abbott Endocrine Inc., submitted a type 4 application for Tradename (NDA 203696) on February 15, 2012 which provides for two proposed co-packaged kits each combining Lupron Depot suspension and Norethindrone Acetate Tablets. Lupron Depot suspension and Norethindrone are approved products, in the market.

One-month co-packaged kit contains:

- Lupron Depot 3.57 mg for 1-month administration kit (one prefilled dual-chamber syringe, one plunger, and two alcohol swabs) (Abbott NDA 020011) and
- Norethindrone Acetate 5 mg; 30 tablets/bottle (Glenmark ANDA 091090)

Three-month co-packaged kit that contains:

- Lupron Depot 11.25 mg for 3-month administration kit (one prefilled dual-chamber syringe, one plunger, and two alcohol swabs) (Abbott NDA 020708) and
- Norethindrone 5 mg; 90 tablets/bottle (Glenmark ANDA 091090)

Both Lupron Depot 3.75 mg for 1-month administration (sNDA 020011/S-021) and Lupron Depot 11.25 mg for 3-month administration (sNDA 020708/S011) were approved by the FDA on September 21, 2001 for the use in endometriosis patients with add-back therapy (Norethindrone 5 mg).

Norethindrone alone is approved for the treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer (Glenmark ANDA 091090: Norethindrone Acetate 5 mg Tablets; 30 tablets/bottle and 90 tablets/bottle; Office of Generic Drugs approval letter dated January 17, 2012.¹

1.2 PRODUCT INFORMATION

The following product information is provided in the April 10, 2012, proprietary name submission.

- Active Ingredients: Leuprolide Acetate and Norethindrone Acetate
- Indication of Use: Initial management of the painful symptoms of endometriosis and management of recurrence of symptoms.

¹ Orleans, R.J and Soule, L.M. Clinical Filing Checklist For a New NDA/BLA. April 12, 2012

- Route of Administration: Intramuscular and oral
- Dosage Form: Injection and Tablets
- Strength: 3.75 mg and 5 mg and 11.25 mg and 5 mg
- Dose and Frequency:
 - Lupron Depot 3.75 mg for 1-month administration given as a single intramuscular injection every 1 month, and Norethindrone Acetate 5 mg Tablets taken orally once per day for one month.
 - Lupron Depot 11.25 mg for 3-month administration given as a single intramuscular injection once every 3 months, and Norethindrone 5 mg tablets taken orally once per day for 3 months.
- How Supplied:

Tradename for 1-month co-packaged kit is available in cartons containing:

 - Lupron Depot 3.75 mg for 1-month administration Kit (one prefilled dual-chamber syringe, one plunger, and two alcohol swabs)
 - Norethindrone Acetate 5 mg 30 count bottle

Tradename for 3-month co-packaged kit is available in cartons containing:

 - Lupron 11.25 mg for 3-month administration Kit (one prefilled dual-chamber syringe, one plunger, and two alcohol swabs)
 - Norethindrone Acetate 5 mg 90 count bottle
- Storage: 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure System: The proposed co-packaged kit is an outer carton container (non-functional secondary packaging material) that will contain the already marketed Lupron Depot syringe Kit and Norethindrone bottle components within the carton, which is secured with an adhesive tamper-evident seal.

Lupron Depot prefilled dual chamber syringe consists of:

- Gray (b) (4) rubber stopper
- Colorless (b) (4) glass cartridge (b) (4) (b) (4) (USP Type I glass)
- Front assembly that consists of a 23 G x 2.5 inch needle, a sheath, and luer lock hub. (b) (4)
- Finger grip made of colored (b) (4)
- Plunger rod made of colored (b) (4)

Norethindrone (30 and 90 count bottles):

50 cc white opaque, high density polyethylene bottle with (b) (4) with heat seal liner, 2 gram sorb-it canister, purified cotton, container label, and literature.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Lupron Depot and Norethindrone medication error reports since these products are co-packaged in the proposed product. We also reviewed the labels, package insert labeling, and packaging configuration submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database on April 19, 2012, using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	Lupron Depot: July 16, 2011 (date of last AERS search in OSE Review #2011-2437, dated August 1, 2011) through April 19, 2012 Norethindrone: No time limit set
Drug Names	Active ingredient: Leuprolide Trade Names: Lupron, Lupron Depot, Lupron Depot-Ped, and Norethindrone Verbatim terms: Leuprolide%, Lupron%, Lupron Depot%, Lupron Depot-Ped%, and Norethindrone%
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (PT) Device Malfunction Events NEC (HLT)

The AERS database search identified a total of 59 reports (54 reports for Lupron Depot and 5 reports on Norethindrone). Each report was reviewed for relevancy and duplication. Duplicate reports were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². After individual review, 25 reports (20 Lupron Depot and 5 Norethindrone reports) were not included in the final analysis for the following reasons:

- Adverse events not related to medication errors (Lupron Depot, n = 1, Norethindrone, n = 5)
- Expired drug (Lupron Depot, n = 4)

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

- Dose omission due to financial reasons, adverse events or drug ineffective (Lupron Depot, n = 5)
- Wrong patient (Lupron Depot, n = 1)
- Medication error with no details provided to determine the type of medication error that occurred (Lupron Depot, n = 1)
- Events related to another concomitant drug (Lupron Depot, n = 2)
- Accidental exposure and burning sensation on hands (Lupron Depot, n = 1)
- Accidental exposure to fetus because the patient inadvertently received an injection (Lupron Depot, n = 1). A similar case was also identified in OSE Review #2011-2437, in which DMEPA concluded that the prescribing information states that the use of Lupron-Depot and Lupron Depot-Ped is contraindicated in pregnancy and should not be used in nursing mothers. Since these errors did not appear to be related to inadequacy of information provided by the labels and labeling, we did not recommend any changes at that time.
- Duplicate cases (Lupron Depot, n = 2)
- Wrong administration which led to adverse events, without sufficient details provided in the case to determine the nature of the incorrect administration (i.e. route of administration) or the cause.
- Report unrelated to Lupron Depot that involved the Leuprolide Acetate Injection 1 mg/0.2 mL, 2.8 mL- 14 Day Patient Administration Kit. The reporter stated that the labeling does not provide clear dosing instructions to patients, and no dosing conversion is provided on the carton labeling. However, our evaluation of the labeling for this product found that clear dosing conversion information is provided in the insert labeling.

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 15, 2012 (Appendix B)
- Carton Labeling submitted February 15, 2012 (Appendix C)
- Insert Labeling submitted February 15, 2012

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed multiple reviews on the Lupron products. OSE Review #2010-377, dated September 10, 2010, OSE Review #2011-1033, dated May 5, 2011, and OSE Review #2011-2437, dated August 1, 2011, evaluated

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

medication errors that were identified in the AERS database, and recommended revisions to the labels and labeling of the entire line of Lupron products, however, they were only applied to NDA 020517 (Lupron Depot 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration) and NDA 020263 (only the Lupron Depot-Ped 11.25 mg and 30 mg for 3-month administration). The remaining formulations that are currently marketed (including NDA's 020011 and 020708; the presentations submitted by the Applicant for this Application) do not appear to have incorporated these labeling revisions because we gave the Applicant the option to include these revisions at the time of next printing.

