

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21945Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY (OCP) ADDENDUM

---

NDA: 021945/ SD # 51	Submission Date(s): 07/12/2010, 02/03/2011
Brand Name	Makena®
Generic Name	17- $\alpha$ Hydroxyprogesterone Caproate
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Hologic Inc.
Submission Type	Resubmission/Class 2
Formulation; Strength(s)	Injection for intramuscular use; 250 mg/mL
Indication	Prevention of Preterm Birth

**Recommendation:** NDA 021945 is acceptable from a Clinical Pharmacology perspective.

**Post-Marketing Commitments (PMCs):** The following Clinical Pharmacology PMCs will be communicated to the sponsor in the NDA action letter:

- To submit an academic publication of pharmacokinetic data on hydroxyprogesterone caproate and metabolites in plasma and urine of pregnant women throughout different stages of gestation:  
*Final Report Submission December 2011*
- If the publication described in the above PMC 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 pregnancy. This study will provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine throughout different stages of gestation.  
*Final Protocol Submission June 2012*  
*Trial Completion Date June 2014*  
*Final Report Submission November 2014*
- To conduct a nonclinical *in vitro* study using human hepatocytes to determine whether HPC induces or alters the metabolic activities of CYP1A2, CYP2A6, and CYP2B6:  
*Final Protocol Submission June 2011*  
*Study Completion Date March 2012*  
*Final Report Submission July 2012*

**Labeling:** The revised labeling for Makena as submitted on 02/03/2011 is acceptable from a Clinical Pharmacology perspective.

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

/s/  
-----

SANDHYA K APPARAJU  
02/03/2011

MYONG JIN KIM  
02/03/2011

EDWARD D BASHAW  
02/03/2011  
Division Director Concurrence

**OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW**

---

NDA: 021945/ SD # 51	Submission Date(s): 07/12/2010
Brand Name	[Pending]
Generic Name	17- $\alpha$ Hydroxyprogesterone Caproate
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Hologic Inc.
Submission Type	Resubmission
Formulation; Strength(s)	Injection for intramuscular use; 250 mg/mL
Indication	Prevention of preterm birth

---

**Table of Contents**

1	Executive Summary .....	2
1.1	Recommendation .....	2
1.2	Phase IV Commitments .....	2
2	Summary of Clinical Pharmacology Findings .....	3
3	Labeling.....	4

# 1 Executive Summary

## 1.1 Recommendation

NDA 021945/ SDN # 51 [submitted on 07/12/2010] is acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached with the Sponsor regarding the labeling language.

## 1.2 Phase IV Commitments

The two Clinical Pharmacology Phase IV Commitments (PMC) listed below should be communicated to the sponsor as part of the NDA action letter:

### Clinical Pharmacology

PMC #1: Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.

The timeline for PMC study # 1 is as follows:

Final Protocol Submission:	June 30, 2012
Study Completion Date:	June 30, 2014
Final Report submission:	November 15, 2014

PMC #2: Conduct an *in vitro* study using human hepatocytes to determine whether hydroxyprogesterone caproate induces the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

The timeline for PMC study # 2 is as follows:

Final Protocol Submission:	June 30, 2011
Study Completion Date:	March 31, 2012
Final Report Submission:	July 31, 2012

## 2 Summary of Clinical Pharmacology Findings

A Complete Response (CR) was issued for NDA 021945 on January 23, 2009 citing clinical deficiencies. The July 12, 2010 resubmission addressed these deficiencies and also included a revised draft labeling in the Physician's Labeling Rule (PLR) format.

There is no new Clinical Pharmacology information in this NDA resubmission. The sponsor was made aware of the above potential Clinical Pharmacology post-marketing studies in the CR letter dated 01/23/2009. Sponsor has noted in this resubmission that they will be addressing the two proposed post-marketing study requests as follows:

*# 1: Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.*

Sponsor commits to submit the expected publication by Dr. Steve Caritis [Study of Pharmacology of 17-hydroxy progesterone caproate in Pregnancy; ClinicalTrials.gov identifier: NCT00409825) that will include characterization of hydroxyl progesterone caproate pharmacokinetics in pregnant women.

