

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21945Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 21945	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Makena Established/Proper Name: 17- α hydroxyprogesterone caproate Dosage Form: Injection (IM) Strengths: 250 mg/ml		
Applicant: Hologic, Inc.		
Date of Receipt: July 12, 2010 (Class 2 Resubmission) April 25, 2008 (Class 2 Resubmission) April 14, 2006 (Original)		
PDUFA Goal Date: April 13, 2011	Action Goal Date (if different): February 3, 2011	
Proposed Indication(s): To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Non-Clinical/Clinical

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

PK/PD Studies

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

NOTE: The Sponsor relied on the Agency's previous findings of safety and efficacy.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If “**YES**”, please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new indication, “to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.”

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): N/A

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): N/A

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

ZETA-MAE C WILLIAMSON
02/03/2011

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 21-945
APPLICANT	Hologic, Inc.
DRUG NAME	MAKENA (hydroxyprogesterone caproate injection)
SUBMISSION DATE	13 July 2010
PDUFA DATE	13 January 2011
SEALD SIGN-OFF DATE	3 February 2011
OND ASSOCIATE DIRECTOR FOR LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed 4 January 2011 for this application have been addressed. The regulatory requirements found in 21 CFR 201.56 and 57 are adequately met for PI approval at this time.

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

/s/

LAURIE B BURKE
02/03/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY MEMO*****

Date: January 6, 2011

To: Charlene Williamson
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 021945**
DDMAC carton and container labeling comments for Makena™
(hydroxyprogesterone caproate injection)

Background

This consult is in response to DRUP's September 24, 2010 request for DDMAC's review on labeling materials for Makena™ (hydroxyprogesterone caproate injection) (Makena). Reference is made to DDMAC's comments dated November 12, 2010 on the draft PI and PPI.

DDMAC has reviewed the draft carton and container labels, submitted to DDMAC on January 5, 2011.

We do not have any comments on the draft carton and container labels for Makena at this time.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
(301) 796-3821, or janice.maniwang@fda.hhs.gov

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

/s/

JANICE L MANIWANG
01/07/2011

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 021945
APPLICANT	Hologic, Inc.
PRODUCT NAME	Makena (hydroxyprogesterone caproate injection)
SUBMISSION DATE	07/13/2010
PDUFA DATE	01/13/2011
SEALD REVIEW DATE	01/04/2011
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

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.

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. **Please remove the space between the product title and “Initial U.S. Approval” year.**

- **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)”

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

/s/

JUN YAN
01/04/2011

ANN M TRENTACOSTI
01/04/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: November 12, 2010

To: Charlene Williamson, Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Carrie Newcomer, PharmD, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA: 021945
DDMAC labeling comments for (b) (4) (hydroxyprogesterone caproate injection)

Background

This consult is in response to DRUP's September 24, 2010 request for DDMAC's review on the labeling materials for (b) (4) (hydroxyprogesterone caproate injection). (b) (4) DDMAC has reviewed the following labeling materials for (b) (4)

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer-Directed:

- Patient Product Information (PPI)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on October 28, 2010. In addition, we have considered the Depo Provera PI and PPI (approved October 2010) in our review of the draft (b) (4) labeling.

We offer the following comments:

PI & PPI

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
301-796-3821, or janice.maniwang@fda.hhs.gov
- Carrie Newcomer (Consumer directed materials)
301-796-1233, or carrie.newcomer@fda.hhs.gov

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

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

/s/

CARRIE A NEWCOMER
11/12/2010

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

PATIENT LABELING REVIEW

Date: November 12, 2010

To: Scott Monroe, M.D., Director
**Division of Reproductive and Urologic Products
(DRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

Melissa Hulett, MSBA, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Risk Management

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

Drug Name: hydroxyprogesterone caproate injection

Application Type/Number: NDA 21-945

Applicant: Hologic, Inc.

OSE RCM #: 2010-2316

1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for hydroxyprogesterone caproate injection.

On July 12, 2010 the Applicant submitted a new NDA for hydroxyprogesterone caproate injection with an indication for the prevention of preterm birth in women with a singleton pregnancy that have a history of a singleton spontaneous preterm birth.

The Applicant proposed the proprietary name [REDACTED] (b) (4) for this new product. As of this date the name [REDACTED] (b) (4) has not been approved, so we referred to the product as "TRADENAME" throughout the PPI.

Please send these comments to the Applicant and let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIALS REVIEWED

- Draft hydroxyprogesterone caproate injection Prescribing Information (PI) submitted on July 12, 2010, revised by DRUP throughout the review cycle and received by DRISK on October 29, 2010.
- Draft hydroxyprogesterone caproate injection Patient Package Insert (PPI) submitted on October 25, 2010 and received by DRISK on October 29, 2010.

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 MG and IFU 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 and is consistent with the 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)

4 CONCLUSIONS

The proposed patient labeling is acceptable with our recommended changes.

5 RECOMMENDATIONS

Please send these comments to the Applicant and copy DRISK on the correspondence.

Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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

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

/s/

ROBIN E DUER
11/12/2010

LASHAWN M GRIFFITHS
11/12/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: October 25, 2010

Application Type/Number: NDA 021945

To: Scott Monroe, Division Director
Division of Reproductive and Urology Products

Through: Melina Griffis, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Lubna Merchant, M.S., Pharm.D, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Gestene (Hydroxyprogesterone Caproate) Injection, 1250 mg/5 mL

Applicant/sponsor: Hologic Inc.

OSE RCM #: 2010-1819

CONTENTS

1. INTRODUCTION	3
2. METHODS AND MATERIALS REVIEWED	3
3. CONCLUSION AND RECOMMENDATIONS.....	3
3.1 Comments to the Applicant:	3
4. APPENDICES.....	5

1. INTRODUCTION

This review evaluates the proposed labels and labeling for (b) (4) (Hydroxyprogesterone Caproate) Injection (NDA 021945) for areas of vulnerabilities that could lead to medication errors.

2. METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, carton and insert labeling. This review focuses on labels and labeling submitted as part of the August 18, 2010 NDA resubmission. See Appendices A-B for images of the proposed container labels and carton labeling. We also reviewed our recommendations presented in previous review (OSE #2008-1779)

3. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 3.2 Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Maria Wasilik at 301-796-0567

3.1 COMMENTS TO THE APPLICANT:

A. Container Label

1. As currently presented, the word “Injection” appears as a stand alone statement above the route of administration. Since injection is already a part of the established name, we request you delete the word “Injection” that appears above the route of administration. Deleting this duplicative word would provide additional space so that the strength (total drug content and concentration) can be increased in size.
2. Relocate the product strength to appear beneath the established name.
3. Increase the prominence of the statement “Caution: Protect from light” by bolding, using a contrasting color, or boxing.
4. Add the statement ‘Use within 5 weeks after first use’ on the side panel below the storage statement.

B. Carton Labeling

See comments A1 –A4

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

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

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

/s/

LUBNA A MERCHANT
10/25/2010

MELINA N GRIFFIS
10/25/2010

CAROL A HOLQUIST
10/25/2010

PHARMACOLOGIST REVIEW OF GLP EIRS (CP 7348.808)

Firm Name:

(b) (4)

Studies Audited during this Inspection

Application: NDA 21-945

Rev Div: DRUP

Test Article: 17-Hydroxyprogesterone Caproate

Sponsor: Cytoc Corporation

Study: #1409-002 - An Intramuscular Multi-Generation Toxicity Study in Rats
Following In-Utero Exposure

Background:

Because of differing results between the above mentioned study and published articles by Pushpalatha et al. (Naturwissenschaften 91:242-244, 2004 and 92:385-388, 2005), namely, Pushpalatha's data showed adverse effects on sperm and decreased fertility in male offspring, while the (b) (4) study came out completely clean, the Pharm/Tox team leader Dr. Lynnnda Reid of DRUP requested an audit of the study at (b) (4). The inspection also confirmed corrective actions following the previous inspection at (b) (4) in April 2007.

Inspectional findings:

At the conclusion of the inspection at (b) (4) no Form FDA 483 was issued. However, during the audit of the study records the following observations were made for Study 1409-002:

- The results of the formulation concentration analyses indicated that the low-dose groups (5 mg/kg/day) in both the "Reproductive Phase 1" and "Teratology Phase" studies had lower concentrations of the test article than intended, outside the acceptance criterion of $\pm 15\%$. Investigations by (b) (4) and the analytical contractor, (b) (4) (b) (4) found no explanation for the out-of-specification results. Instead, the concentration measurements were confirmed by repeat analysis, and the results were properly reported. This observation concerned only the low-dose formulation.
- Not all changes in reproductive and fertility parameters in F1 and F2 generations were directly related to dose: The F1 male fertility index was lower in the mid-dose group than in the high-dose group; body weights of F2 male and female pups were lower in the high-dose groups than in other dose groups. The changes in fertility index and body weight were within the ranges found in historical background data at (b) (4).

(b) (4) staff suggested that possible differences in outcomes might be ascribed to strain differences (Sprague-Dawley at (b) (4) Wistar at Pushpalatha) and day of first dosing (GD 8 at (b) (4) GD 1 at Pushpalatha).

Corrective actions since previous inspection:

- Individually signed and dated reports of the contributing scientists in the audited study were provided to the study director and included in the final study report. This corrective action responded to the objectionable condition observed during the previous inspection.

Recommendations:

- This inspection revealed no deficiencies that affect the acceptance of the (b) (4) study data, and no other explanation for the differences among studies.
- Appropriate corrective action has been taken on the objectionable condition observed in the previous inspection. Surveillance GLP inspection in two years is recommended.
- Recommended HQ classification: NAI

(This EIR cover was drafted prior to receiving the EIR from the ORA inspector)

Dylan Dalin Yao, M.D., Ph.D.