3 MEDICATION ERROR RISK ASSESSMENT

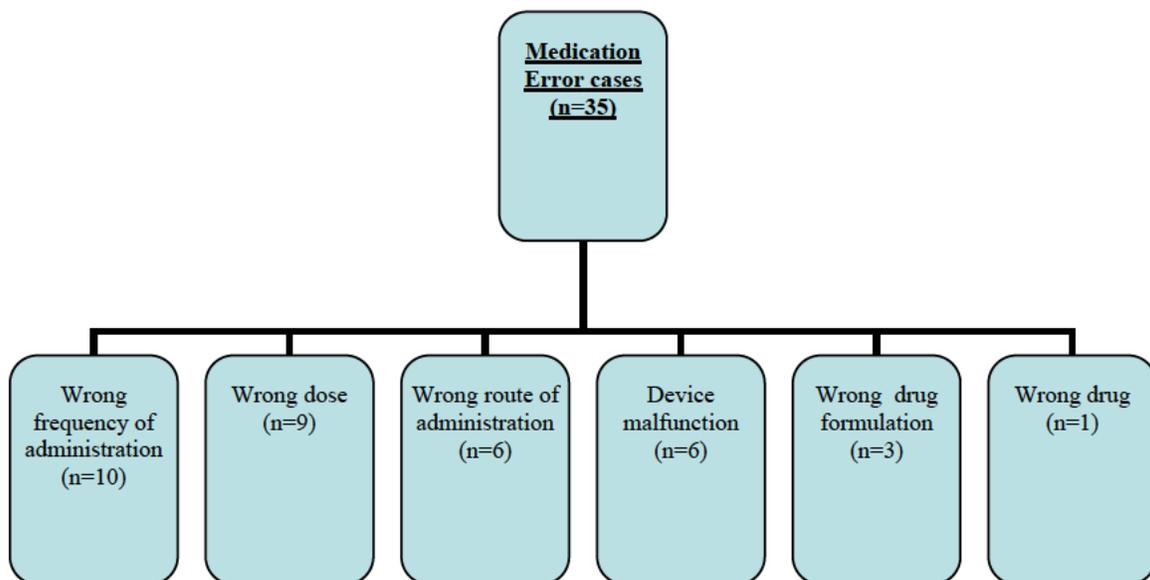
The following sections describe the results of our AERS search and the risk assessment of the proposed product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, thirty-four medication error cases related to only Leuprolide Acetate remained for our detailed analysis. However, one case consisted of two types of medication errors (i.e. wrong dose and wrong route of administration), therefore, we evaluated a total of 35 medication error cases.

Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D provides listings of all ISR numbers, Appendix E contains a summary of the 35 relevant cases, and Appendix F contains a more detailed listing of these cases.

Figure 1: Medication errors (n = 35) categorized by type of error



3.2 PRODUCT DESIGN

The proposed co-packaged product will be available in cartons containing Lupron Depot 3.75 mg for 1-month administration Kit or 11.25 mg for 3-month administration Kit (the Kit contains one prefilled dual-chamber syringe, one plunger, and two alcohol swabs), and Norethindrone acetate 5 mg 30 count (or 90 count bottle). The proposed product

design is appropriate for the proposed indication of initial management of the painful symptoms of endometriosis and management of recurrence of symptoms.

3.3 LABELS AND LABELING

DMEPA has previously recommended revisions to Lupron container labels and carton labeling. However the Applicant has not implemented DMEPA's recommendations from OSE Review #2010-377, dated September 10, 2010, OSE Review #2011-1033, dated May 5, 2011, and OSE Review #2011-2437, dated August 1, 2011 for Lupron Depot 3.75 mg for 1-month administration and Lupron Depot 11.25 mg for 3-month administration container labels and carton labeling because they were given the option to incorporate these edits at the time of next printing. Additionally, there are more comments regarding the proposed labels and labeling that are unique to this product.

The product strength is not displayed on the outer carton labeling under the established name. The route of administration statement is not presented on the principal display panel of the syringe label and carton labeling per 21 CFR 201.10 (b)(3). The presentation of the product strength and frequency of administration lacks prominence on all Lupron Depot container labels and carton labeling. The two different frequencies of administration on the outer carton labeling, lack visual differentiation.

The Dosage and Administration section of the insert labeling does not clarify if the patient can initiate therapy with the higher dose which allows for an extended time between administrations or if the patient should start with 3.75 mg once monthly initially and then convert to the longer acting formulation. The Dosage and Administration Sections of Highlights for 1-month administration insert labeling refers to the frequency of administration of Lupron Depot and Norethindrone Acetate as 'every 4 weeks' and 'for 4 weeks' respectively, which is inconsistent with the phrase used in the Dosage and Administration Section of the Full Prescribing Information (i.e. 'monthly' and 'for one month') as well as the Dosage and Administration Sections of the Highlights and Full Prescribing Information of Tradename for 3-month administration (i.e. 'every 3 months' and 'for 3 months'). The abbreviation 'IM' is used in the Dosage and Administration section of the Full Prescribing Information as well as the How Supplied/Storage and Handling section. The word 'monthly' (vs. every 3 months) is used to indicate the dosage for the 3-month administration formulation of Lupron Depot in the Dosage and Administration section of the Full Prescribing Information. The dosing recommendations in the Norethindrone Acetate Administration section is not consistent with that of the Dosage and Administration section of Tradename (i.e. taken orally once a day for 1 month or 3 months) and may be confusing to prescribers and patients. Furthermore, the dosing section of Norethindrone lists additional indications and doses that are not part of this co-packaged product.

4 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The Applicant is proposing a co-packaged product containing Lupron Depot 3.75 mg for 1-month administration (or Lupron Depot 11.25 mg for 3-month administration) and Norethindrone Acetate Tablets, 5 mg, 30 count (or 90 count) bottle. The proposed product design is appropriate for the proposed indication of the initial

management of the painful symptoms of endometriosis and management of recurrence of symptoms. However, the labels and labeling do not accurately reflect the one indication that this co-packaged product is intended for. The labeling also includes other indications for which Norethindrone Acetate is currently approved for as a stand alone treatment. We are concerned that combining the inserts may be confusing to healthcare providers and patients because the dosing information provided in this section differs from the recommended once daily dosing for 1 month (or 3 months) for the proposed indication. We recommend only the Norethindrone dosing regimen for the proposed Tradename indication to be included under Section 2.3 Norethindrone Acetate Administration.

Our AERS search identified six types of errors with only the Lupron Depot component. Since this product contains Lupron Depot, similar types of errors may occur with this combination product. Ten cases of wrong frequency of administration errors were reported with Lupron injections. Although none of the cases provided sufficient details to conclude that these errors occurred due to label and labeling confusion, improvements can be made to the presentation of the frequency of administration on the proposed outer carton labeling, as well as the clam shell kit label to make the frequency of administration more prominent and reduce the risk of wrong frequency of administration errors with the proposed product.

Additionally, nine wrong dose errors were retrieved from AERS. Six of the nine cases reported that the patients received the wrong dose, without providing any information to conclude if the errors occurred due to prescribing errors or selection errors in the pharmacy. To minimize pharmacy dispensing errors due to selection errors like these with the proposed product, it is important to display the active ingredients and the product strength (i.e. 3.75 mg and 5 mg or 11.25 mg and 5 mg) prominently on the proposed outer carton labeling.

Six cases of wrong route of administration errors were reported with 3 cases describing subcutaneous administration of Lupron Depot instead of the recommended intramuscular administration. Displaying the route of administration prominently on all container labels and carton labeling would help minimize the risk of medication errors due to the wrong route of administration.

Device malfunctions were another reported cause of errors. A total of 28 cases of device malfunction were identified from OSE Reviews #2010-377 (n=19), #2011-1033 (n=1), #2011-2437 (n=4), and 6 cases identified in this review. We advise Abbott Laboratories conduct a root cause analysis to resolve the ongoing issues associated with Lupron Depot syringes.