If the researcher does not provide access to the results by December 31, 2011 or the results do not include all relevant findings then the sponsor agrees to conduct their own study per the following timeline:

Final Protocol Submission:	June 30, 2012
Study Completion Date:	June 30, 2014
Final Report submission:	November 15, 2014

*# 2: Conduct an in vitro study using human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.*

Hologic states that they commit to conducting the above study in human hepatocytes and submit the results to the NDA upon completion. The sponsor has proposed the following timeline in this regard:

Final Protocol Submission:	June 30, 2011
Study Completion Date:	March 31, 2012
Final Report Submission:	July 31, 2012

*Reviewer comments: The proposed timelines for the two post-marketing studies are acceptable from a Clinical Pharmacology perspective.*

### 3 Labeling

Draft labeling submitted in the PLR format has been reviewed. Labeling recommendations communicated by the agency during an earlier review cycle (sent on October 2, 2008) have been accepted by the sponsor in this revised version. Additional revisions to the labeling were proposed by the OCP during this review including the following related to drug metabolism:

In vitro information from a 2008 publication in Drug Metabolism and Disposition by Sharma et al (Vol. 36, No.9; pages 1896-1902) [Identification of Enzymes Involved in the Metabolism of 17 $\alpha$ -Hydroxyprogesterone Caproate: An Effective Agent for Prevention of Preterm Birth] was employed by Clinical Pharmacology discipline to recommend addition of the following statement to Section 12.3 of the proposed labeling:

*“In vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5”.*

In vitro data from this published study indicated that approximately 60 % of the parent drug was metabolized within 60 minutes and the metabolite M2 (structure not yet identified) accounted for almost 50 % of the metabolites formed. In vitro data also indicated the involvement of CYP3A4/5 in the formation of the major metabolite M2. Published data therefore justify inclusion of the above statement related to the involvement of CYP3A isozymes in the section 12.3 of the label.

At this time, further in vivo studies evaluating the effects of enzyme inhibitors or inducers on the systemic exposure (and dosage) of this drug are not warranted. Currently, there is no dose/exposure-response information tied to the efficacy or safety of this drug in the target population (pregnant women at high risk of pre-term labor). Only a single dose of the drug has been evaluated to date in the target population in the completed clinical trial and is currently being evaluated in the ongoing confirmatory trial (#17P-ES-003). The dose selection [fixed dose regimen of 250 mg/mL administered weekly] is empiric and not based on evidence of dose/exposure information. Thus it precludes us from effectively translating any in vivo drug interaction findings into clinically relevant dosage adjustments. In addition, although in vitro data suggests an important role for CYP3A4/3A5, the metabolic pathway of this drug is not yet completely elucidated, particularly with respect to the formation of other metabolites that account for the remaining 50 % of the metabolism.

**Conclusions:** With these revisions, the proposed labeling in PLR format is acceptable from a Clinical Pharmacology perspective.

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

/s/  
-----

SANDHYA K APPARAJU  
12/07/2010

MYONG JIN KIM  
12/09/2010

EDWARD D BASHAW  
12/09/2010

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW AMENDMENT

---

NDA: 21-945	Submission Date(s): 4/24/2008, 8/28/2008
Brand Name	Gestiva
Generic Name	17 $\alpha$ -Hydroxyprogesterone Caproate (17-HPC)
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Cytyc
Submission Type	Resubmission
Formulation; Strength(s)	Solution for injection, 250 mg/mL
Indication	Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth

---

### 1 Executive Summary

After the original Clinical Pharmacology review of this resubmission was entered into DFS on 8/26/2008, the sponsor replied to several Clinical Pharmacology requests (letter dates 8/6/2008 and 8/21/2008) on 8/28/2008. This amendment addresses the sponsor's reply and provides an updated recommendation.

#### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 21-945 acceptable provided the labeling comments and Phase IV commitment requests are adequately addressed.

If the NDA is to be approved, the Phase IV commitments in section 1.2 should be included in the approval letter. If a Complete Response (CR) is to be issued, the Phase IV commitments in section 1.2 should be noted in a CR letter to document that the sponsor has agreed to provide such information post-approval as part of conditions for approval.

#### 1.2 Phase IV Commitments

- The sponsor will provide data characterizing the pharmacokinetics (PK) of 17  $\alpha$ -hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women throughout different gestational stages.
- The sponsor will conduct an in vitro study using human hepatocytes to determine whether 17-HPC induces or alters the metabolic activities of CYP1A2, CYP2A6, and CYP2B6.

## **2 Question Based Review**

### **2.1 What information was requested of the Sponsor during the review and what was the sponsor's response?**

Two letters with Clinical Pharmacology related requests and recommendations were sent to the sponsor on 8/6/2008 and 8/21/2008. The sponsor provided response to both letters on 8/28/2008. A summary of the Clinical Pharmacology related requests and recommendations and sponsor's response are presented below.