Pharmacologist

Supervisory Concurrence:

Concur: _____ Date: _____

Nonconcurrency: _____ Date: _____
(see attached supervisory memorandum)

Date Assigned: 8/11/08
EI Dates: (b) (4)

District Offices: (b) (4)
FEI: (b) (4)

Investigators: William D. Tingley, KAL-RP, (b) (4)
Dylan Dalin Yao, M.D., Ph.D., DSI

Inspection Type: Routine Surveillance Directed
FDA-483 Issued: No Yes
Letter Issued: None PI Letter
 Untitled Letter

1st Draft Review Completed: 10/20/08

Site: (b) (4)
District Office: (b) (4)
Inspection Conclusion: NAI
District Decision: NAI
Final HQ Classification: NAI

cc: via DFS
DRUP: Reid/Jordan
DSI: Vaccari
DSI: DY/MFS/Viswanathan/Patague
Draft: DY 10/20/08
Edits: MFS 10/21/08
DSI File: GLP0668
O:\GLP\EIRCover\FY08\ (b) (4) doc

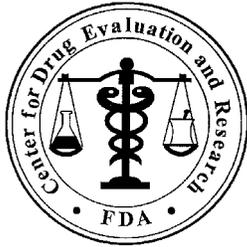
cc: via e-mail
KAL-RP, (b) (4) -DO/Tingley

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

/s/

Da-Lin Yao
10/23/2008 12:01:04 PM
PHARMACOLOGIST

Michael Skelly
10/23/2008 02:27:38 PM
PHARMACOLOGIST



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

Date: October 22, 2010

To: Scott Monroe, MD, Director
Division of Reproductive and Urologic Products (DRUP)
Office of New Drugs (OND), CDER

Audrey Gassman, MD, Deputy Director of Safety
DRUP, OND, CDER

Through: Bindi Nikhar, MD, Deputy Director
DPV II, OSE, CDER

From: Teresa Rubio, Pharm.D, Safety Evaluator
DPV II, OSE, CDER

Adrienne Rothstein, Pharm.D., Team Leader
DPV II, OSE, CDER

Subject: Adverse event reports for compounded preparations of 17 α -hydroxyprogesterone caproate from May 27, 2008 to October 6, 2010

Drug Name(s): Gestiva (17 α -hydroxyprogesterone caproate)

Application Type/Number: NDA #21-945

Applicant/sponsor: Hologic, Inc.

OSE RCM #: 2010-2117

CONTENTS

EXECUTIVE SUMMARY	1
1 BACKGROUND	1
1.1 INTRODUCTION	1
2 METHODS.....	2
2.1 AERS DATA.....	2
3 RESULTS.....	2
4 DISCUSSION.....	2
5 CONCLUSION.....	3
6 RECOMMENDATIONS.....	3
7 APPENDICES	4
7.1 APPENDIX 1. LINE LISTING OF AERS CASES.....	4

EXECUTIVE SUMMARY

The Division of Reproductive and Urologic Products (DRUP) is currently reviewing a Complete Response for 17 α -hydroxyprogesterone caproate (NDA 21-945) for the prevention of recurrent pre-term birth. DRUP has requested an update from the Division of Pharmacovigilance II (DPV II) of any adverse event reports received since the last OSE review completed in June 2008.

There are a total of 166 reports in AERS for 17 α -hydroxyprogesterone caproate as of October 6, 2010. One unique case was received since May 27, 2008, the data cut-off for the last OSE review.

The case described a woman who used 17 α -hydroxyprogesterone caproate during pregnancy, and gave birth to a male infant with microcephaly in 1985. The mother reported alcohol use during pregnancy and that the child had a chromosomal abnormality (monosomy of chromosome 8p). No definitive conclusion can be drawn from the single report, but the event is considered unlikely to be related to 17 α -hydroxyprogesterone caproate. We will continue to monitor reports for 17 α -hydroxyprogesterone caproate for any substantial changes in the safety profile.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Reproductive and Urologic Products (DRUP) is currently reviewing a Complete Response for 17 α -hydroxyprogesterone caproate for pre-term birth. The division previously requested in 2006 that the Division of Drug Risk Evaluation (DDRE) review any adverse event reports related to compounded preparations of 17 α -hydroxyprogesterone caproate received from 2003 to August 2006.¹ The June 2003 start date was chosen to coincide with the publication date of a study regarding 17 α -hydroxyprogesterone caproate use to prevent recurrent pre-term birth.² DRUP subsequently requested an update in 2008 of adverse event reports received from August 2006 to May 2008,³ and the current update describes any adverse event reports received since the last review.

¹ Rothstein A. OSE postmarketing safety review, August 22, 2006. OSE PID # D0600555, NDA 21-945.

² Meis PJ, Klebanoff M, Thom E, et al.; National Institute of Child Health (NICHD) and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003 Jun 12;348(24):2379-85. Erratum in: *N Engl J Med* 2003 Sep 25;349(13):1299.

³ Wassel, R. OSE postmarketing safety review, June 23, 2008, RCM 2008-833, NDA 21-945.

2 METHODS

2.1 AERS DATA

The Adverse Event Reporting System (AERS) was searched on 10/6/2010 with 17 α -hydroxyprogesterone caproate (active ingredient) as a suspect drug for all reports received by the FDA without regard to a received date.

3 RESULTS

There are a total of 166 reports in AERS for 17 α -hydroxyprogesterone caproate as of 10/6/2010. Sixteen reports were received from June 2003, of which there are total 10 unique cases. Of the 10 unique cases, 9 were discussed in the previous OSE reviews. Therefore, there is one unique case that was received from 5/27/2008 until the present.

4 DISCUSSION

The unique case (AERS ISR # 6434663) was reported by a patient (a nurse) who had received 17 α -hydroxyprogesterone caproate (Delalutin) during gestation weeks 5 through 17. The patient reported alcohol use during the pregnancy- a “sip of wine” at 8 to 9 weeks gestation, “more wine” during gestation weeks 12-17, and “an intense ‘drinking problem’ developed during the third trimester”. The patient gave birth to a male infant with monosomy of chromosome 8p and microcephaly (number of weeks gestation not provided) in 1985. The patient was concerned that the product interacted with the alcohol that she consumed in the first trimester, resulting in microcephaly.

Annually, approximately 25,000 infants in the United States will be diagnosed with microcephaly (head circumference <2 SD). Genetic etiologies have been reported in 15.5% to 53.3% of patients.⁴ The patient also admitted to an “intense drinking problem” with alcohol, which is a well known teratogen.⁵ Offspring of mothers using ethanol during pregnancy are known to suffer from developmental delays and/or a variety of behavioral changes.⁶ With very high repetitive doses, there is a 6–10% chance of the fetus developing the fetal alcohol syndrome manifested by prenatal and postnatal growth deficiency, specific craniofacial dysmorphic features (including microcephaly), mental retardation, behavioral changes and a variety of major anomalies.⁵ The alcohol exposure

⁴ Ashwal, S. Practice parameter: evaluation of the child with microcephaly (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology and the practice committee of the Child Neurology Society. *Neurology* 2009;73:887-897

⁵ Kumar, V. Robbins and Cotran-Pathologic Basis of Disease, 8th edition. Philadelphia: Saunders, 210, p. 452.

⁶ Onroy, A. *Int J Environ Res Public Health*. 2010 February; 7(2): 364–379.

and the presence of the child's genetic condition (monosomy of chromosome 8p, which can result in microcephaly⁷) make the relationship of microcephaly to the drug unlikely.

The complete AERS case is included as Appendix 1.

5 CONCLUSION

The new case was reported by a patient who had received 17 α -hydroxyprogesterone caproate during her pregnancy during gestation weeks 5 through 17 and gave birth to a male infant with monosomy of chromosome 8p and microcephaly in 1985. The mother admitted to routine consumption of alcohol, which is a well known cause of fetal alcohol syndrome, which can lead to microcephaly. The presence of a chromosomal abnormality in the infant further confounds interpretation of this single case report. No definitive conclusions can be drawn from this report.

6 RECOMMENDATIONS

We will continue to monitor reports for 17 α -hydroxyprogesterone caproate in AERS to determine if there are any changes in the safety profile.