Three cases of wrong drug formulations were identified in AERS. All three cases reported pediatric patients who received adult formulations. Marketing the proposed co-packaged product under a different name (i.e. Tradename), providing prominent pictures of the intended user population, and providing the combination product strength statement on the carton labeling may help mitigate the risk of medication errors due to dispensing the wrong formulations.

5 CONCLUSIONS

DMEPA finds the proposed co-packaged product, Tradename, appropriate for the proposed indication of initial management of the painful symptoms of endometriosis and management of recurrence of symptoms. Marketing this product under a unique proprietary name is a better option than marketing this product with the root name, Lupron, and a modifier because the unique name carries the risk of concomitant administration between the proposed product and Lupron which can be minimized by prominently displaying the contents of the co-packaged product, while the option of using a modifier in the root name, Lupron, carries the risk of omission of the modifier which can lead to wrong drug errors.

Although the co-package design is appropriate for this product, label and labeling revisions are needed to ensure the safe use of the proposed product.

Errors related to device malfunction continue to occur that are not user errors. Therefore, we request the Applicant provide a root cause analysis of these malfunctions so that we can determine if product re-design is required.

6 RECOMMENDATIONS

DMEPA evaluated the container labels, carton, and insert labeling for each of the individual components of the co-packaged product. Our evaluation found the Norethindrone Acetate container labels acceptable in their current presentation. However, based upon postmarketing errors with the Lupron product line and analysis of the proposed labels and labeling for Lupron Depot and Tradename labeling, we recommend the following to be implemented prior to approval of this NDA:

A. *General Comments for all Labels and Labeling*

Remove the proprietary name, (b)(4), from all container labels and carton labeling as this name was found unacceptable.

B. *Container Labels*

1. Lupron Depot syringe (3.75 mg and 11.25 mg)

- a. Relocate the established name to appear directly under the name, Lupron Depot, followed by the product strength, and frequency of administration on the Lupron Depot syringe. The revised presentation should appear as follows (note the use of title case lettering):

Lupron Depot

(Leuprolide Acetate for Depot Suspension)

3.75 mg (or 11.25 mg)

For 1-month (or 3 month) administration

For intramuscular injection

- b. Remove the color block currently used for the NDC number and product description and use it to present the strength and the frequency of administration (see the presentation above). Additionally, use a lighter color

purple for the 3.75 mg strength to increase the visual contrast between the color block and the black font of the text.

- c. Include the route of administration, 'For intramuscular injection' on the principal display panel of the Lupron Depot syringe label (see the presentation above). This information can be placed under the color block containing the product strength and the frequency of administration, in bold letters.
2. Diluent for the 3.75 mg and 11.25 mg strengths of Lupron Depot
- a. Increase the prominence of the 'Sterile Diluent' on the Diluent syringe label so that 'Sterile Diluent' appears more prominent than 'Lupron Depot' by increasing the font size and bolding the statement. Since this syringe contains the Diluent and not the actual product, the name 'Sterile Diluent' should have more prominence to prevent inadvertent injection of the Diluent instead of Lupron Depot after mixing with the Diluent. For example:

Sterile Diluent

for
Lupron Depot

- b. Include the ingredients of the Sterile Diluent on the label. This information may appear before the manufacturer's information on the label. As currently presented, it is not clear what the Sterile Diluent consist of.
- C. *Carton Labeling (3.75 mg/5 mg and 11.25 mg/5 mg)*
1. Clam shell Kit labeling
- a. Present the established name in parenthesis, followed by the product strength, the frequency of administration, and the route of administration (see the presentation in A1).
 - b. Box the strength statement and the frequency of administration with the same color band that is used for each strength and frequency of administration at the top of the clam shell labeling to increase visual differentiation between the 3.75 mg and 11.25 mg strengths. Although, the color differentiation between the two strengths of Lupron Depot kits placed inside of the proposed outer carton may not be as critical for the proposed product, for the purpose of consistency, the changes in the presentation of information should be implemented in all the available Lupron products.
 - c. Remove the 'front chamber' contents and 'second chamber' contents information and place in the prescriber information. This will provide an area on the front of the clam shell 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. Although, pharmacies will most likely place the pharmacy label on the outer carton labeling and not the clam shell

labeling, this revision will provide consistency for the Lupron Depot products.

- d. Revise the interior of the clam shell labeling 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 of the carton and clam shell labeling, the practitioner who is administering the drug may see this information when the clam shell is opened.

1. Tradename Outer Carton Labeling

- a. Revise the established name to have a prominence commensurate with the prominence of the proprietary name, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
- b. Revise the established name presentation to include the strength of each component of Tradename following the dosage form statement. Additionally, ensure the strength of the Leuprolide Acetate component (i.e. 3.75mg and 11.25 mg) is prominent (i.e. using a larger font size). Incorporating the strength statement can provide another tool (in addition to the frequency of administration; ‘1-month’ and ‘3-month’) to help differentiate the two different Tradename products and may help mitigate the risk of medication errors due to product selection. The revised presentation may appear as follows:

‘Tradename

Leuprolide Acetate for Depot Suspension,
3.75 mg for intramuscular injection only
and Norethindrone Acetate Tablets, 5 mg for oral administration

Tradename

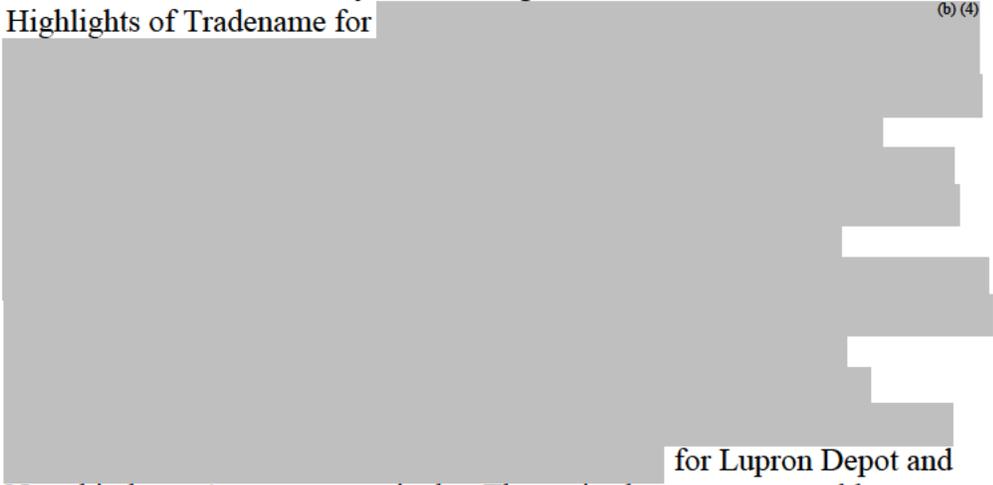
Leuprolide Acetate for Depot Suspension, 11.25 mg for intramuscular injection only and
Norethindrone Acetate Tablets, 5 mg for oral administration’

- c. Replace the ‘plus sign’ within the established name with the word ‘and’.
- d. Remove the large plus sign that appears on the left hand side of the proprietary and the established names, as well as the lower right hand side of all the side panels where it appears. As currently presented, the large plus sign can distract from the proprietary name and the frequency of administration.
- e. Remove the two-toned color band that contains the proprietary and the established names, as well as the frequency of administration. The color band should be used only for the frequency of administration, consistent with DMEPA’s recommendations for the Lupron Depot products.