#### **Letter dated 8/6/2008:**

The following recommendations were sent to sponsor:

*We have the following requests and recommendations regarding the design of the phase 4 safety and efficacy study protocol:*

- *Collection of the 3<sup>rd</sup> pharmacokinetic (PK) sample at 1 to 4 days post Dose 8, 9, or 10 should be stratified such that the numbers of samples collected are evenly distributed among days 1, 2, 3, and 4 post dose. This would ensure that there will be appropriate data for the population PK modeling.*
- *Sponsor should consider storing a separate aliquot of each PK blood sample from the phase 4 safety and efficacy study for potential future analysis of any important metabolite(s) that may be identified following completion of the phase 1 PK study (i.e., the study being conducted by Dr. Steve Caritis).*

#### **Reviewer's comments:**

- The first request was modified in a letter dated 8/21/2008 (see below). See sponsor's response to the amended request below.
- The sponsor agreed to the recommendation and incorporated the collection of an additional aliquot of each PK blood sample in section 4.7 of the protocol.

#### **Letter dated 8/21/2008:**

The following recommendations were sent to sponsor:

##### ***Clinical Pharmacology***

*In the Advice letter dated August 6, 2008; we made the following request regarding the design of the Phase 4 safety and efficacy study protocol:*

- *Collection of the 3<sup>rd</sup> pharmacokinetic (PK) sample at 1 to 4 days post Dose 8, 9, or 10 should be stratified such that the numbers of samples collected are evenly distributed among days 1, 2, 3, and 4 post-dose. This would ensure that there will be appropriate data for the population PK modeling.*

*We would like to revise our previous request listed above to the following:*

- *Collection of the 3<sup>rd</sup> pharmacokinetic (PK) sample at 1 to 4 days post Dose 8, 9, or 10 should be expanded to capture the entire dosing interval of 7 days. We*

*recommend that the 3rd PK sampling be stratified such that the samples collected are evenly distributed among the following 5 time intervals: day 1, day 2, day 3, day 4, and days 5-6 post-dose. Each patient is still required to provide only 3 PK samples.*

**Reviewer's comments:** The sponsor agreed to the recommendation and the collection of the 3<sup>rd</sup> PK sample was expanded and incorporated in section 6.3 of the protocol.

#### ***Additional Clinical Pharmacology comment***

- *In vitro metabolism study with human liver microsomes (Study report 304-1177-02) indicated that 17-alpha hydroxyprogesterone caproate (17-HPC) increased the metabolic activity of CYP1A2, CYP2A6, and CYP2B6. We recommend that you conduct follow up studies in human hepatocytes in vitro to determine whether 17-HPC induces or alters the metabolic activities of these CYP isoforms.*

**Reviewer's comments:** The sponsor agreed to conduct post approval in vitro studies using human hepatocytes to determine whether 17-HPC induces or alters these CYP isoforms. This agreement should be captured in the Complete Response or Approval letter.

## **2.2 What are the changes to the Phase IV commitments?**

The original review of the resubmission included 2 phase 4 commitments as listed below.

1. *The sponsor will provide data characterizing the pharmacokinetics (PK) of 17  $\alpha$ -hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women at several periods throughout the pregnancy.*
2. *The sponsor will obtain sparse PK samplings as agreed to in the planned Phase 4 efficacy and safety study and analyze the data to assess exposure-response relationships (e.g., time to birth) and effect of body weight and other covariates, as needed, on the PK of 17-HPC.*

At this time, commitment #1 should remain as we are not certain that the sponsor's proposal to provide literature data would be sufficient. Commitment #2 is no longer necessary since the sponsor has agreed to perform the additional safety and efficacy study. In addition, the Division of Reproductive and Urologic Products has indicated that approval will be granted only after the sponsor starts the study.

A new commitment should be added to reflect the agreement by sponsor to conduct follow up in vitro studies to determine whether 17-HPC induces or alters CYP1A2, CYP2A6, and CYP2B6.