⁷ Gilmore L. Deletion of 8p: A report of a child with normal intelligence. *Developmental Medicine and Child Neurology*, Vol. 43, No. 12, pp. 843-846, December 2001, Copyright 2001 Cambridge University Press

7 APPENDICES

7.1 APPENDIX 1. LINE LISTING OF AERS CASES

AERS Case from 5/27/2008-10/5/2010 with 17 α -hydroxyprogesterone caproate, N=1

ISR #	FDA Received Date	Manufacturer Control #	Event Date	Preferred Terms (PT)
6434663	9-Nov-09	CTU 398335	19-Jan-85	
<p>Suspected interaction between Delalutin -17 alpha-hydroxyprogesterone caproate- and alcohol -1/2 ounce of wine- . . . consumed during pregnancy. . .pregnancy was supplemented with weekly injections of Delalutin 250mg per week intramuscularly during gestation weeks 5 through 17. A sip of wine was consumed at 8-9 weeks gestation -estimate 48 days -+ or - 2days- after conception.. .which was thought to interact with the Delalutin, permitting the acetaldehyde to serve as the teratogen AND the mutagen.. .More wine was consumed during gestation ~weeks 12-17 during continued Delalutin supplementation. . .mother developed an "addiction" to alcohol which was not accompanied by a desire for INCREASED amounts of wine and which was not thought to cause withdrawal symptoms. An intense "drinking problem" developed during the third trimester, evident at 26-28 gestation weeks. . . -while there was no hormonal supplementation with Delalutin- - Previous MEDWATCH reports have been filed. Today's date is November 7, 2009. Related MEDWATCH reports regarding the same individuals -mother ^{(b) (6)} and son ^{(b) (6)}- have been filed: ^{(b) (6)}. The purpose of submitting this supplemental report -written by the patient's biological mother who happens to be a RN-. .is to add detail to explain our son's complex condition which includes microcephaly, a complex congenital cardiac condition, a chromosome deletion of a section of chromosome 8p, stunted growth, and an intellectual disability. The detail is in regard to his microcephaly. Although our son has been seen by at least 3 different Neurologists for the purpose of evaluating his microcephaly, there has been no consensus on the etiology of this condition. So, I am offering my own explanation, which is logical from my own perspective, and this narrative highlights the complexity of his existing condition. It is my opinion that there are 2 contributing causes to his microcephaly. The #1 cause is most likely due to his genetic condition, a partial monosomy of 8p. The medical description is -8-p23.1p23.3 -8-pter+ This section of chromosome 8p is associated with some chromosomal fragility at breakpoint 23.1, and the remainder of the section is associated with a high incidence of cardiac anomalies -see MEDWATCH report dated 02/20/2009 for these details- and there is also an association with primary recessive microcephaly on this section. A partial monosomy of 8p might allow expression of a recessive allele on the single, existing allele, or the absence of any portion of 8p might be serious enough to impede full brain growth and development. He is 24 years old. His occipital head circumference is 51-53 cm, and is hard to measure consistently due to a somewhat flattened occiput and a slightly sloping forehead. As described in earlier MEDWATCH reports.. .the suspected reason for the chromosome deletion is an interaction between nelalutin -17P- and a small unverifiable amount of wine consumed between 8-9 gestation weeks, I suspect that the 17 P restricted the metabolism of acetaldehyde at that point in time -which also coincides with the embryological development of the tricuspid valve which is also affected in our son-. THIS IS A REALLY, REALLY POTENT INTERACTION. I recognize that the cell counts from the genetic tests would lead one to believe that this problem occurred at conception, but this assumption is not consistent with our son's overall physical findings, and I have challenged others to try to replicate these findings. Some chromosome info can be found on RareChromo.org website under 8p deletions. The OTHER suspected contributing factor to his microcephaly is my alcohol consumption during my third trimester, when I experienced a bizarre "drinking problem" which was NOT intoxication. By gestation week 26 or so, I had already experienced -i.e., felt-ongoing intrauterine growth retardation/inhibition which fluctuated in relationship to the frequency of my</p>				

alcohol consumption -2 days in a row or every other day. . .sometimes could go to every third day-. I would characterize this microcephaly as “dynamic” and it was an intensely unpleasant experience for me. He has had many behavioral/learning indicators which would lead one to suspect intrauterine exposure to alcohol. It would be very difficult to sort through and separate out the results of two separate causes of microcephaly, but this is the hypothesis which “fits” the best. I cannot ignore the deletion on 8p as contributory, and I cannot ignore my own symptoms related to the third trimester, and I cannot ignore his gross motor/fine motor/interpersonal/behavioral/emotional/language delays which we have been privy to for 24+ years. He has some of the mild dysmorphology which is associated with fetal alcohol exposure, though he does not meet all the diagnostic criteria. One physician said that the features were within a spectrum consistent with alcohol exposure and that it depended which classification system was used. There has been little if any, collaboration among his various physicians though I have begged for this to occur.

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

/s/

TERESA M RUBIO
10/22/2010

ADRIENNE M ROTHSTEIN
10/22/2010

BINDI M NIKHAR
10/22/2010

PHARMACOLOGIST REVIEW OF GLP EIRS (CP 7348.808)

Firm Name:

(b) (4)

Studies Audited during this Inspection

Application: NDA 21-945

Rev Div: DRUP

Test Article: 17-Hydroxyprogesterone Caproate

Sponsor: Cytoc Corporation

Study: #1409-002 - An Intramuscular Multi-Generation Toxicity Study in Rats
Following In-Utero Exposure

Background:

Pharm/Tox team leader Dr. Lynnda Reid of DRUP requested an audit of the study at (b) (4) because of differing results between the above mentioned study and published articles by Pushpalatha et al. (Naturwissenschaften 91:242-244, 2004 and 92:385-388, 2005). Pushpalatha's data showed adverse effects on sperm and decreased fertility in male offspring, while the (b) (4) study did not find adverse effects. The inspection also confirmed corrective actions following the previous inspection at (b) (4) in April 2007.

Inspectional findings:

At the conclusion of the inspection at (b) (4) no Form FDA 483 was issued. However, during the audit of the study records the following observations were made for Study 1409-002:

- The results of the formulation concentration analyses indicated that the low-dose groups (5 mg/kg/day) in both the "Reproductive Phase 1" and "Teratology Phase" studies had lower concentrations of the test article than intended, outside the acceptance criterion of $\pm 15\%$. Investigations by (b) (4) and the analytical contractor, (b) (4) found no explanation for the out-of-specification results. Instead, the concentration measurements were confirmed by repeat analysis, and the results were properly reported. This observation concerned only the low-dose formulation.
- Not all changes in reproductive and fertility parameters in F1 and F2 generations were directly related to dose: The F1 male fertility index was lower in the mid-dose group than in the high-dose group; body weights of F2 male and female pups were lower in the high-dose groups than in other dose groups. The changes in fertility index and body weight were within the ranges found in historical background data at (b) (4)

(b) (4) staff suggested the possibilities that differences in outcomes might be related to strain differences (Sprague-Dawley at (b) (4) Wistar at Pushpalatha) and day of first dosing (GD 8 at (b) (4) GD 1 at Pushpalatha).

Corrective actions since previous inspection:

- Individually signed and dated reports of the contributing scientists in the audited study were provided to the study director and included in the final study report. This corrective action responded to the objectionable condition observed during the previous inspection.

Recommendations:

- This inspection revealed no deficiencies that affect the acceptance of the (b) (4) study data, and no other explanation for the differences among studies.
- Appropriate corrective action has been taken on the objectionable condition observed in the previous inspection. Surveillance GLP inspection in two years is recommended.
- Recommended HQ classification: NAI

Dylan Dalin Yao, M.D., Ph.D.

Pharmacologist

Supervisory Concurrence:

Concur: _____ Date: _____

Nonconcurrency: _____ Date: _____
(see attached supervisory memorandum)

Date Assigned: 8/11/08
EI Dates: (b) (4)

District Offices: (b) (4)
FEI: (b) (4)

Investigators: William D. Tingley, KAL-RP, (b) (4)
Dylan Dalin Yao, M.D., Ph.D., DSI

Inspection Type: Routine Surveillance Directed
FDA-483 Issued: No Yes
Letter Issued: None PI Letter
 Untitled Letter

1st Draft Review Completed: 10/20/08

Site: (b) (4)
District Office: (b) (4)
Inspection Conclusion: NAI
District Decision: NAI
Final HQ Classification: NAI

cc: via DFS
DRUP: Reid/Jordan
DSI: Vaccari
DSI: DY/MFS/Viswanathan/Patague
Draft: DY 10/20/08
Edits: MFS 10/21/08; 1/6/09
DSI File: GLP0668
O:\GLP\EIRCover\FY08\ (b) (4) doc

cc: via e-mail
KAL-RP, (b) (4)/Tingley

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

/s/

Da-Lin Yao

1/6/2009 09:25:04 AM

PHARMACOLOGIST

The similar contents of this EIR cover have been
forwarded to DRUP (Dr. L. Reid) in October,
2009 before the PDUFA deadline.

Michael Skelly

1/6/2009 04:04:29 PM

PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Date: December 30, 2008

To: Charlene Williamson
Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.
Regulatory Review Officer
Division of Drug Advertising, Marketing, and Communications (DDMAC)

Re: Consult request for Gestiva™ (17 α -Hydroxyprogesterone Caproate Injection, 250 mg/mL)
NDA #21-945

DDMAC has reviewed the proposed product (PI), carton and vial labeling for Gestiva (17 α -hydroxyprogesterone caproate) submitted on May 21, 2008. DDMAC understands that this label will include safety and risk studies that have not been submitted by the sponsor to date.

At this time, DDMAC would like to defer labeling comments until further revisions are submitted by the sponsor.

If you have any questions, please contact Janice Maniwang at (301) 796-3821 or janice.maniwang@fda.hhs.gov.

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

/s/

Janice Maniwang
12/30/2008 10:55:57 AM
DDMAC REVIEWER



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

Date: November 24, 2008

To: Scott Monroe, MD
Director, Division of Reproductive and Urologic Products

Through: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MSED, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review for Gestiva

Drug Name: Gestiva (Hydroxyprogesterone Caproate) Injection
250 mg/mL

Application Type/Number: NDA 21-945

Applicant: Cytoc Corporation

OSE RCM #: 2008-1779 revised labeling

1 INTRODUCTION

This memorandum is in response to an October 2, 2008, email request from the Division Reproductive and Urologic Products, for a review of the revised container labels, and carton and insert labeling for Hydroxyprogesterone Caproate Injection.

We found the proprietary name “Gestiva” acceptable in OSE review #2008-832 dated October 22, 2008.

2 MATERIAL REVIEWED

Revised container labels and carton labeling submitted via email October 2, 2008 (see Appendices A and B), revised insert labeling dated October 16, 2008, and the review Division’s CMC review dated September 22, 2006. We also evaluated the recommendations pertaining to the label and labeling presented in OSE review #2008-1051.

