

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**21945Orig1s000**

***Trade Name:*** Makena

***Generic Name:*** Hydroxyprogesterone Caproate Injection

***Sponsor:*** Hologic, Inc.

***Approval Date:*** 02/03/2011

***Indications:*** To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

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**APPROVAL LETTER**



NDA 021945

**ACCELERATED APPROVAL**

Hologic, Inc.  
Attention: Robb Hesley  
Vice President, Business Development  
1240 Elko Drive  
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) dated April 14, 2006, received April 20, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Makena (hydroxyprogesterone caproate) injection, 250 mg/ml.

We acknowledge receipt of your amendments dated April 20, June 23, July 14, 21, 28, 30, August 14 (2), 22 (2), 23, September 7, 12, 19 (2), 25, October 10, 15, 30, November 3, 2006, January 4, 19, March 14, April 27, June 15, 2007, January 30, April 24 (2), May 16, June 12, August 28, September 3, 25, October 1 (2), 16, 31, December 12, 2008, January 15, 16, March 9, June 4, October 16, 2009, January 15, June 11, July 12, 22, August 18, September 24, October 14 (2), October 25, November 5, 23, 29, December 16, 2010, January 7, 10 (2), 12, 14, 24, 25, and February 3, 2011.

The July 12, 2010, submission constituted a complete response to our January 23, 2009, action letter.

This new drug application provides for the use of Makena (hydroxyprogesterone caproate) injection to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

**CONTENT OF LABELING**

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

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

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the your submission dated December 16, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).”

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 021945.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **ACCELERATED APPROVAL REQUIREMENTS**

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. We remind you of your postmarketing requirements specified in your submission dated January 14, 2011. These requirements, along with required completion dates, are listed below.

1722-1 To complete the clinical trial of hydroxyprogesterone caproate in women with a singleton pregnancy who had a previous spontaneous preterm birth (Protocol #17P-ES-003):

Revised Protocol Submission:	March 2011
Trial Completion:	June 2016
Final Report Submission:	December 2016

1722-2 To complete the clinical follow-up study (Protocol #17P-FU-004) of children born to women who participated in Protocol #17P-ES-003:

Revised Protocol Submission	March 2011
Study Completion Date	July 2018
Final Interim Report Submission	December 2016
Final Report Submission	October 2018

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

## **REQUIRED PEDIATRIC ASSESSMENTS**

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

We are waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is because premenarcheal patients are not at risk of becoming pregnant and the use of this product before menarche is not indicated. We note that you have fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of efficacy data in adults.

## **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 1722-3 Submission of an academic publication of pharmacokinetic data on hydroxyprogesterone caproate and its metabolites in plasma and urine of pregnant women throughout different stages of gestation.

The timetable you submitted on January 14, 2011, states that you will submit this report according to the following schedule:

Final Report Submission: December 2011

- 1722-4 If the publication listed in the above postmarketing commitment is not submitted by December 31, 2011 or if the results from the publication do not include all the relevant findings (e.g., urinary metabolites), you will conduct the following clinical trial:

A non-randomized clinical pharmacokinetic trial of hydroxyprogesterone caproate and its metabolites in pregnant women. This trial will provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine throughout the different gestational stages.

The timetable you submitted on January 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: June 2012

Trial Completion: June 2014

Final Report Submission: November 2014

If the publication in support of postmarketing commitment 1722-3 is submitted on time and deemed adequate, then postmarketing commitment 1722-4 may be released.

1722-5 An *in vitro* study in human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6:

The timetable you submitted on January 14, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 2011  
Study Completion: March 2012  
Final Report Submission: July 2012

Submit clinical protocols to your IND 68108 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

### **PROMOTIONAL MATERIALS**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

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

Please submit one market package of the drug product when it is available.

## **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B-05  
5600 Fishers Lane  
Rockville, MD 20857

## **REPORTING REQUIREMENTS**

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

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIE G BEITZ  
02/03/2011