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

/s/

-----  
Doanh Tran  
1/15/2009 12:16:24 PM  
PHARMACOLOGIST

Myong-Jin Kim  
1/15/2009 12:37:29 PM  
BIOPHARMACEUTICS

Dennis Bashaw  
1/15/2009 01:10:10 PM  
BIOPHARMACEUTICS

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

---

NDA: 21-945	Submission Date(s): 4/24/2008
Brand Name	Gestiva
Generic Name	17 $\alpha$ -Hydroxyprogesterone Caproate (17-HPC)
Reviewer	Doanh Tran, Ph.D.
Team Leader (Acting)	Sandhya Apparaju, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Cytec
Submission Type	Resubmission
Formulation; Strength(s)	Solution for injection, 250 mg/mL
Indication	Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth

---

### Table of Contents

Table of Contents .....	1
1 Executive Summary .....	1
1.1 Recommendation .....	1
1.2 Phase IV Commitments .....	1
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings .....	2
2 Question Based Review .....	3
3 Detailed Labeling Recommendations .....	11
4 Appendices.....	12
4.1 Clinical Pharmacology review of original NDA 21-945. ....	12
4.2 Proposed labeling (Original with Clinical Pharmacology’s recommended revisions) .....	12
4.3 Clinical Pharmacology memo at time of resubmission .....	12

### 1 Executive Summary

#### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 21-945 acceptable provided the labeling comments and Phase IV commitment requests are adequately addressed.

#### 1.2 Phase IV Commitments

1. The sponsor will provide data characterizing the pharmacokinetics (PK) of 17  $\alpha$ -hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women at several periods throughout the pregnancy.
2. The sponsor will obtain sparse PK samplings as agreed to in the planned Phase 4 efficacy and safety study and analyze the data to assess exposure-response relationships (e.g., time to birth) and effect of body weight and other covariates, as needed, on the PK of 17-HPC.

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

NDA 21-945 for 17-HPC was submitted on April 14, 2006. It was found acceptable from a Clinical Pharmacology perspective with a recommendation to obtain additional data post-approval. The original NDA received an Approvable action on October 20, 2006 due to Clinical, Pharmacology and Toxicology, and Chemistry, Manufacturing and Controls deficiencies. The current submission is a resubmission of NDA 21-945. No new clinical pharmacology studies were done since the original submission. The resubmission is seeking the same indication of prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth and the same dosing regimen of 250 mg 17-HPC intramuscularly once weekly that was sought in the original NDA.

There were 2 new literature reports on the in vitro and preclinical metabolism of 17-HPC since the original NDA review. The new data was consistent with and support previous findings that 17-HPC can be metabolized but the caproate ester bond appears to remain intact. One of these reports refer to other results from the same laboratory (report in press and was not available for a direct review) showing that 17-HPC and its metabolites enters the fetal circuit in an in vitro dual perfused placental lobule experiment when 17-HPC was introduced to the maternal circuit. These data suggest that the fetus may be exposed to 17-HPC and its metabolites when 17-HPC is administered to a pregnant woman. Fetal exposure to 17-HPC and its metabolites has not been evaluated in a clinical study.

The following is the summary as was provided in the Clinical Pharmacology review of the original NDA submission (Signed off in DFS on 09/21/2006).

- Limited pharmacokinetics (PK) information in pregnant women is derived from a published report (DAVIS et al. 1960) where single doses of Carbon-14 labeled 17-HPC were given to 4 pregnant women at 10 to 12 weeks gestation. The data showed that approximately 50% of radioactivity was excreted in the feces and an average of 29.7% of radioactivity was excreted in urine over 12 - 15 days. Maximum total plasma radioactivity was reached 5 days following IM injection followed by a slow decline. The dose in mg and formulation were not specified.
- PK information in non-pregnant women is derived from a literature report by Onsrud et al. (1985) using a formulation that is very similar to the to-be-marketed formulation. In this report, single dose of 1000 mg 17-HPC in endometrial cancer patients (n=5) resulted in a mean serum  $C_{max}$  of 65 nM,  $T_{max}$  of 4.6 days, and terminal half-life of 7.8 days. The same report also contained trough serum 17-HPC at weeks 1, 2, 3, 4, 5, and 13 after 5 daily loading doses of 1000 mg each followed by weekly or bi-weekly administration of 1000 mg 17-HPC (n = 6 – 9). The serum trough 17-HPC levels at week 13 were approximately 130 nM and 70 nM for the weekly and bi-weekly doses, respectively.
- Sponsor provided a preliminary in vitro metabolic profile study in human hepatocytes. About 70% was metabolized in 3 hours and there was no additional metabolism by 4 hour. Metabolism in the first 3 hours was apparently linear with half-life of 1.56 hr. The main metabolic reactions were reduction, hydroxylation, and conjugation. 17-HPC appeared to be metabolized by both phase I and phase II reactions. The study was not designed to determine the specific enzyme(s) responsible for 17-HPC metabolism. The major metabolites identified with LC/MS/MS were all acetyl conjugates with the caproate group retained. Report by Davis et al. (1960) suggested that in humans the majority of 17-HPC metabolizes into glucuronide, sulfate, and an unknown conjugate, as measured in urine and feces.
- In vitro enzyme inhibition study using human liver microsomes showed that 17-HPC slightly inhibited (15.5 – 37.7% inhibition at 20  $\mu$ M) CYP2C8, 2C9, and 2C19 with  $IC_{50}$  values >20  $\mu$ M. 17-HPC inhibited CYP3A4 by 49.4% at 20  $\mu$ M. These  $IC_{50}$  values are much higher than the 17-HPC concentrations observed in non-pregnant women (Onsrud, 1985).