3 DISCUSSION

The Applicant provided entirely new carton labeling and container labels to replace the labels that were previously submitted on April 24, 2008. The Applicant revised the labels to incorporate new anticipated marketing campaign colors, font style, and logo element. We have identified areas of concern/vulnerability as discussed below.

3.1 CONTAINER LABELS AND CARTON LABELING

The word “Injection” appears above the route of administration (for intramuscular use). This is redundant as ‘injection’ is a part of the established name. The removal of this word would allow more room to increase the prominence of the product strength.

We note that a “Protect from light” statement appears on the side of the carton labeling and container label. However, because of the location and the fact that it is displayed in the same font size and boldness as the other text, it could be overlooked leading to improper storage of the product.

3.2 PACKAGE INSERT

No comment.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA recommends the label and labeling recommendations outlined below be implemented to minimize the risk of confusion and medication errors.

1. Delete the word “Injection” that appears above the route of administration (see image below). Deleting this duplicative word would provide additional space so that the strength (total drug content and concentration) can be increased in size.



2. On the carton labeling and container label, increase the prominence of the statement “Caution: Protect from light” by bolding, using a contrasting color, or boxing.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryle Milburn, Project Manager, at 301-796-2084.

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

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

/s/

Felicia Duffy
11/24/2008 11:10:11 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/24/2008 01:31:06 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/24/2008 04:28:20 PM
DRUG SAFETY OFFICE REVIEWER

**Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research**

Date: October 14, 2008
Reviewer: Lynnda Reid, Ph.D.
Supervisory Pharmacologist
NDA #/SS#/date: 21-945 / N000 / April 25, 2008
Sponsor: CYTYC Corp.
Drug Product: 17 alpha-hydroxyprogesterone caproate
Indication: Prevention of recurrent preterm birth
Recommended Action: Approval

Drug History: The subject of this NDA is 17 Alpha-Hydroxyprogesterone Caproate Injection, 250 mg/mL for the proposed indication of prevention of recurrent preterm birth. The use of 17 alpha-hydroxyprogesterone caproate (17 α -HPC) will be limited to pregnant women with a history of at least one spontaneous preterm birth at less than 37 weeks of gestation.

This NDA was originally filed on April 20, 2006 by Adeza Biomedical. Following review of the submitted data, it was determined that there was insufficient clinical and nonclinical data to support approval. The primary deficiencies in the nonclinical studies included insufficient numbers of animals, use of unconventional species, lack of any PK/ADME data, correlation between gestational timing of exposures and pregnancy outcome, and lack of developmental studies in offspring exposed in utero.

The submission filed on June 16, 2008, contained a multigenerational study in rats in which offspring exposed in utero were evaluated for potential effects on development, learning and behavior. This study was conducted under Good Laboratory Procedures and was also audited by FDA inspectors. No deficiencies which would affect the results were identified. The study did not find any potential adverse effects on neurologic or reproductive development of offspring exposed to 17 α -HPC in utero.

Unresolved Toxicology Issues: Embryo lethality reported in Rhesus monkeys at doses equivalent to the human dose were not observed in Cynomolgus monkeys or rodents, and does not appear to be a risk factor in humans.

Conclusions and Recommendations: I concur with the nonclinical reviewer, Dr. Alexander Jordan, in recommending approval of this NDA.

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

/s/

Lynnda Reid
10/14/2008 04:14:24 PM
PHARMACOLOGIST



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

Date: September 25, 2008

To: Scott Monroe, MD
Director, Division of Reproductive and Urologic Products

Through: Kellie Taylor, PharmD, MPH, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review for Gestiva

Drug Name: Gestiva (17 α -hydroxyprogesterone caproate) Injection

Application Type/Number: NDA 21-945

Submission Number: Not Applicable

Applicant/sponsor: Cytoc Corporation

OSE RCM #: 2008-1051 labeling

1 INTRODUCTION

This memorandum is in response to a May 21, 2008, request from the Division Reproductive and Urologic Products, for a review of the revised container labels, and carton and insert labeling for 17 α -hydroxyprogesterone caproate injection.

We found the proprietary name “Gestiva” unacceptable from a safety perspective in OSE review #06-0134 (dated August 7, 2006). The Applicant submitted a rebuttal in support of the proprietary name which is being addressed in a separate review (OSE review #2008-832).

2 MATERIAL REVIEWED

Revised container labels, carton and insert labeling submitted on April 24, 2008 (see Appendices A and B for revised container labels and carton labeling). We also evaluated the recommendations pertaining to the label and labeling presented in OSE review #06-0134.

3 DISCUSSION

The majority of the recommendations put forward in our previous review were accepted with the following exceptions indicated below. Additionally, we have identified areas of concern/vulnerability and in some aspects, not in compliance with regulatory requirements.

3.1 CONTAINER LABELS AND CARTON LABELING

In reviewing the labels and labeling, we note that the yellow line beneath the proprietary name separates the proprietary name from the established name and strength. This intervening matter is not in accordance with 21 CFR 201.10(a). Additionally, the established name appears less than $\frac{1}{2}$ the size of the proprietary name. We recognize that the dosage form cannot appear on the same plane as the established name due to the length of the established name; however, we note the dosage form (injection) appears further disjointed from the established name because it appears is in all capital letters and does not appear in the same font as the established name.

We note that a “Protect from light” statement appears on the side of the carton labeling and container label; however, it may be overlooked because it is not prominent, which could possibly lead to improper storage of the product.

3.2 INSERT LABELING

The information in the Dosage and Administration section of the package insert (highlights and section 2.1) is confusing in the way it is written, specifically with respect to the statement “...beginning at 16 weeks, 0 days to 20 weeks, 6 days of gestation....” The complete sentence reads as follows:

Gestiva is administered intramuscularly at a dose of 250 mg (1 mL) once each week beginning at 16 weeks, 0 days to 20 weeks, 6 days of gestation until week 37 of gestation or birth.

The way the statement is phrased, it seems as though treatment can begin at 16 weeks of gestation, *or* between 0 days to 20 weeks + 6 days of gestation, which is conflicting. This section should be broken down into three separate sentences or presented in a table. If this section remains in paragraph form, the first sentence should clearly indicate the gestation range of when the product can be initially administered. The second sentence should indicate the maintenance phase, and the last sentence should indicate when to cease treatment. This section should be revised in order to minimize confusion on when to start and stop treatment.

In the 'Geriatric Use' section of the insert (section 8.5), it states that "Gestiva is not intended for use in elderly patients". The term 'elderly' is not clearly defined and it is not clear what 'elderly' means. An upper limit should be specified in years to help minimize misinterpretation.

The 'How Supplied/Storage and Handling' section (section 16) does not indicate how long Gestiva can be stored once it is opened. Since Gestiva is supplied in a multi-dose vial, there should be instructions on the stability of the drug once the vial has been punctured in order to prevent use of a potentially contaminated product. This information should also be included in the Dosage and Administration section of the insert.

4 CONCLUSIONS AND RECOMMENDATIONS

DMETS recommends the label and labeling recommendations outlined below be implemented to comply with regulatory requirements and minimize the risk of medication errors.

1. Delete the yellow line (intervening matter) that appears beneath the proprietary name per 21 CFR 201.10(a).
2. On the carton labeling and container labels, ensure the established name, which includes the dosage form, is at least ½ the size of the proprietary name and commensurate with the prominence of the proprietary name, per 21 CFR 201.10(g)(2).
3. Revise the dosage form (injection) so that it appears in the same font and size as the remainder of the established name.
4. On the carton labeling and container label, increase the prominence of the statement "Caution: Protect from light" by contrasting color or boxing.
5. In the package insert, consider revising the Dosage and Administration section by breaking it down into three separate sentences, or presented in a table. If this section remains in paragraph form, the first sentence should clearly indicate the gestation range of when the product can be initially administered (e.g., between 16 weeks + 0 days to 20 weeks + 6 days of gestation). The second sentence should indicate the maintenance instructions (e.g., continue once weekly injections until 37 weeks of gestation or birth). The last sentence should indicate when to cease treatment (e.g., Medication should not be given after 37 weeks). This section should be revised in order to minimize confusion on when to start and stop treatment.
6. In the 'Geriatric Use' section of the insert, specify what 'elderly' means in terms of years.
7. In the 'How Supplied/Storage and Handling' section of the insert, include information about the stability of Gestiva once the multi-dose vial has been opened. This information should also be included in the Dosage and Administration section of the insert.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryle Milburn, Project Manager, at 301-796-2084.

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

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

/s/

Felicia Duffy
9/25/2008 04:44:18 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
9/25/2008 05:42:46 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/30/2008 04:34:55 PM
DRUG SAFETY OFFICE REVIEWER



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

Date: June 23, 2008

To: Barbara Wesley, M.D., Medical Officer
Division of Reproductive & Urologic Products (DRUP)

From: Ronald Wassel, Pharm.D., Safety Evaluator
Division of Adverse Event Analysis II

Through: Melissa Truffa, R.Ph., Team Leader
Division of Adverse Event Analysis II

Through: Ann W. McMahon, M.D., Acting Director
Division of Adverse Event Analysis II

Subject: Any adverse events related to compounded preparations of
17 α -hydroxyprogesterone caproate from August 2006 to
present

Drug Name(s): Gestiva™ (17 α -hydroxyprogesterone caproate)

Application
Type/Number: NDA # 21-945

Applicant/sponsor: Cytoc Corporation

OSE RCM #: 2008-833

EXECUTIVE SUMMARY

The Division of Reproductive & Urologic Products (DRUP) is currently reviewing an NDA for 17 α -hydroxyprogesterone caproate for the prevention of recurrent pre-term birth and has requested an update from the Division of Adverse Event Analysis II (DAEA II) of any adverse event reports received since a previous review in August 2006.