- f. Increase the prominence of the frequency of administration statement on the top right hand side of the display panel by increasing the font size, bolding, and using dark ink against a light purple color block, to increase contrast. It is important to provide visual differentiation between the 1-month and the 3-month frequency of administrations of Tradename to minimize medication errors due to selection errors in the pharmacy.
- g. Include the Usual Dose for Norethindrone Acetate on the principal display panel. As currently presented, this information does not appear under the second bullet point. The statement may appear as:

‘Usual Dose: Take one tablet orally once a day for 1 month (or 3 months). See package insert for full prescribing information.’
- h. Relocate the ‘Rx only’ statement to the lower right hand side of the principal display panel. As currently presented, the statement appears too close to the Lupron Depot Kit content information, and clutters the area.
- i. Reduce the prominence of the company name and logo on the principal display panel. As currently presented, this information competes in prominence with the proprietary name and the frequency of administration statement.

D. Insert Labeling (1-month and 3-month)

1. 1-month administration only: The Dosage and Administration Sections of Highlights of Tradename for (b) (4)

 for Lupron Depot and Norethindrone Acetate respectively. The revised statements would appear as follow:

 (b) (4)

2. Delete the parenthesis around the Lupron Depot’s strength and frequency of administration in some areas of the package insert. The use of parenthesis is unnecessary and is inconsistent. The parenthesis presentation appears in the

Dosage and Administration Sections of the highlights and the Full Prescribing Information, Reconstitution and Administration, Dosage Forms and Strengths, and Description sections.

3. Replace the abbreviation 'IM' with 'intramuscular' in the Dosage and Administration, as well as the How Supplied/Storage and handling sections.
4.  (b) (4)
5.  (b) (4)
5.  (b) (4)
6. Norethindrone Acetate Administration: The dosing information provided for Norethindrone Acetate in this section differs from the recommended once daily dosing for 1 month (or 3 months) for the proposed indication, and may be confusing for healthcare providers or patients. We defer to the Division regarding the different dosing recommendations provided in this section.
7. Description, Lupron Depot 11.25 for 3-month administration: Remove the trailing zero from 'D-mannitol (75.0 mg)'. The revised format should appear as 'D-mannitol (75 mg)'. The use of trailing zeros is error-prone and can result in ten-fold dosing error if the Decimal is not seen. As part of a national campaign to prevent the use of error-prone dose designations such as trailing zeros in prescribing, FDA agreed not to approve error-prone dose designations in labeling because they are carried on to the prescribing practice.

If you have further questions or need clarifications, please contact Maria Wasilik, project manager, at 301-796-0567.

REFERENCES

OSE Review 2011-2437, Lupron Depot-Ped Label and Labeling Review, McMillan, T. August 11, 2011.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

Appendix D: Listings of all ISR numbers

Lupron Depot

ISRNUM	CK	CSENUM			
8081923		1	8362778	8081966	8 8362817
8081945		0	8362798	8081987	5 8362838
8081974		7	8362825	8007690	5 8311618
8007781		9	8311687	8201076	6 8453239
8007783		2	8311688	7836651	1 8196733
8200994		2	8453167	8007726	1 8311642
7837293		4	8197029	7837116	3 8196946
7836833		9	8196817	7837535	5 8197143
7836872		8	8196834	8007673	5 8311604
7836930		8	8196862	8007727	3 8311643
8007716		9	8311637	8007815	1 8311717
8007731		5	8311647	8007817	5 8311718
8007809		6	8311711	8200943	7 8453122
8200875		4	8453058	8201051	1 8453214
7837247		8	8197006	7837275	2 8197020
7837909		2	8197284	7836817	0 8196809
7836492		5	8196656	8007710	8 8311631
7836653		5	8196734	8007737	6 8311651
8107024		1	8384866	8007740	6 8311654
8081917		6	8362773	8007821	7 8311721
8081929		2	8362782	8200884	5 8453064
8007756	X		8311669	8201068	7 8453231
8200945		0	8453124	8176680	4 8435049
8201104		8	7847968	7647460	0 8046312
7837452		0	8197105	7836488	3 8196654
7836282		3	8196552	8103028	3 8382179
8010901		3	8265488	8200906	1 8453085

Norethindrone Acetate

ISRNUM	CK	CSENUM	
5441751	X		6406410
4713479		2	5841658
7990051		2	8309988
6871339		5	7601169
6298046		4	7080274

Appendix E: Summary of the 35 cases of medication errors related to Leuprolide Acetate

Wrong Frequency of Administration (n=10)

We identified 10 wrong frequency of administration error cases with Lupron Depot.

Four of the 10 cases reported that the injection was given late (one or two weeks late or not indicated in the case) and patients experienced menstrual bleeding, bloating, or pain. Two of the ten cases reported an early injection by one week. One case noted that the next dose of Lupron was given one week early by the physician. None of these cases provided details regarding the reason for the late or early administration of Lupron.

The remaining four cases of wrong frequency of administration consisted of the 3-month formulation of Lupron injected after only one month (n=2) with no details provided to determine the cause, patient accidentally injecting a 3 month formulation after one month for an off-label indication (i.e. suppression of estrogen due to intrinsic allergy to patient's own progesterone) (n=1), and patient receiving a 3-month and a 4-month formulation of Lupron, 4 days apart due to failure to communicate with the new physician (n=1).

Wrong Dose (n=9)

Nine cases of wrong dose errors for Lupron Depot were identified.

One of the 9 cases described a physician injecting 4 mg of Leuprolide Acetate instead of 3.75 mg of Lupron Depot. This case did not provide enough information to determine the cause to be a prescribing error, or a pharmacy dispensing error. The outcome of this case was not reported.

Another case reported a non-serious overdose with no additional details provided.

One of the nine cases reported the nurse administered the 3.75 mg dose of Lupron to the patient, not realizing that the patient had been switched to, and administered the 11.25 mg for 3-month administration, one month prior. The patient did not experience any adverse reactions.

The remaining six cases reported the patient received the wrong dose (ex. 7.5 mg instead of 22.5 mg (n=1), 22.5 mg instead of 11.25 (n=2), 11.25 mg instead of 22.5 mg (n=2), and 3.75 mg instead of 7.5 mg (n=1)). No adverse events were reported. None of the six cases provided details regarding the reason for the wrong doses administered.

Wrong Route of Administration (n=6)

Six cases of wrong route of administration errors for Lupron Depot were identified.

Three of the 6 cases reported subcutaneous route of administration instead of intramuscular. Patient outcome was not reported in two of these cases, and the third case reported the patient experienced right hip abscess which resolved. All 3 cases lacked sufficient details to determine the cause for the wrong route of administration.

One of the six cases reported the physician injected a subcutaneous formulation (12 mg vial containing Leuprolide Acetate), intramuscularly. No outcome was reported in this case.

Another case reported that an intramuscular formulation was administered by other route (route of administration not specified in the case). Patient experienced red, hot, and swollen abdomen.

The last case was a foreign case, in which the nurse administered Lupron Depot intravenously instead of intramuscularly. Patient was hospitalized for one day as precaution. No adverse events were reported.

Device Malfunction (n=6)

We identified 6 cases of device malfunction with Lupron Depot.

In one of the 6 cases a nurse stated that the syringe bell cracked during the injection and the medication leaked out on to the injection site, and the patient did not receive the full dose. The nurse did not report any adverse events. No further information was available in the case.

A second case reported a nurse was accidentally pricked by needle when attempting to activate the needle guard on Lupron Depot syringe. No other information was presented in this case.

The third case reported that the needle detached from the syringe at the luer lock and the needle pierced the nurse when attempting to discard the syringe in to the sharps container.

The fourth case reported the nurse experienced accidental needle stick while injecting the patient, and experienced headaches due to exposure to Lupron Depot.