Data not available in the NDA:

- In vivo drug interaction studies
- Quantitative in vivo metabolism
- Enzyme induction studies
- Studies examining the effect of intrinsic factors such as age, hepatic impairment, and renal impairment

The formulation in the phase 3 clinical trial is the same as the proposed commercial formulation. Sponsor provided comparability data between the commercial manufacturer and the 2 manufacturers of the clinical lots and they were found acceptable.

## 2 Question Based Review

### 2.1 What is the regulatory history of NDA 21-945?

NDA 21-945 for 17-HPC was submitted on April 14, 2006. The proposed indication was prevention of recurrent preterm birth in pregnant women with a history of at least one spontaneous preterm birth. The proposed therapeutic dose was 250 mg 17-HPC intramuscularly once weekly beginning at 16 weeks 0 days to 20 weeks 6 days of gestation and ending at birth or week 37 of gestation.

The NDA contained limited pharmacokinetic (PK) and clinical pharmacology information of 17-HPC. The NDA was found acceptable from a Clinical Pharmacology perspective for the following reasons: 1) The final formulation, the labeled dose and duration of use are identical to those used in the Phase 3 safety and efficacy trial, 2) The Phase 3 trial allowed normal medical care including other concomitant treatments. Additionally, the medical need for effective prevention of preterm birth was considered. The Clinical Pharmacology review included 3 recommendations for sponsor to obtain additional PK data (Clinical Pharmacology review of the original NDA 21-945 by Dr. Doanh Tran, signed off in DFS on September 21, 2006; Attached in Appendix 4.1).

An Approvable action was issued on October 20, 2006 and listed Clinical, Pharmacology and Toxicology, and Chemistry, Manufacturing and Controls deficiencies. The approvable letter included 3 Clinical Pharmacology issues (listed below) that would need to be addressed postmarketing, if the product were to be approved upon resubmission.

The Clinical Pharmacology issues were included in the Approvable letter under the section entitled "Additional issues that would need to be addressed postmarketing, if the product were to be approved" were as follow:

"In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of [17-]HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy [comment #1].
- Assess the [17-]HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects [comment #2].

- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on [17-<sup>3</sup>H]HPC pharmacokinetics [comment #3].”

In the current submission, the sponsor is seeking the same indication, dose, and dosing regimen as was sought in the original NDA submission.

## 2.2 How is this review of the resubmission organized?

No new Clinical Pharmacology studies were done since the original NDA submission. However, the sponsor discussed the following, which formed the focus of this review: 1) new literature data involving the metabolism of 17-HPC and 2) the sponsor's proposal to address to the three Clinical Pharmacology comments in the Approvable letter.

For background information and a review of data in the original submission, please see Appendix 4.1, Clinical Pharmacology review of the original NDA 21-945 submission (signed off in DFS on September 21, 2006).

## 2.3 What is the new information on the metabolism of 17-HPC and does it change any previous conclusions?

There are 2 new literature reports (Yan et al., American Journal of Obstetrics and Gynecology 2008; 198:229.e1-229.e5 (report #1) and Yan et al., Biochemical Pharmacology 2008; 75:1848-1857 (report #2)) on the in vitro metabolism of 17-HPC. The following conclusions can be drawn from these reports:

- The results from both reports indicated that the caproate ester bond is not hydrolysed in vitro in human plasma or liver and placental S9 fraction or microsomes, consistent with the previous conclusion in the review of the original NDA that the caproate ester bonds remained intact.
- Results from report #2 indicated that 17-HPC is metabolized by human liver and placental microsomes in vitro, likely by one or more Cytochrome p450 isozymes, to hydroxylated metabolites. This data is inline with previous studies by the sponsor using human hepatocytes that indicated the presence of hydroxylation, reduction, and conjugation reactions.
- The authors of report #2 indicated that a separate report (in press, not available for review) from the same laboratory showed that 17-HPC and its metabolites entered the fetal circuit in a dual perfused placental lobule in vitro experiment in which 17-HPC was introduced to the maternal circuit. These data suggest that the fetus may be exposed to 17-HPC and its metabolites when 17-HPC is administered to a pregnant woman. Fetal exposure to 17-HPC and its metabolites has not been evaluated in a clinical study. The sponsor indicated that an ongoing clinical pharmacology study includes assessment of cord 17-HPC and its metabolites concentrations (See section 2.4).

The following provides additional details of the experiments and results.

Literature report #1 evaluated the metabolism of 50 µmol/L of [3H, 14C]17-HPC to [3H]17-HP and [14C]caproate in the presence of human plasma or liver and placental S9 fractions. Neither [3H]17-HP or [14C]caproate were detected (femtomole levels) after incubation at 37 °C for 60 minutes. Separate incubations using rabbit liver carboxyesterase, porcine liver carboxyesterase and equine serum butyrylcholinesterase also showed no hydrolysis of [3H, 14C]17-HPC to [3H]17-HP and [14C]caproate. These data indicate that the caproate ester bond was not hydrolyzed in vitro under the conditions studied.

Literature report #2 evaluated the metabolism of 60 µmL of [3H, 14C]17-HPC by human liver and placenta microsomes. Incubation with human liver microsomes for 60 minutes resulted in the metabolism of 55% of 17-HPC and the formation of 21 metabolites. All metabolites retained the caproate moiety. The metabolites only formed in the presence of NADPH-generating system indicating the reaction is catalyzed by one or more Cytochrome P450 isozyme(s). Further analysis with LC/MS suggested that 1, 2, or 3 hydroxyl groups were introduced into 17-HPC.

Incubation with human placenta microsomes yielded 5 metabolites (report #2). Three of the metabolites were the same as identified in the liver microsome incubations. The other 2 metabolites were not observed in the liver microsomes incubations. They were suggested by the report's authors to be mono-hydroxylated 17-HPC based on LC/MS analysis. About 3% of 17-HPC was metabolized in this incubation, indicating that metabolism of 17-HPC was less in the placenta compared to the liver.

The literature report #2 also indicated that results from a separate study by the same laboratory (In press, not yet published as of 7/29/2008) evaluating the placental transfer, metabolism, and distribution of [3H, 14C]17-HPC using in vitro dual perfused placental lobule revealed that 17-HPC was metabolized and retained by the placental tissue. The authors also reported that the metabolite formed was more polar than the parent compound. Both the parent 17-HPC and the metabolite were transferred to the fetal circuit. The complete literature report is not available for review. These data suggest there is a potential for maternal-fetal transfer of 17-HPC and its metabolites.

2.4 In the resubmission of NDA 21-945, did the sponsor adequately address Clinical Pharmacology comment #1 in the Approvable letter?

Clinical Pharmacology comment #1 requested the sponsor to characterize the pharmacokinetics of 17-HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.

The rationale for this request was as follows (as stated in the original NDA review):

*This would provide an understanding of the pharmacokinetic properties of 17-HPC in the target population. The metabolite characterization would provide more clarity to the in vivo metabolic fate of 17-HPC that showed inconsistency between in vivo and in vitro in the currently available data. Steady state concentration in target population would also aid in assessing potential drug interactions. Consistent with the usefulness of PK information, several members of the Reproductive and Urology Product Advisory Committee suggested the need to understand 17-HPC PK in pregnant women.*

In this resubmission, the sponsor stated that a study evaluating the pharmacology of 17P in pregnant women with a previous history of preterm birth (ClinicalTrials.gov identifier: NCT00409825) is being conducted by the University of Pittsburgh and NIH (Principal Investigator: Steve Caritis, MD). The sponsor has spoken with Dr. Caritis regarding the status of the study and the projected completion date of December 2008. A summary of the study protocol was provided by the sponsor and presented below. The sponsor proposed to provide to the Division a literature summary of the data that emerge from this study to address comment #1.