There are a total of 164 reports in AERS for 17 α -hydroxyprogesterone caproate as of 5/27/2008. Fourteen reports were received from June 2003, of which there are nine unique cases. Of the nine unique cases, three were discussed in the previous review. Therefore, there are six unique cases that were received from August 2006 until the present.

Of the six new cases, three were related to preterm labor and, as such, could not be considered an adverse event of the drug. No definitive conclusions can be drawn from the single report each of syncope, depression, and congenital heart defect, but are considered unlikely related.

We will continue to monitor reports for 17 α -hydroxyprogesterone caproate to determine any changes.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Reproductive & Urologic Products (DRUP) is currently reviewing an NDA for 17 α -hydroxyprogesterone caproate for the prevention of recurrent pre-term birth. The division previously requested in 2006 that the Division of Drug Risk Evaluation (DDRE) review any adverse event reports related to compounded preparations of 17 α -hydroxyprogesterone caproate received from June 2003 to August 2006. The June 2003 start date was chosen to coincide with the publication date of a study regarding 17 α -hydroxyprogesterone caproate use to prevent recurrent pre-term birth.¹ Following publication of that study, physicians began prescribing the drug for pre-term labor prevention, which was in part supported by the American College of Obstetricians and Gynecologists.² The review from DDRE was communicated to DRUP on August 22, 2006 and is attached as Appendix 1. DRUP has requested an update from the Division of Adverse Event Analysis II (DAEA II) of any adverse event reports received since the previous review.

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

The Adverse Event Reporting System (AERS) was searched on 5/27/2008 with 17 α -hydroxyprogesterone caproate as a suspect drug for all reports received by the FDA without regard to a received date.

3 RESULTS

3.1 ADVERSE EVENT CASES

There are a total of 164 reports in AERS for 17 α -hydroxyprogesterone caproate as of 5/27/2008. Fourteen reports were received from June 2003, of which there are nine unique cases. Of the nine unique cases, three were discussed in the previous review. Therefore, there are six unique cases that were received from 8/16/2006 until the present.

4 DISCUSSION

4.1 ADVERSE EVENT CASES

Of the six cases received from August 2006, five were reported from a study evaluating the pharmacokinetics of 17 α -hydroxyprogesterone caproate in women receiving the drug for therapeutic purposes (IND 72,283; principal investigators Steve N. Caritis, M.D., Pittsburgh, PA [1 case] and Mary F. Hebert, Pharm.D., Seattle, WA [4 cases]).

AERS ISR # 5281471-8—A 36-year-old female at 33 1/7 weeks gestation was admitted to the hospital after a **syncopal episode with loss of consciousness** for two to three minutes. She has had previous episodes of intermittent diaphoresis/palpitations and a history of presyncope since a gastric bypass surgery. The patient was discharged after two days with no further episodes.

AERS ISR # 5218355-7—A 24-year-old gravida 5, para 1 (2), female presented at her normal appointment with **frequent contractions** (gestational age 32 4/7 weeks). She was admitted for observation and started on nifedipine and received a course of betamethasone. The patient was discharged after three days as her contractions had stabilized.

AERS ISR # 5311445-X—A 32-year-old gravida 3, para 1 (0), female presented at her regular appointment and was found on ultrasound to be 2 cm **dilated with funneling to the external os** (gestational age 24 0/7 weeks). She was admitted and received a rescue cerclage. She was placed on tocolytic ibuprofen therapy and, at the time of the report, was being monitored with a plan to discharge if her cervical length remained stable.

AERS ISR # 5154721-6—A 37-year-old gravida 2, para 2, female presented at 28 6/7 weeks gestation with **preterm labor**. She was completely dilated with bulging membranes. A male infant was delivered by an uncomplicated standard vaginal delivery. The baby was diagnosed with respiratory distress syndrome and was admitted to the NICU in critical condition on respiratory support because of extreme pulmonary immaturity. He is also on phototherapy for jaundice.

AERS ISR # 5272646-2—A 28-year-old gravida 6, para 0 (5), female who was approximately 24 weeks gestation was admitted to the hospital for **depression, paranoia, anxiety, and suicidal ideation**. The subject has a history significant for rapid cycling bipolar disorder and bulimia, with a strong family history of mental illness. She had not been on psychiatric medication for four years prior to this event. She had received two doses of 17 α -hydroxyprogesterone caproate and the events occurred five weeks after the second dose. She had not kept her scheduled appointments for follow-up injections. The patient later admitted that she was not truly feeling suicidal but used those statements because she knew that would result in her hospitalization. She was discharged after four days in stable condition.

The sixth case (AERS ISR # 5143070-8) was reported by a patient who had received hydroxyprogesterone caproate during her pregnancy for 16 weeks and gave birth to a female infant with a **congenital heart defect** who subsequently died at six days of age.

5 CONCLUSION

Of the six new cases, three were related to preterm labor and, as such, could not be considered an adverse event of the drug.

No definitive conclusions can be drawn from the single report each of syncope, depression, and congenital heart defect. The patient who experienced syncope had a

previous history of presyncopal episodes, and the patient who experienced psychiatric events had a significant personal and family history of mental illness. Congenital heart defects are the most common type of birth defect, affecting 8 of every 1,000 newborns.³ There is considerable evidence that favors 17 α -hydroxyprogesterone caproate not being associated with birth defects.⁴⁻⁸ In addition, most congenital heart defects occur from errors early in the heart's development, which occurs well before the currently recommended use of the drug.

6 RECOMMENDATIONS

We will continue to monitor reports for 17 α -hydroxyprogesterone caproate to determine any changes.

7 REFERENCES

1. Meis PJ, Klebanoff M, Thom E, et al.; National Institute of Child Health (NICHD) and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003 Jun 12;348(24):2379-85. Erratum in: *N Engl J Med* 2003 Sep 25;349(13):1299.
2. ACOG Committee Opinion. Use of progesterone to reduce preterm birth. *Obstet Gynecol.* 2003 Nov;102(5 Pt 1):1115-6.
3. American Heart Association. Congenital heart defects in children factsheet. Available online at <http://www.americanheart.org/presenter.jhtml?identifier=12012>; 2005.
4. Raman-Wilms L, Tseng AL, Wighardt S, et al. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995;85:141-149.
5. Katz Z, Lancet M, Skornik J, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. *Obstet Gynecol* 1985 Jun;65(6):775-80.
6. Resseque LJ, Hick JF, Bruen JA, et al. Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota, 1936-1974. *Fertil Steril* 1985;43(4):514-9.
7. Dudas I, Gidai J, Czeizel AE. Population-based case-control teratogenic study of hydroxyprogesterone treatment during pregnancy. *Congenit Anom (Kyoto)* 2006; 46(4):194-8.
8. Christian MS, Brent RL, Calda P. Embryo-fetal toxicity signals for 17alpha-hydroxyprogesterone caproate in high-risk pregnancies: a review of the non-clinical literature for embryo-fetal toxicity with progestins. *J Matern Fetal Neonatal Med* 2007;20(2):89-112.

APPENDIX 1.

<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</p>	<p>OSE POSTMARKETING SAFETY REVIEW</p>
<p>FROM: Adrienne Rothstein, PharmD Safety Evaluator, Division of Drug Risk Evaluation (DDRE)</p>	<p>DATE: August 22, 2006 OSE PID#: D060555</p>
<p>TO: Barbara Wesley, MD Medical Officer, Division of Reproductive & Urologic Products (DRUP)</p>	<p>THROUGH: Mark Avigan, MD, CM, Director, Division of Drug Risk Evaluation (DDRE)</p>
<p>DRUG NAME: Gestiva (17α-hydroxyprogesterone caproate)</p>	<p>THERAPEUTIC CLASSIFICATION: Synthetic progestin</p>
<p>NDA #: 21-945</p>	<p>SPONSOR: Adeza Biomedical</p>
<p>EVENT: Any adverse events related to compounded preparations of 17α-hydroxyprogesterone caproate from June 2003 to present</p>	
<p>Executive Summary:</p> <p>The Division of Reproductive & Urologic Products (DRUP) is reviewing an NDA from Adeza Biomedical for 17α-hydroxyprogesterone caproate for the prevention of recurrent pre-term birth. A search of the AERS database was conducted to identify all reports for 17α-hydroxyprogesterone caproate. A total of 154 reports were retrieved, only 4 reports were received since June 2003. At the request of DRUP, this review will focus on the reports received since the June 2003 publication of an article about 17α-hydroxyprogesterone caproate use to prevent recurrent pre-term birth.¹ For the 4 reports received since June 2003, three reports referred to product use up to 17 weeks gestation and one report was a duplicate. These four MedWatch reports have been previously provided to the medical officer. These few reports of early gestational exposure are of limited value to an assessment of 17α-hydroxyprogesterone caproate for the prevention of recurrent pre-term birth.</p> <p>Thus, no conclusions can be made at this point in time from the limited number of reports in AERS for 17α-hydroxyprogesterone caproate. A summary listing of preferred terms for all 17α-hydroxyprogesterone caproate reports in the AERS database (154 reports) is provided in Appendix A as a supplement to this consult.</p>	

¹ Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al.; National Institute of Child Health (NICHD) and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun 12;348(24):2379-85. Erratum in: N Engl J Med. 2003 Sep 25;349(13):1299.