In another case, the nurse stated the safety needle did not close properly, the needle bent, and she stuck herself while administering a dose of Lupron Depot to a patient.

The last case reported a needle stick when disengaging the Lupron Depot safety device. The nurse stated that the picture showing to disengage the safety device was confusing because it showed an arrow pointing laterally towards the needle, and wasn't really clear on how to disengage the safety device.

Wrong Drug Formulation (n=3)

We identified 3 cases of wrong drug formulation errors. All 3 cases reported pediatric patients who received adult doses. One of the 3 cases reported the

patient received the adult 7.5 mg strength of Lupron Depot instead of the pediatric 7.5 mg strength, for 3 months. A second case reported that the patient was given the adult 11.25 mg strength instead of the pediatric 11.25 mg for 3-month administration formulation. The third case reported a 9 year old patient who received four adult dose injections with Lupron Depot 11.25 mg. No patient outcome was reported in any of the 3 cases.

Wrong Drug (n=1)

One case stated that a patient received Lupron Depot 3.75 mg instead of Depo Provera. No other details were provided in this case to determine the causality. No patient outcome was reported.

Appendix F: Details of Medication Error Cases Retrieved from AERS involving Tradename

ISR #	Date Received	Narratives	Comments
8081923	1/30/12	Spontaneous report from the USA of non-serious WRONG DOSE GIVEN with LUPRON DEPOT 7.5 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced WRONG DOSE GIVEN. The patient was supposed to get 22.5 milligrams of LUPRON DEPOT, but the nurse gave the patient 7.5 milligrams instead. The pharmacist declined contact.	Wrong dose
8081945	1/30/12	Spontaneous report from the USA of non-serious RECEIVED SUBCUTANEOUS INJECTION INSTEAD OF INTRAMUSCULAR INJECTION with LUPRON DEPOT INJECTION (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced RECEIVED SUBCUTANEOUS INJECTION INSTEAD OF INTRAMUSCULAR INJECTION. Patient's family reported that she has a family member who received his injection of LUPRON DEPOT via subcutaneous injection instead of intramuscular injection on an unknown date.	Wrong route
8081974	1/30/12	Spontaneous report from the USA of non-serious STERILE ABSCESS, TOOK MEDICATION WRONG ROUTE, PATIENT GOT MEDICATION SUBCUTANEOUSLY INSTEAD OF IM and SKIN IRRITATION LEFT HIP with LUPRON DEPOT INJECTION (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced PATIENT GOT MEDICATION SUBCUTANEOUSLY INSTEAD OF IM. In February 2011, the patient experienced STERILE ABSCESS and TOOK MEDICATION WRONG ROUTE. The physician reported that he thinks the patient got the LUPRON SQ instead of LUPRON IM on his last injection. In February 2011, the TOOK MEDICATION WRONG ROUTE resolved. In August 2011, the patient experienced SKIN IRRITATION LEFT HIP. It was reported that the patient was referred to a plastic surgeon for an opinion on a non healing right hip abscess. The physician reported that the right hip abscess developed from the first LUPRON DEPOT injection site. It is his opinion that the injection was administered SQ instead of IM. It was reported that the patient received his second injection and had developed a skin irritation at the new injection site on the left hip. CHANGE HISTORY On 09 Aug 2011, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information and narrative description.	Wrong route
7837293	10/24/11	Solicited report from the USA of non-serious LATE DOSE, MENSTRUAL BLEEDING and MENSTRUAL CRAMPS with LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). On 29 Aug 2011, the patient experienced LATE DOSE and MENSTRUAL BLEEDING. The patient received her LUPRON dose late on 29 Aug 2011 instead of 15 Aug 2011. In September 2011, the patient experienced MENSTRUAL CRAMPS. The patient's	Wrong frequency of administration

ISR #	Date Received	Narratives	Comments
		physician was aware of the bleeding and cramps. On an unknown date, LATE DOSE resolved.	
7836833	10/24/11	Spontaneous report from the USA of non-serious WRONG MEDICATION GIVEN, WRONG DOSE and WRONG ROUTE USED with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). In December 2010, the patient experienced WRONG MEDICATION GIVEN, WRONG DOSE and WRONG ROUTE USED. The physician injected 4mg of LEUPROLIDE ACETATE generic instead of 3.75 milligrams of LUPRON DEPOT in Dec 2010. The LEUPROLIDE ACETATE was a subcutaneous formulation, in a 12 mg vial, and the physician injected it intramuscularly. It was unclear if the physician prescribed the medication incorrectly or the pharmacy filled it incorrectly. No other information was available. LEUPROLIDE ACETATE (LEUPRORELIN ACETATE) was also considered suspect.	Wrong dose
7836872	10/24/11	Spontaneous report from the USA of non-serious DOSE LATE BY 2 WEEKS, BLOATING and MENSTRUAL BLEEDING with LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). In July 2011, the patient experienced DOSE LATE BY 2 WEEKS, BLOATING and MENSTRUAL BLEEDING. On an unknown date, DOSE LATE BY 2 WEEKS resolved.	Wrong frequency of administration
8007716	12/27/11	Spontaneous report from the USA of non-serious OVERDOSE with LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced OVERDOSE. No additional information was available.	Wrong dose
8007731	12/27/11	Spontaneous report from the USA of non-serious DEVICE CRACKED DURING INJECTION ALLOWING MEDICATION TO LEAK OUT AND SCATTER ALL OVER THE PATIENT'S INJECTION SITE and PATIENT DID NOT RECEIVE ENOUGH OF THE MEDICATION with LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). On 24 Nov 2010, the patient experienced DEVICE CRACKED DURING INJECTION ALLOWING MEDICATION TO LEAK OUT AND SCATTER ALL OVER THE PATIENT'S INJECTION SITE and PATIENT DID NOT RECEIVE ENOUGH OF THE MEDICATION. The nurse stated that the syringe bell had cracked, and therefore the PATIENT DID NOT RECEIVE ENOUGH OF THE MEDICATION, so another injection was given that same day. The nurse stated that the injection site was normal, and she denied that the patient had experienced any events after injection. The registered nurse stated that the event was related to the syringe malfunctioning. No further information was available from the registered nurse. It was clarified that the lot number of the suspect drug was 936592E22. CHANGE HISTORY On 12 Jan 2011, received updates to suspect drug information and narrative description	Device malfunction
8007809	12/27/11	Spontaneous report from the USA of non-serious MEDICATION GIVEN TOO SOON with LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). In 2011, the patient experienced MEDICATION GIVEN TOO SOON. In 2011, about one month ago, the patient had been given LUPRON DEPOT 22.5 mg a three month dose; about one month after an injection, the patient had been LUPRON DEPOT again, this time he had received the medication too soon.	Wrong frequency of administration
8200875	3/12/12	Spontaneous report from the USA of non-serious TOOK INCORRECT DOSE with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced TOOK INCORRECT DOSE. The patient was prescribed the 11.25mg dose, however received the 22.5mg dose in error. On an unknown date, TOOK INCORRECT DOSE resolved.	Wrong dose