**Summary of the study being conducted by Dr. Caritis:**

Based on the information provided by the sponsor and on the ClinicalTrials.gov website, the following is known: The Caritis/NIH study is enrolling approximately 60 subjects that would receive weekly intramuscular injections of 250 mg 17-HPC. The source of the 17-HPC study drug is (b) (4), the same source of 17-HPC study drug used in the Phase 3 study (17P-CT- 002). During the study, blood samples will be drawn at several periods throughout

the second and third trimesters of pregnancy. Specifically, 10 mL of blood will be drawn prior to the 5<sup>th</sup> weekly administration of 17-HPC during the second trimester of pregnancy, and then once daily for seven consecutive days post-dose. Ctroughs will be drawn prior to weekly administration of 17-HPC from the sixth weekly dose in the second trimester until the last scheduled dose in the 3<sup>rd</sup> trimester. A full intensive PK sampling as was performed following the 5<sup>th</sup> dose would also be done on the last scheduled dose.

The primary outcome measure is the change in area under the concentration vs. time curve in the second and third trimesters of pregnancy. Secondary outcome measures include standard pharmacokinetic parameters (C<sub>max</sub>, T<sub>max</sub>, C<sub>1/F</sub>, Cl<sub>r</sub>, V<sub>F</sub>, MRT, and t<sub>1/2</sub>); plasma concentrations of 17-HPC prior to each injection; metabolites of 17-HPC in maternal blood and urine; genotype of 17-HPC metabolizing enzymes; CRP, CRH, and other progestational biomarkers; plasma progesterone, 17 alpha-hydroxyprogesterone, estradiol; fetal and neonatal outcomes including cord 17-HPC and metabolite concentrations; maternal:fetal drug ratios.

The sponsor proposed that because of the comprehensive scope and size of the Caritis/NIH 17-HPC pharmacokinetic study and the invasive nature of conducting such a study, particularly in pregnant women, the sponsor believes it is not necessary or appropriate to duplicate this study. The sponsor included the following statement in their submission: "Provided that the results of the Caritis/NIH study are sufficient to characterize the pharmacokinetics of 17P [17-HPC] and its metabolites, Cytac would anticipate conducting no further research in this area."

*Reviewer's comments:*

1. *Based on the description provided by the sponsor, the Caritis/NIH study should provide substantial data on the PK of 17-HPC and its metabolites in pregnant women. However, the details of the study being conducted by Dr. Caritis were not provided and therefore the summary provided could not be confirmed. Furthermore, the sponsor plans to submit the literature report of the Caritis/NIH and it is not known at this time what will be included in the literature report or the level of details that would be included. Due to these uncertainties, it is not clear if this study would adequately address the issues in comment #1.*
2. *This reviewer agrees with Sponsor that if the Caritis/NIH study does provide sufficient data to characterize the PK of 17-HPC and its metabolites in pregnant women, then additional studies by the sponsor would not be needed. The sponsor should consider obtaining and provide to the FDA the study protocol and study results including the raw data and results of bioanalytical methods validation to aid in the review of this study.*
3. *If NDA 21-945 is to be approved, it should be reiterated as a postmarketing commitment that the sponsor will provide data characterizing the PK of 17-HPC and its metabolites in plasma and urine in pregnant women at several periods throughout the pregnancy. The sponsor has the option to conduct their own study or provide literature data to satisfy the commitment. Literature reports are best when supplemented by the actual study protocol, bioanalytical methods validation results, and raw PK data that may provide insights that are not captured in the literature report.*

2.5 In the resubmission of NDA 21-945, did the sponsor adequately address Clinical Pharmacology comment #2 in the Approvable letter?

Clinical Pharmacology comment #2 requested the sponsor to assess the 17-HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.

The rationale for this request was as follows (as stated in the original NDA review):

*Sparse serum levels of 17-HPC would allow an analysis of exposure-response relationship that may be helpful in optimizing therapy. Exposure response data is also useful in assessing the effect of any changes in PK due to intrinsic or extrinsic factors.*

*This valuable data can be obtained from blood collections at some of the scheduled weekly injection visits or other office visits and should not substantially increase burden on enrolled patients or the sponsor.*

*Varied body weight may affect the pharmacokinetic of 17-HPC. 17-HPC serum levels collected for exposure response analysis can be used to determine the effect (if any) of body weight on 17-HPC exposure. The AC committee rightfully pointed out that the large range of body mass index (BMI) may lead to different individual drug concentrations and that it should be evaluated.*

In this resubmission, the sponsor proposed to use a population pharmacokinetic/pharmacodynamic (PK/PD) approach to explore the exposure-response relationship and the effect of BMI on the pharmacokinetics of 17P. The sponsor has incorporated a population pharmacokinetic substudy into the postmarketing efficacy and safety study (note: there is one postmarketing safety and efficacy study protocol being proposed, the protocol has not been given an identification number). Pharmacokinetic assessments will be made on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) enrolled in the PK substudy stratified according to BMI in order to analyze the dose-plasma concentration-time relationship of 17-HPC (See overview of study protocol below).