Search Date: 08/15/2006	Search Type(s): x AERS ۞ Literature
Search Criteria and Strategy: 17 α -hydroxyprogesterone caproate as a suspect drug	
Search Results: There are a total of 154 reports in AERS for 7 α -hydroxyprogesterone caproate. Only 4 reports were received since June 2003.	
<p data-bbox="235 510 565 541">Discussion/Conclusions:</p> <p data-bbox="235 615 1550 1014">According to the request from DRUP, the Maternal Fetal Medicine Units (MFMU) Network conducted a multicenter, randomized placebo-controlled, double-blinded study on the efficacy and safety of 17α-hydroxyprogesterone caproate in pregnant women with a previous pre-term birth. The results of this study were published in the New England Journal of Medicine in June 2003. The drug substance used in this study was previously approved under the trade name of Delalutin® for gynecologic indications. Delalutin® was used off-label to prevent miscarriage in early pregnancy (prior to 20 weeks gestation), but the data to support this use was sparse and the practice discontinued over time. Drug marketing was discontinued in the early 1990s because of decreased product usage. However, after publication of the MFMU Network study in June 2003, physicians began to prescribe this drug for pre-term labor prevention and this practice was in part supported by the American College of Obstetricians and Gynecologists.²</p> <p data-bbox="235 1056 1550 1381">Progesterone has been used for pre-term labor prevention because studies have shown that there is an adverse progesterone:estrogen ratio present in preterm labor and progesterone antagonists given at term increase the rate of spontaneous labor. A number of tocolytic drugs have been used to prevent or inhibit preterm labor, including beta-adrenergic receptor agonists, magnesium sulfate, prostaglandin inhibitors, calcium channel blockers, and nitric oxide donors; however, none has been shown to be completely effective.³ DRUP is currently reviewing an NDA from Adeza Biomedical for 17α-hydroxyprogesterone caproate for the prevention of recurrent pre-term birth. As such the division requested that DDRE review any adverse event reports related to compounded preparations of 17α-hydroxyprogesterone caproate received from June 2003 to present.</p> <p data-bbox="235 1423 1550 1703">There were a total of 154 reports in AERS for 17α-hydroxyprogesterone caproate, 4 reports were received since June 2003. Two reports described 17α-hydroxyprogesterone caproate use for the prevention of miscarriage in the first trimester of pregnancy. One report described 17α-hydroxyprogesterone caproate use during weeks 5-17 of gestation. The fourth report was a duplicate report. These four MedWatch reports have been previously provided to the medical officer. A summary listing of preferred terms for all 17α-hydroxyprogesterone caproate reports in the AERS database (154 reports) is provided in Appendix A as a supplement to this consult. Additional MedWatch reports can be provided upon request.</p>	

² ACOG Committee Opinion. Use of progesterone to reduce preterm birth. Obstet Gynecol. 2003 Nov;102(5 Pt 1):1115-6.

³ From Williams Obstetrics 22nd edition. Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC, Wenstrom KD editors McGraw Hill 2005, Chapter 36. Preterm birth.

At this point in time, no conclusions can be drawn from the limited number of reports in AERS for 17 α -hydroxyprogesterone caproate.

Reviewer's Signature / Date

Adrienne Rothstein / 08-15-06

Team Leader's Signature / Date

Melissa Truffa / 08-16-06

Appendix A. All Preferred Terms in 17 α -Hydroxyprogesterone Caproate Reports (Any Indication) Received in AERS from 06/01/1969 – 08/15/2006

(n=154)

Preferred Term (PT)	Count of PTs	Percent of Total
Congenital Anomaly	47	30.52
Multiple Congenital Abnormalities	16	10.39
Injection Site Hypersensitivity	10	6.49
Urticaria	8	5.19
Pruritus	5	3.25
Dermatitis	4	2.60
Breast Cancer Female	3	1.95
Congenital Musculoskeletal Anomaly	3	1.95
Deep Vein Thrombosis	3	1.95
Drug Exposure During Pregnancy	3	1.95
Heart Disease Congenital	3	1.95
Injection Site Reaction	3	1.95
Limb Reduction Defect	3	1.95
Abdominal Pain	2	1.30
Abnormal Labour	2	1.30
Anaphylactoid Reaction	2	1.30
Colitis Ulcerative	2	1.30
Congenital Central Nervous System Anomaly	2	1.30
Cough	2	1.30
Eczema	2	1.30
Headache	2	1.30
Hepatitis	2	1.30
Hirsutism	2	1.30
Hormone Level Abnormal	2	1.30
Injection Site Pain	2	1.30
Injection Site Urticaria	2	1.30
Jaundice	2	1.30
Mental Retardation Severity Unspecified	2	1.30
Myocardial Infarction	2	1.30
Pyrexia	2	1.30
Skin Discolouration	2	1.30
Visual Disturbance	2	1.30
Weight Increased	2	1.30
Abscess	1	0.65
Acute Lymphocytic Leukaemia	1	0.65
Alcohol Interaction	1	0.65
Alcoholism	1	0.65

Preferred Term (PT)	Count of PTs	Percent of Total
Alopecia	1	0.65
Anaesthetic Complication	1	0.65
Anomaly Of External Ear Congenital	1	0.65
Asthenia	1	0.65
Benign Neoplasm Of Skin	1	0.65
Blood Alkaline Phosphatase Increased	1	0.65
Blood Follicle Stimulating Hormone Increased	1	0.65
Bone Disorder	1	0.65
Calcium Metabolism Disorder	1	0.65
Cerebrovascular Accident	1	0.65
Cervix Carcinoma	1	0.65
Chest Pain	1	0.65
Chondrodystrophy	1	0.65
Complications Of Maternal Exposure To Therapeutic Drugs	1	0.65
Congenital Heart Valve Disorder	1	0.65
Congenital Tongue Anomaly	1	0.65
Convulsion	1	0.65
Cyanosis Neonatal	1	0.65
Cyst	1	0.65
Dermatitis Bullous	1	0.65
Dermatitis Contact	1	0.65
Drug Ineffective	1	0.65
Dwarfism	1	0.65
Dysmenorrhoea	1	0.65
Ebstein's Anomaly	1	0.65
Eye Disorder	1	0.65
Facial Palsy	1	0.65
Falot's Tetralogy	1	0.65
False Labour	1	0.65
Fibromyalgia	1	0.65
Hernia	1	0.65
Hip Dysplasia	1	0.65
Hydrocele	1	0.65
Hypersensitivity	1	0.65
Hypertrophy	1	0.65
Hypocalcaemia	1	0.65
Hypospadias	1	0.65
Infertility Male	1	0.65
Injection Site Inflammation	1	0.65
Injection Site Oedema	1	0.65
Jaundice Neonatal	1	0.65

Preferred Term (PT)	Count of PTs	Percent of Total
Leiomyoma	1	0.65
Limb Deformity	1	0.65
Limb Malformation	1	0.65
Maternal Drugs Affecting Foetus	1	0.65
Microcephaly	1	0.65
Migraine	1	0.65
Muscle Spasms	1	0.65
Myalgia	1	0.65
Neoplasm	1	0.65
Oedema	1	0.65
Off Label Use	1	0.65
Ovarian Disorder	1	0.65
Parkinsonism	1	0.65
Penis Disorder	1	0.65
Premature Baby	1	0.65
Progesterone Decreased	1	0.65
Pulmonary Embolism	1	0.65
Refraction Disorder	1	0.65
Rhinitis	1	0.65
Sleep Disorder	1	0.65
Smear Cervix Abnormal	1	0.65
Spinal Osteoarthritis	1	0.65
Swelling	1	0.65
Talipes	1	0.65
Urinary Tract Disorder	1	0.65
Uterine Haemorrhage	1	0.65
Uterine Leiomyoma	1	0.65
Vitiligo	1	0.65

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

/s/

Ronald Wassel
6/23/2008 11:10:31 AM
DRUG SAFETY OFFICE REVIEWER

Melissa Truffa
6/23/2008 11:12:27 AM
DRUG SAFETY OFFICE REVIEWER

Ann W McMahon
6/24/2008 08:44:43 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: January 4, 2007

TO: Eufrecinia DeGuia, Regulatory Project Manager
Barbara Wesley, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Chief, Good Clinical Practice Branch I (GCPB1, HFD-46)
Division of Scientific Investigations (DSI)

FROM: Roy Blay, Ph.D.
Reviewer, GCPB1, DSI, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-945

APPLICANT: Adeza Biomedical

DRUG: Gestiva[®] (17 α -Hydroxyprogesterone Caproate)

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Prevention of Preterm Birth in High Risk Women

CONSULTATION REQUEST DATE: March 24, 2006

DIVISION ACTION GOAL DATE: August 26, 2006

PDUFA DATE: October 20, 2006
(Clinical Inspection Summary generated after PDUFA date by agreement with the review division)

I. BACKGROUND

The indication for the investigational drug 17 α -hydroxyprogesterone caproate is the prevention of preterm birth in high risk women. This drug is not a new molecular entity. Progesterone has been shown to have actions which support gestation and inhibit uterine activity. 17-hydroxyprogesterone (17P) is a naturally occurring metabolite of progesterone. The primary efficacy endpoint for this study is the delivery/gestation date.

The protocol number and title for all three sites is CT-002, A Randomized Trial of 17 α -Hydroxyprogesterone Caproate for prevention of Preterm Birth in High Risk Women

The following sites were selected for inspection because of their relatively large enrollments.

II. RESULTS (by protocol/site):

Name	City, Country	Protocol	Insp. Date	EIR Received Date	Final Classification
Baha Sibai, M.D.	Memphis, TN	CT-002	16-19 Oct 2006	17 Nov 06	VAI
Michael Varner, M.D.	Salt Lake City, UT	CT-002	14-24 Aug 2006	17 Oct 06	VAI
John C. Hauth, M.D.	Birmingham, AL	CT-002	24-25 Jul 2006	2 Aug 06	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol # CT-002

1. Site #04, 45 subjects enrolled

Baha Sibai, M.D.