ISR #	Date Received	Narratives	Comments
7836653	10/24/11	Spontaneous report from the USA of non-serious PRICK FROM NEEDLE with LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). On 12 Jul 2011, the patient experienced PRICK FROM NEEDLE. The medical assistant completed the patient's LUPRON DEPOT injection and was accidentally pricked by needle when attempting to activate the needle guard on LUPRON DEPOT syringe. On an unknown date, PRICK FROM NEEDLE resolved.	Device malfunction
8081917	1/30/12	Spontaneous report from the USA of non-serious DIFFICULTY WALKING, LEG PAIN, SCIATIC NERVE HIT UPON INJECTION, MUSCLE CRAMPING IN LEG, HOT FLASHES, HARDNESS AT THE INJECTION SITE, WARMTH AT THE INJECTION SITE and INJECTION HAD BEEN ADMINISTERED INCORRECTLY with LUPRON DEPOT 7.5 MG (LEUPROLIDE ACETATE DEPOT). On unknown dates, the patient experienced HOT FLASHES and INJECTION HAD BEEN ADMINISTERED INCORRECTLY. In December 2010, the patient experienced DIFFICULTY WALKING, LEG PAIN, SCIATIC NERVE HIT UPON INJECTION, MUSCLE CRAMPING IN LEG, HARDNESS AT THE INJECTION SITE and WARMTH AT THE INJECTION SITE. In Dec 2010, the patient received his initial dose of LUPRON DEPOT. The patient suffered from intense pain and difficulty walking for three months following the injection. The pain traveled up and down the patients leg. The patient contacted his urologist who was not concerned. The patient then followed up with his primary care physician and a neurologist. Initially the patient was worried about a possible blood clot causing the intense pain. A Doppler was performed, results were normal. A blood clot was ruled out. The neurologist informed the patient that the injection had been administered incorrectly, inadvertently hitting the sciatic nerve and causing the pain. The patient was concerned about getting his upcoming second injection. On unknown dates, HARDNESS AT THE INJECTION SITE and WARMTH AT THE INJECTION SITE resolved. The patient was treated with ADVIL.	Wrong dose
8007756	12/27/11	Spontaneous report from the USA of non-serious RECEIVED THE WRONG DOSE OF MEDICATION with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). On 05 Apr 2011, the patient experienced RECEIVED THE WRONG DOSE OF MEDICATION. The pharmacist stated the patient received the wrong dose of LUPRON DEPOT, the patient received 22.5 mg instead of 11.25. No events have been reported. The pharmacist stated the physician does not contact. On 05 Apr 2011, the RECEIVED THE WRONG DOSE OF MEDICATION resolved.	Wrong dose
8200945	3/12/12	Spontaneous report from the USA of non-serious THREE MONTH LUPRON ADMINISTERED AFTER ONE MONTH with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On 30 Aug 2011, the patient experienced THREE MONTH LUPRON ADMINISTERED AFTER ONE MONTH. The physician reported that the patient was administered another LUPRON DEPOT injection 11.25 mg today after only one month. The physician did not report any other reactions	Wrong frequency of administration
7837452	10/24/11	Spontaneous report from the USA of non-serious INCORRECT MEDICATION GIVEN with LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). On 15 Sep 2011, the patient experienced INCORRECT MEDICATION GIVEN. The patient was supposed to receive DEPO PROVERA. On an unknown date, INCORRECT MEDICATION GIVEN resolved.	Wrong drug
7836282	10/24/11	Protocol Number: FACILITATED COLLECT Study Title: FACILITATED COLLECTION Solicited report from the USA of non-serious PAIN and INJECTION WAS LATE with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). On unknown dates, the patient experienced PAIN and INJECTION WAS LATE. The patient stated she had pain, because injection was late. No other information was available.	Wrong frequency of administration

ISR #	Date Received	Narratives	Comments
8081987	1/30/12	Solicited report from the USA of non-serious RECEIVED WRONG DOSE with LUPRON DEPOT 7.5 MG (LEUPROLIDE ACETATE DEPOT). In October 2011, the patient experienced RECEIVED WRONG DOSE. The patient's mother reported that the patient received a total of three doses of LUPRON DEPOT Adult 7.5 milligrams monthly since Oct 2011. The patient was supposed to receive LUPRON DEPOT PEDIATRIC 7.5 milligrams. The patient's mother notified the physician's office and was awaiting a follow-up from the physician.	Wrong drug formulation
8007690	12/27/11	Spontaneous report from the USA of non-serious INTRAMUSCULAR FORMULATION ADMINISTERED BY OTHER ROUTE, ABDOMEN TURNED RED, ABDOMEN TURNED HOT, SWOLLEN ABDOMEN and ABDOMEN TURNED HARD with LUPRON DEPOT 30 MG (LEUPROLIDE ACETATE DEPOT). On 17 Jan 2011, the patient experienced INTRAMUSCULAR FORMULATION ADMINISTERED BY OTHER ROUTE, ABDOMEN TURNED RED, ABDOMEN TURNED HOT, SWOLLEN ABDOMEN and ABDOMEN TURNED HARD. The healthcare professional reported that on 17 Jan 2011, LUPRON DEPOT injection was administered on the left side of the patients abdomen. The healthcare professional added that the abdomen turned red, hot, swollen and hard. The healthcare professional did not report any treatment.	Wrong route of administration
8201076	3/12/12	Spontaneous report from the USA of non-serious PATIENT WAS ACCIDENTLY GIVEN ADULT DOSE INSTEAD OF PEDIATRIC DOSE with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced PATIENT WAS ACCIDENTLY GIVEN ADULT DOSE INSTEAD OF PEDIATRIC DOSE. The LUPRON DEPOT PEDIATRIC DOSE given once every three months was intended to be given. On an unknown date, PATIENT WAS ACCIDENTLY GIVEN ADULT DOSE INSTEAD OF PEDIATRIC DOSE resolved. The pharmacist declined to provide any additional information.	Wrong drug formulation
7836651	10/24/11	Spontaneous report from the USA of non-serious SECONDARY EXPOSURE, FINGERSTICK and NEEDLE DETACHED FROM THE SYRINGE AT THE LUER LOCK HUB with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced NEEDLE DETACHED FROM THE SYRINGE AT THE LUER LOCK HUB. The nurse successfully gave the patient the injection of LUPRON, however, the nurse was on her way to discard the SYRINGE into the sharps container when the needle detached from the SYRINGE at the luer lock and the needle pierced the nurse. On 29 Jun 2011, the patient experienced SECONDARY EXPOSURE and FINGERSTICK. No patient information available for follow-up. On 29 Jun 2011, the SECONDARY EXPOSURE and FINGERSTICK resolved. CHANGE HISTORY On 05 Aug 2011, received updates to event information, reporter opinion of causality and narrative description.	Device malfunction
8007726	12/27/11	Solicited report from the USA of non-serious RECEIVED A SECOND LUPRON DEPOT INJECTION with LUPRON DEPOT 30 MG (LEUPROLIDE ACETATE DEPOT) and LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced RECEIVED A SECOND LUPRON DEPOT INJECTION. The patient received an injection of LUPRON DEPOT 3-month injection on 31 Oct 2011 at another physician's office in OR. The patient did not notify the reporting physician's office. When the patient went to the reporting physician's office four days later, on 04 Nov 2011, the patient had received an injection of LUPRON DEPOT 4-month injection. The reporting physician was shocked to subsequently learn that the patient had been injected with a 3 month LUPRON DEPOT by another physician. The patient never mentioned the first injection to the reporting physician who is attributing the lack of information to the patient's dementia. The patient did not experience any untoward reactions as the result of receiving two injections. The error was only discovered when the physician's office requested the patient's medical records from another physician's office. CHANGE HISTORY On 16 Dec 2011, received updates to medical history and narrative description.	Wrong frequency of administration