Professor and Chair OBGYN

University of Cincinnati

Dept of Obstetrics and Gynecology

231 Albert Sabin Way

Cincinnati, Ohio 45267-0526

(study records were maintained at the University of TN, Memphis)

- a. The records of 16 subjects were audited in depth. The audit included, but was not limited to, review of the primary efficacy endpoint, ultrasound records, source documents, CRFs, drug accountability records, serious adverse event reporting, and audit queries and responses.
- b. There were no limitations to the inspection.

- c. The inspection revealed some regulatory violations including the incorrect reporting of the gestational age for subject 035 based on the last menstrual period (LMP) rather than the protocol-required ultrasound dating; the unreported use of a concomitant antibiotic for subject 052; the lack of a Case Report Form for subjects 004 and 052; an incorrectly reported bilirubin value for subject 023; and inadequate records of drug disposition.
 - d. The data appear acceptable in support of the relevant indication.
- 2. Site # 020, 43 subjects enrolled
Michael Varner, M.D.
1151 East 3900 South
Salt Lake City, UT
 - a. The records for 18 subjects were audited in detail. The audit included, but was not limited to, review of the primary efficacy endpoint, ultrasound records, source documents, CRFs, drug accountability records, serious adverse event reporting, and audit queries and responses.
 - b. There were no limitations to the inspection.
 - c. The inspection revealed some regulatory violations including inadequate informed consent for subjects 0036, 0039, 0053, 0057, and 0062; protocol-required procedures performed out-of date for subjects 0022, 0023, and 0056; lack of signatures by the recording individual for data forms for subjects 0021, 0039, and 0060; four instances of missing data or data forms including a Randomization Log for one site (LDSH/Site 2) that was not available for review, a Pregnancy Outcome form for subject 0021 that was not available for review, and an Eligibility and Randomization Form for subject 0049 which contained information regarding a prior pregnancy; and a lack of initials or dates for several corrections to data for subjects 0022, 0033, 0046, 0021, 0039, 0055, 0062, and 0060. Consideration should be given to excluding the data from subject 0021 from the safety and efficacy analysis as the randomization code for this subject was not recorded.
 - d. The data appear acceptable in support of the relevant indication.
- 3. Site #08, 126 subjects enrolled
John C. Hauth, M.D.
618 20th Street South
Birmingham, AL 35233
 - a. The records of 42 subjects were audited. The audit included, but was not limited to, review of the primary efficacy endpoint (delivery date/gestation), adherence to inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.
 - b. There were no limitations on the inspection.

- c. The inspection did not reveal any regulatory violations in the conduct of these studies.
- d. The data appear acceptable in support of the relevant indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Sibai, Hauth, and Varner did not identify any regulatory violations that would appear to have a significant impact on data reliability or patient safety. No follow up action is anticipated for any of these clinical sites at this time. Overall, the data appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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

/s/

Roy Blay
1/10/2007 10:41:55 AM
CSO

Constance Lewin
1/10/2007 02:29:08 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-945**

Supplement # N/A

Efficacy Supplement Type SE-

Trade Name: **Gestiva™**

Established Name: **17- α -Hydroxyprogesterone Caproate Injection**

Strengths: **250mg/mL**

Applicant: **Adeza Biomedical Corporation**

Agent for Applicant:

Date of Application: **April 14, 2006**

Date of Receipt: **April 20, 2006**

Date clock started after UN: N/A

Date of Filing Meeting: **May 30, 2006**

Filing Date: **June 19, 2006**

Action Goal Date (optional): **October 20, 2006**

User Fee Goal Date: **October 20, 2006**

Indication(s) requested: prevention of recurrent preterm labor

Type of Original NDA: (b)(1) (b)(2)
OR

Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

(2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) **5**

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)

Waived (e.g., small business, public health)

Small Business Waiver granted on May 26, 2005

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b).*

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act 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”

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. **YES.**

- List referenced IND numbers: **IND 68,108, IND 53,730, IND (b)(4)**

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **June 27, 2005 (clinical); April 18, 2005 (CMC)** NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic “Content of Labeling” submitted? YES NO
If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Risk Management Plan consulted to ODS/IO? N/A YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application: Not Applicable.

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 30, 2006

BACKGROUND:

The subject of this Priority Review NDA (**PDUFA Goal Date – October 20, 2006**) is 17 α -Hydroxyprogesterone Caproate Injection, 250 mg/mL (or 17P) for the proposed indication of prevention of recurrent preterm birth. The use of 17P will be limited to pregnant women with a prior history of at least one spontaneous preterm birth at less than 37 weeks. The product is intended to be administered once weekly by intramuscular injection of 1 mL. The use of 17P for the prevention of recurrent preterm birth was investigated by the National Institute of Child Health and Human Development (Meis 2003). The results of this research form the clinical basis of this NDA. Meetings were held between Adeza and the Division on January 30, April 5 and July 26, 2004 under PIND 68,108 to discuss the overall program leading to a 505(b)(2) NDA for the product.

Fast track designation was granted by the Division during pre-NDA meeting on June 27, 2005.

Adeza Biomedical's request for a small business waiver of the application fee was granted by the Agency on May 26, 2005.

ATTENDEES: Eufrecina DeGuia, Scott Monroe, Barbara Wesley, Daniel Shames, Julie Beitz, Doanh Tran, Wafa Harrouk, Lynda Reid, Donna Christner, Ameeta Parekh, Shahla Farr, Bronwyn Collier, John Metcalfe, Lisa Kammerman, Teresa Watkins

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Barbara Wesley
Secondary Medical:	Scott Monroe
Statistical:	Lisa Kammerman
Pharmacology:	WafaHarrouk/Lynnda Reid
Statistical Pharmacology:	N/A
Chemistry:	Monica Cooper/Donna Christner/Moo Jhong Rhee
Environmental Assessment (if needed):	Monica Cooper
Biopharmaceutical:	Donny Tran
Microbiology, sterility:	John Metcalfe
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Roy Blay
Regulatory Project Management:	DeGuia/Mercier
Other Consults:	DMETS, DDMAC, DSI, DDRE, MICROBIOLOGY

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed? YES NO

- Advisory Committee Meeting needed? YES, date if known 8-29-2006 NO
- 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? N/A YES NO

CLINICAL MICROBIOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
STATISTICS	N/A		FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
					YES	<input type="checkbox"/> NO <input checked="" type="checkbox"/>
					YES	<input type="checkbox"/> NO <input checked="" type="checkbox"/>
PHARMACOLOGY	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
					YES	<input type="checkbox"/> NO <input checked="" type="checkbox"/>
CHEMISTRY			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
					YES	<input checked="" type="checkbox"/> NO <input type="checkbox"/>
					YES	<input checked="" type="checkbox"/> NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments: **NONE**

**REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Eufrecina DeGuia

Regulatory Health Project Manager
Division of Reproductive and Urologic Products

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES **X** NO

NOTE: The sponsor referenced previously approved drug Delalutin (NDA 10-347 (approved in February 2, 1956) and NDA 16-911 (approved in February 24, 1972). Both applications were withdrawn as requested by the sponsor, Bristol Myer Squibb, on January 20, 2000. The drug has not been marketed for more than 15 years prior to the sponsor's request for withdrawal on September 13, 1999. From review of old records (including Supplements, Periodic Safety Reports, Annual Reports and Division Files) of both NDAs, there is no indication that the applications were withdrawn due to safety or efficacy concerns. The reason for withdrawal was solely due to the discontinuance of marketing of the product.

Addendum: Per October 12, 2006 email from Kim Colangelo, Associate Director for Regulatory Affairs, Office of New Drugs, in her consultation with Office of Regulatory Policy (ORP) and Office of Chief Counsel (OCC), it is acceptable to rely upon our previous findings of safety and efficacy for a withdrawn application AS LONG AS the products were not withdrawn for reasons of safety and efficacy.

The use of 17- α hydroxyprogesterone caproate injection, 250mg/mL for the prevention of recurrent pre-term birth was investigated by the National Institute of Child Health and Human Development under INDs 53,730 and 69,094. NICHD has provided right of reference to information in these INDs and the sponsor included these letters in their NDA submission.

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 10-347 – Delalutin (hydroxyprogesterone caproate injection)
NDA 16-911 – Delalutin (hydroxyprogesterone caproate injection)
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES **X** NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES **X** NO

(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If “Yes,” skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If “No,” please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

NOTE: Please see Comment in Question 1. Delalutin is no longer a listed drug, although it was previously approved. There is no approved hydroxyprogesterone caproate. The drug that is being used in clinical practice for this indication is made through hospital/pharmacy compounding.

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If “Yes,” skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If “No,” please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of “pharmaceutical equivalent” or “pharmaceutical alternative,” as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If “No,” skip to question 6.

If “Yes,” please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This

application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

This drug provides for a new indication; prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth. (Delalutin (NDA 10-347) was approved for treatment of benign gynecological abnormalities and NDA 16-911 was approved for use in advanced adenocarcinoma of the uterus corpus).

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO
9. Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
- NOTE: IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must *subsequently* submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].**
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
 - 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the

labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO

NOTE: Adeza requested a waiver of bioavailability (BA) requirements but the Division believes that waiver is not needed since there is a submitted trial of efficacy and safety which would satisfy the BA requirements if the trial is found to establish safety and efficacy of Gestiva.