ISR #	Date Received	Narratives	Comments
7837116	10/24/11	Spontaneous report from the USA of non-serious INCREASED ABDOMINAL PAIN, GI DISTRESS and GIVEN INJECTION AFTER THREE WEEKS INSTEAD OF THE REGULARLY SCHEDULED FOUR WEEKS with LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). On unknown dates, the patient experienced GI DISTRESS and GIVEN INJECTION AFTER THREE WEEKS INSTEAD OF THE REGULARLY SCHEDULED FOUR WEEKS. In August 2011, the patient experienced INCREASED ABDOMINAL PAIN. The abdominal pain and GI distress began after the third injection. The patient did report it to the physician. The patient said there were no diagnostic tests or blood tests ordered. The physician gave the next injection of LUPRON DEPOT after three weeks (18 days) instead of the regularly scheduled dose at four weeks.	Wrong frequency of administration
7837535	10/24/11	Solicited report from the USA of non-serious EXTRA DOSE OF MEDICATION with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT) and LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). In January 2011, the patient experienced EXTRA DOSE OF MEDICATION. In Dec 2010 the patient was switched to the 11.25 every 3 month dose. In Jan 2011 the nurse gave the patient a dose of 3.75 mg by mistake. On an unknown date, EXTRA DOSE OF MEDICATION resolved. The RN reported that the physician was aware and did not believe there would be any problems.	Wrong dose
8007673	12/27/11	Spontaneous report from the USA of non-serious INJECTED SUBCUTANEOUSLY INSTEAD OF INTRAMUSCULARLY with LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced INJECTED SUBCUTANEOUSLY INSTEAD OF INTRAMUSCULARLY.	Wrong route of administration
8007727	12/27/11	Spontaneous report from the USA of non-serious PROSTATE SPECIFIC ANTIGEN LEVEL INCREASED and INCORRECT DOSE ADMINISTERED with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT) and LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). In January 2011, the patient experienced INCORRECT DOSE ADMINISTERED. The healthcare professional reported that in Jan 2011, the patient was administered LUPRON DEPOT 11.25 milligrams instead of LUPRON DEPOT 22.5 milligrams in error. In January 2011, the INCORRECT DOSE ADMINISTERED resolved. In February 2011, the patient experienced PROSTATE SPECIFIC ANTIGEN LEVEL INCREASED. The healthcare professional did not report any treatment.	Wrong dose
8201051	3/12/12	Spontaneous report from the USA of non-serious TOOK AN EXTRA DOSE OF MEDICATION and SUPPRESSION OF ESTROGEN DUE AN INTRINSICT ALLERGY TO HER OWN PRORGEREONE with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced SUPPRESSION OF ESTROGEN DUE AN INTRINSICT ALLERGY TO HER OWN PRORGEREONE. In Dec 2011, the patient took her usual dose of LUPRON DEPOT three month formulation. On 12 Jan 2012, the patient experienced TOOK AN EXTRA DOSE OF MEDICATION. Last night the patient accidentally took another dose of LUPRON DEPOT three month injection. The patient had no adverse events from the extra dose noted. The patient was taking LUPRON DEPOT for the unapproved indication of an intrinsic allergy to her own progesterones requiring suppression of estrogen.	Wrong frequency of administration
7837275	10/24/11	Spontaneous report from the USA of non-serious WRONG DOSE with LUPRON DEPOT 3.75 MG (LEUPROLIDE ACETATE DEPOT). On 02 Sep 2011, the patient experienced WRONG DOSE. The patient was given 3.75 mg of LUPRON DEPOT and should have been given 7.5 mg of LUPRON DEPOT for prostate cancer. The pharmacist is asking should the recommendation be to give another one time dose of 3.75 mg or when should dose of 7.5 mg began (i.e. 2 weeks from the injection of 3.75mg or one month).The patient was given the wrong dose of LUPRON DEPOT 3.75 milligrams for the treatment of prostate cancer on 2 September 2011 then a week later was given another 3.75 milligrams of LUPRON DEPOT as ordered by prescribing physician. On an unknown date, WRONG DOSE	Wrong dose

ISR #	Date Received	Narratives	Comments
		resolved. CHANGE HISTORY On 09 Sep 2011, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information and narrative description.	
7836817	10/24/11	Spontaneous report from the USA of non-serious ACCIDENTAL NEEDLESTICK WHILE ADMINISTERING INJECTION TO A PATIENT and HEADACHES with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). In November 2010, the patient experienced ACCIDENTAL NEEDLESTICK WHILE ADMINISTERING INJECTION TO A PATIENT and HEADACHES. The nurse who received the needle stick stated she began to experience headaches the same day as accidental needle stick occurred. No further information available.	Device malfunction
8007737	12/27/11	Spontaneous report from the USA of non-serious DOSE GIVEN EARLY with LUPRON DEPOT 22.5 MG (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced DOSE GIVEN EARLY. The patient was administered initial dose of 22.5 milligrams of LUPRON DEPOT in July 2011 and then administered another 22.5 milligrams of LUPRON DEPOT on 10 August 2011. The reporter declined to report or provide further information on the adverse event and declined physician contact	Wrong frequency of administration
8007821	12.27/11	Spontaneous report from the USA of non-serious ACCIDENTAL NEEDLESTICK with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). On 21 Dec 2010, the patient experienced ACCIDENTAL NEEDLESTICK. Per manager of clinical research, the nurse experienced an accidental needle stick with LUPRON DEPOT 22.5 mg syringe on 21 Dec 2010 while administering dose to patient. Per manager, nurse stated the safety needle did not close properly, the needle bent and she stuck herself accidentally.	Device malfunction
8200884	3/12/12	Spontaneous report from the USA of non-serious MEDICATION ERROR and RECEIVED FOUR ADULT DOSE INJECTIONS with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On unknown dates, the patient experienced MEDICATION ERROR and RECEIVED FOUR ADULT DOSE INJECTIONS. The pharmacist reported that a nine year old female patient received four adult doses of LUPRON DEPOT 11.25 mg-three month injections. Nurse stated that pharmacy contacted the medical office to inform them that they had just realized that patient received four adult dose injections of LUPRON DEPOT. Nurse stated that she instructed the pharmacist to call the patient's family to make them aware of this. Nurse stated that she has not heard from the family and she does not know if the pharmacy has already contacted the family. Nurse stated that patient receives her injections at her primary care doctor's office and not at the office of the prescriber. Nurse stated that the doctor plans to hold LUPRON DEPOT therapy for three months and will recheck patient hormone levels then. Nurse stated that doctor does not know how the medication error may have occurred, stated that all of their prescriptions are e-prescribed. CHANGE HISTORY On 12 May 2011, received updates to reporter opinion of causality and narrative description.	Wrong formulation
8201068	3/12/12	Solicited report from the USA of non-serious BREAKTHROUGH BLEEDING and WEEK LATE FOR NEXT INJECTION with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). In February 2011, the patient experienced WEEK LATE FOR NEXT INJECTION. In January 2012, the patient experienced BREAKTHROUGH BLEEDING. In January 2012, the BREAKTHROUGH BLEEDING resolved. The patient declined to provide any further information, and declined further contact	Wrong frequency of administration
7647460	8/1/11	Spontaneous report from (b) (6) of ADMINISTERED LUCRIN INJECTION INTRAVENOUSLY INSTEAD OF INTRAMUSCULAR with LUCRIN DEPOT (LEUPROLIDE ACETATE DEPOT). On 14 Jul 2011, the patient experienced ADMINISTERED LUCRIN INJECTION INTRAVENOUSLY INSTEAD OF INTRAMUSCULAR. The patient was administered her second LUCRIN injection in a village clinic on (b) (6). The nurse had administered the	Wrong route of administration