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
YES NO
- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 53,730 and (b)(4) _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Eufrecina deGuia
10/16/2006 09:43:05 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		OSE POSTMARKETING SAFETY REVIEW	
FROM: Adrienne Rothstein, PharmD Safety Evaluator, Division of Drug Risk Evaluation (DDRE)		DATE: August 22, 2006	
		OSE PID#: D060555	
TO: Barbara Wesley, MD Medical Officer, Division of Reproductive & Urologic Products (DRUP)		THROUGH: Mark Avigan, MD, CM, Director, Division of Drug Risk Evaluation (DDRE)	
DRUG NAME: Gestiva (17 α -hydroxyprogesterone caproate)		THERAPEUTIC CLASSIFICATION: Synthetic progestin	
NDA #: 21-945		SPONSOR: Adeza Biomedical	
EVENT: Any adverse events related to compounded preparations of 17 α -hydroxyprogesterone caproate from June 2003 to present			
Executive Summary: The Division of Reproductive & Urologic Products (DRUP) is reviewing an NDA from Adeza Biomedical for 17 α -hydroxyprogesterone caproate for the prevention of recurrent pre-term birth. A search of the AERS database was conducted to identify all reports for 17 α -hydroxyprogesterone caproate. A total of 154 reports were retrieved, only 4 reports were received since June 2003 . At the request of DRUP, this review will focus on the reports received since the June 2003 publication of an article about 17 α -hydroxyprogesterone caproate use to prevent recurrent pre-term birth. ¹ For the 4 reports received since June 2003, three reports referred to product use up to 17 weeks gestation and one report was a duplicate. These four MedWatch reports have been previously provided to the medical officer. These few reports of early gestational exposure are of limited value to an assessment of 17 α -hydroxyprogesterone caproate for the prevention of recurrent pre-term birth. Thus, no conclusions can be made at this point in time from the limited number of reports in AERS for 17 α -hydroxyprogesterone caproate. A summary listing of preferred terms for all 17 α -hydroxyprogesterone caproate reports in the AERS database (154 reports) is provided in Appendix 1 as a supplement to this consult.			
Search Date: 08/15/2006		Search Type(s): x AERS ﻓ Literature	
Search Criteria and Strategy: 17 α -hydroxyprogesterone caproate as a suspect drug			

¹ Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al.; National Institute of Child Health (NICHD) and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun 12;348(24):2379-85. Erratum in: N Engl J Med. 2003 Sep 25;349(13):1299.

Search Results:

There are a total of 154 reports in AERS for 7 α -hydroxyprogesterone caproate. Only 4 reports were received since June 2003.

Discussion/Conclusions:

According to the request from DRUP, the Maternal Fetal Medicine Units (MFMU) Network conducted a multicenter, randomized placebo-controlled, double-blinded study on the efficacy and safety of 17 α -hydroxyprogesterone caproate in pregnant women with a previous pre-term birth. The results of this study were published in the New England Journal of Medicine in June 2003. The drug substance used in this study was previously approved under the trade name of Delalutin® for gynecologic indications. Delalutin® was used off-label to prevent miscarriage in early pregnancy (prior to 20 weeks gestation), but the data to support this use was sparse and the practice discontinued over time. Drug marketing was discontinued in the early 1990s because of decreased product usage. However, after publication of the MFMU Network study in June 2003, physicians began to prescribe this drug for pre-term labor prevention and this practice was in part supported by the American College of Obstetricians and Gynecologists.²

Progesterone has been used for pre-term labor prevention because studies have shown that there is an adverse progesterone:estrogen ratio present in preterm labor and progesterone antagonists given at term increase the rate of spontaneous labor. A number of tocolytic drugs have been used to prevent or inhibit preterm labor, including beta-adrenergic receptor agonists, magnesium sulfate, prostaglandin inhibitors, calcium channel blockers, and nitric oxide donors; however, none has been shown to be completely effective.³ DRUP is currently reviewing an NDA from Adeza Biomedical for 17 α -hydroxyprogesterone caproate for the prevention of recurrent pre-term birth. As such the division requested that DDRE review any adverse event reports related to compounded preparations of 17 α -hydroxyprogesterone caproate received from June 2003 to present.

There were a total of **154 reports** in AERS for 17 α -hydroxyprogesterone caproate, **4 reports were received since June 2003**. Two reports described 17 α -hydroxyprogesterone caproate use for the prevention of miscarriage in the first trimester of pregnancy. One report described 17 α -hydroxyprogesterone caproate use during weeks 5-17 of gestation. The fourth report was a duplicate report. These four MedWatch reports have been previously provided to the medical officer. A summary listing of preferred terms for all 17 α -hydroxyprogesterone caproate reports in the AERS database (154 reports) is provided in Appendix 1 as a supplement to this consult. Additional MedWatch reports can be provided upon request.

At this point in time, no conclusions can be drawn from the limited number of reports in AERS for 17 α -hydroxyprogesterone caproate.

Reviewer’s Signature / Date
Adrienne Rothstein / 08-15-06

Team Leader’s Signature / Date
Melissa Truffa / 08-16-06

² ACOG Committee Opinion. Use of progesterone to reduce preterm birth. Obstet Gynecol. 2003 Nov;102(5 Pt 1):1115-6.

³ From Williams Obstetrics 22nd edition. Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC, Wenstrom KD editors McGraw Hill 2005, Chapter 36. Preterm birth.

**Appendix 1. All Preferred Terms in 17 α -Hydroxyprogesterone Caproate Reports
(Any Indication) Received in AERS from 06/01/1969 – 08/15/2006
(n=154)**

Preferred Term (PT)	Count of PTs	Percent of Total
Congenital Anomaly	47	30.52
Multiple Congenital Abnormalities	16	10.39
Injection Site Hypersensitivity	10	6.49
Urticaria	8	5.19
Pruritus	5	3.25
Dermatitis	4	2.60
Breast Cancer Female	3	1.95
Congenital Musculoskeletal Anomaly	3	1.95
Deep Vein Thrombosis	3	1.95
Drug Exposure During Pregnancy	3	1.95
Heart Disease Congenital	3	1.95
Injection Site Reaction	3	1.95
Limb Reduction Defect	3	1.95
Abdominal Pain	2	1.30
Abnormal Labour	2	1.30
Anaphylactoid Reaction	2	1.30
Colitis Ulcerative	2	1.30
Congenital Central Nervous System Anomaly	2	1.30
Cough	2	1.30
Eczema	2	1.30
Headache	2	1.30
Hepatitis	2	1.30
Hirsutism	2	1.30
Hormone Level Abnormal	2	1.30
Injection Site Pain	2	1.30
Injection Site Urticaria	2	1.30
Jaundice	2	1.30
Mental Retardation Severity Unspecified	2	1.30
Myocardial Infarction	2	1.30
Pyrexia	2	1.30
Skin Discolouration	2	1.30
Visual Disturbance	2	1.30
Weight Increased	2	1.30
Abscess	1	0.65
Acute Lymphocytic Leukaemia	1	0.65
Alcohol Interaction	1	0.65
Alcoholism	1	0.65
Alopecia	1	0.65
Anaesthetic Complication	1	0.65
Anomaly Of External Ear Congenital	1	0.65
Asthenia	1	0.65
Benign Neoplasm Of Skin	1	0.65

Preferred Term (PT)	Count of PTs	Percent of Total
Blood Alkaline Phosphatase Increased	1	0.65
Blood Follicle Stimulating Hormone Increased	1	0.65
Bone Disorder	1	0.65
Calcium Metabolism Disorder	1	0.65
Cerebrovascular Accident	1	0.65
Cervix Carcinoma	1	0.65
Chest Pain	1	0.65
Chondrodystrophy	1	0.65
Complications Of Maternal Exposure To Therapeutic Drugs	1	0.65
Congenital Heart Valve Disorder	1	0.65
Congenital Tongue Anomaly	1	0.65
Convulsion	1	0.65
Cyanosis Neonatal	1	0.65
Cyst	1	0.65
Dermatitis Bullous	1	0.65
Dermatitis Contact	1	0.65
Drug Ineffective	1	0.65
Dwarfism	1	0.65
Dysmenorrhoea	1	0.65
Ebstein's Anomaly	1	0.65
Eye Disorder	1	0.65
Facial Palsy	1	0.65
Fallot's Tetralogy	1	0.65
False Labour	1	0.65
Fibromyalgia	1	0.65
Hernia	1	0.65
Hip Dysplasia	1	0.65
Hydrocele	1	0.65
Hypersensitivity	1	0.65
Hypertrophy	1	0.65
Hypocalcaemia	1	0.65
Hypospadias	1	0.65
Infertility Male	1	0.65
Injection Site Inflammation	1	0.65
Injection Site Oedema	1	0.65
Jaundice Neonatal	1	0.65
Leiomyoma	1	0.65
Limb Deformity	1	0.65
Limb Malformation	1	0.65
Maternal Drugs Affecting Foetus	1	0.65
Microcephaly	1	0.65
Migraine	1	0.65
Muscle Spasms	1	0.65
Myalgia	1	0.65
Neoplasm	1	0.65
Oedema	1	0.65

Preferred Term (PT)	Count of PTs	Percent of Total
Off Label Use	1	0.65
Ovarian Disorder	1	0.65
Parkinsonism	1	0.65
Penis Disorder	1	0.65
Premature Baby	1	0.65
Progesterone Decreased	1	0.65
Pulmonary Embolism	1	0.65
Refraction Disorder	1	0.65
Rhinitis	1	0.65
Sleep Disorder	1	0.65
Smear Cervix Abnormal	1	0.65
Spinal Osteoarthritis	1	0.65
Swelling	1	0.65
Talipes	1	0.65
Urinary Tract Disorder	1	0.65
Uterine Haemorrhage	1	0.65
Uterine Leiomyoma	1	0.65
Vitiligo	1	0.65

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

/s/

Adrienne Rothstein
8/22/2006 09:54:47 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
8/22/2006 05:05:07 PM
DRUG SAFETY OFFICE REVIEWER