ISR #	Date Received	Narratives	Comments
7836488	10/24/11	<p>patient's LUCRIN DEPOT therapy dose intravenously instead of intramuscular administration. That is why the patient was hospitalized; as a precaution. On an unknown date, ADMINISTERED LUCRIN INJECTION INTRAVENOUSLY INSTEAD OF INTRAMUSCULAR resolved. No evaluations or imaging studies were performed, the patient did not have any risk factors and did not experience any adverse reactions after receiving LUCRIN intravenously. The patient was taken under control for a day and discharged at the end of the day. CHANGE HISTORY On 28 Jul 2011, received updates to narrative description.</p> <p>Spontaneous report from the USA of non-serious STUCK WITH NEEDLE WHEN DISENGAGING THE SAFETY DEVICE with LUPRON DEPOT (LEUPROLIDE ACETATE DEPOT). On an unknown date, the patient experienced STUCK WITH NEEDLE WHEN DISENGAGING THE SAFETY DEVICE. The nurse was attending a safety committee yesterday when he heard about the event about another nurse who got stuck by the needle when disengaging the safety device. The nurse administered the LUPRON DEPOT injection to a patient, withdrew the injection, went to advance the safety device, and their finger slid over the needle. The nurse got stuck by the needle. The nurse calling stated that the picture showing to disengage the safety device was confusing because it showed an arrow pointing laterally towards the needle, and wasn't really clear on how to disengage the safety device. On an unknown date, STUCK WITH NEEDLE WHEN DISENGAGING THE SAFETY DEVICE resolved.</p> <p>Leuprolide Acetate Injection 1mg/0.2ml, 2.8ml - 14 Day Patient Administration Kit does not give clear dosing directions to patient. It tells you the dose is 1mg, but gives you an insulin syringe to draw up the dose. No dosing conversion on the outside of the box. Patient would have to specifically look at the package insert to be able to find a conversion. The product needs a more prominent conversion on the box so the patient can clearly see it. NDC of product is 41616-0936-40. wilsonj: [*****] 2012-02-01-08.13.42 [*****]</p>	Device malfunction
8103028	2/1/12	<p>USFDAMWVOLUNTARY_200560_13355_20120131.xml Route To: AERS : Electronic Route To: DQRS : : Paper Possible medication error</p> <p>Spontaneous report from the USA of non-serious RECEIVED INCORRECT DOSE with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On 18 May 2011, the patient experienced RECEIVED INCORRECT DOSE. The patient received the LUPRON 11.25mg dose instead of the LUPRON 22.5mg dose in error. On an unknown date, RECEIVED INCORRECT DOSE resolved.</p>	Concern
8200906	3/12/12	<p>USFDAMWVOLUNTARY_200560_13355_20120131.xml Route To: AERS : Electronic Route To: DQRS : : Paper Possible medication error</p> <p>Spontaneous report from the USA of non-serious RECEIVED INCORRECT DOSE with LUPRON DEPOT 11.25 MG (LEUPROLIDE ACETATE DEPOT). On 18 May 2011, the patient experienced RECEIVED INCORRECT DOSE. The patient received the LUPRON 11.25mg dose instead of the LUPRON 22.5mg dose in error. On an unknown date, RECEIVED INCORRECT DOSE resolved.</p>	Wrong dose

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/s/

MANIZHEH SIAHPOUSHAN
07/19/2012

ZACHARY A OLESZCZUK
07/20/2012

KELLIE A TAYLOR
07/20/2012

CAROL A HOLQUIST
07/23/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 203696

Name of Drug: leuprolide acetate for depot suspension and norethindrone acetate

Applicant: Abbott Endocrine, Inc.

Labeling Reviewed

Submission Date: February 15, 2012

Receipt Date: February 15, 2012

Background and Summary Description

NDA 203696 proposes approval of two co-packaged kits each combining Lupron Depot suspension for injection and norethindrone acetate tablets for the proposed indication as treatment of endometriosis (b) (4)

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by May 18, 2012. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

KIMBERLY A SHILEY
04/26/2012

MARGARET M KOBER
04/26/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 203696	NDA Supplement #:S- BLA Supplement #
Efficacy Supplement Type SE-	
Proprietary Name: TBD Established/Proper Name: leuprolide acetate for depot suspension and norethindrone acetate Dosage Form: suspension for injections; tablets Strengths: 1-month 3.75 inj/5mg tab and 3-month 11.25mg inj/5mg tab	
Applicant: Abbott Endocrine, Inc. Agent for Applicant (if applicable): n/a	
Date of Application: February 15, 2012 Date of Receipt: February 15, 2012 Date clock started after UN: n/a	
PDUFA Goal Date: December 15, 2012 (Saturday)	Action Goal Date (if different): December 14, 2012 (Friday)
Filing Date: April 15, 2012	Date of Filing Meeting: April 10, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only)	
Proposed indication(s)/Proposed change(s): treatment of endometriosis (b) (4)	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, 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.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>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 Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears																			
<p>505(b)(2) N/A (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		X		
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
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 per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		X		No new studies
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) 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...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>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)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>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.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

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? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted. MISSING BUT MENTIONED: PPI AND IFU	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input checked="" type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? NO Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11-10-2011 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 10, 2012

NDA #: 203696

PROPRIETARY NAME: to be determined

ESTABLISHED/PROPER NAME: Leuprolide acetate for depot suspension and norethindrone acetate tablets co-packaged kit

DOSAGE FORM/STRENGTH: 3.75 mg inj/5mg tab kit and 11.25mg inj/5mg tab kit

APPLICANT: Abbott Endocrine, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of endometriosis

BACKGROUND: NDA 203696 proposes two co-packaged kits combining Lupron Depot suspension and norethindrone acetate tablets. Abbott intends to provide the proposed co-packaged kits with an outer carton container that will contain the Lupron Depot syringe kit and NETA bottle components within one carton, which is secured with an adhesive seal. Both Lupron Depot 3.75 mg and Lupron Depot 11.25 mg are FDA-approved for the management of endometriosis, including pain relief and reduction of endometriotic lesions. NETA alone is approved for the treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Shiley	Y
	CPMS/TL:	Margie Kober	Y
Cross-Discipline Team Leader (CDTL)	Lisa Soule		Y
Clinical	Reviewer:	Ron Orleans	Y
	TL:	Lisa Soule	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC</i>	Reviewer:		

<i>products)</i>	TL:		
	Reviewer:		
Clinical Microbiology (<i>for antimicrobial products)</i>)	TL:		
	Reviewer:		

Clinical Pharmacology	Reviewer:	Li Li	Y, phone
	TL:	MJ Kim	Y, phone
Biostatistics	Reviewer:	Xin Fang	Y
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Krishan Raheja	N
	TL:	Alex Jordan	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Zhengfang Ge	Y, phone
	TL:	Donna Christner/	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Roy Blay	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Manizhen Siahpoushan	Y
	TL:	Zachary Oleszczuk	Y, phone
OSE/DRISK (REMS)	Reviewer:		

	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers OC/OMPQ/DGMPA/NDMAB	OC Facility Reviewer: Vipul Dholakia		Y
Other attendees OND/ODE III/DRUP	Julie Beitz, Victoria Kusiak, Audrey Gassman		Y
OSE/PMS	Maria Wasilik		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: received February 15, 2012</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No new studies</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
<p>Comments: PLR labeling discussion scheduled for mid-cycle meeting</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Audrey Gassman, M.D., Acting Deputy Director</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> 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)

<input type="checkbox"/>	<ul style="list-style-type: none"> notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Kim Shiley	04-13-2012
Regulatory Project Manager	Date
Margie Kober	04-16-2012
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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/s/

KIMBERLY A SHILEY
04/18/2012

MARGARET M KOBER
04/19/2012