A population pharmacokinetic model will be built using a nonlinear mixed-effect modeling approach. The structural pharmacokinetic model will contain pharmacokinetic parameters, such as clearance and volume, as fixed-effect parameters. The relationship of 17P steady-state exposure, with relevant pharmacodynamic response markers, such as gestational age at delivery, will be defined using an appropriate PK/PD model, such as an inhibitory maximum observed effect (Emax) model.

#### **Overview of the proposed postmarketing safety and efficacy study protocol:**

##### **Study objectives:**

The primary objective of this study is to determine if treatment with 17P reduces the rate of preterm birth < 35<sup>0</sup> weeks (note: 35<sup>0</sup> denotes 35 weeks 0 day gestation) of gestation in women with a singleton pregnancy, aged 16 years or older, with a previous singleton spontaneous preterm delivery.

One of the secondary objectives is to evaluate the PK/PD of 17P in a subset of pregnant women.

##### **Study design:**

This study is a multi-center, randomized, double-blind, placebo-controlled clinical trial in women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. A total of 1230 subjects will be randomized in a 2:1 ratio to receive either 17-HPC or placebo, respectively. Subjects will receive weekly intramuscular injections of 250 mg 17-HPC from randomization (16<sup>0</sup> through 20<sup>6</sup> weeks of gestation) until 36<sup>6</sup> weeks of gestation or delivery, whichever occurs first. Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo), stratified according to BMI ( $\leq 28$  and  $> 28$ ) to analyze the dose-plasma concentration-time relationship of 17-HPC. Randomized subjects will be followed up to 30  $\pm$  7 days after the last dose of study drug or discharge from the delivery hospitalization, whichever occurs later. Neonates of randomized subjects will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first.

**Table 1: Schedule of Events**

Procedures	Baseline <sup>a</sup>	Initial Evaluation <sup>b</sup>	Active Treatment Period <sup>c</sup>	Delivery and Hospitalization	End of Study Visit <sup>d</sup>
	Visit 1	Visit 2	Visits 3 to 36 <sup>6</sup> Weeks of Gestation or Delivery		
Informed consent <sup>e</sup>	X				
Medical records release <sup>f</sup>	X				
Medical/obstetrical history	X				
Demographic information/social history	X				
Ultrasound (14 <sup>0</sup> through 20 <sup>3</sup> )	X <sup>g</sup>				
Document previous preterm delivery	X				
Brief physical examination <sup>h</sup>	X				
Height	X				
Weight	X	X	X		
Prior medications <sup>i</sup>	X	X			
Concomitant medications <sup>j</sup>			X	X	X
Determine project gestational age and estimated date of confinement	X				
Schedule initial evaluation and randomization visit	X				
Trial injection		X			
Randomization <sup>k</sup>			X		
Collect blood sample for pharmacokinetic analysis			X <sup>l</sup>		
Study drug administration			X <sup>m</sup>		
Record adverse events (AEs) <sup>n</sup>		X <sup>o</sup>	X	X	X
Record pregnancy complications			X	X	
Record additional risk factors of early fetal loss	X			X	
Maternal delivery information				X	
Neonatal information <sup>p</sup>				X	

<sup>a</sup> Visit will occur within 7 days before randomization.

<sup>b</sup> No later than 20<sup>3</sup> weeks of gestation and at least 3 days before randomization.

<sup>c</sup> Subject will report to the clinical site weekly for study drug administration until 36<sup>6</sup> weeks of gestation or delivery, whichever occurs first.

<sup>d</sup> Should occur 30 ± 7 days after the last dose of study drug or 30 ± 7 days after delivery, whichever occurs later.

<sup>e</sup> To be completed before performing any baseline procedures.

<sup>f</sup> Must be signed by subject/legal guardian in order to obtain medical records of previous deliveries.

<sup>g</sup> If a 14<sup>0</sup> to 20<sup>3</sup> weeks of gestation ultrasound to rule out fetal anomalies has not been performed as part of standard prenatal care, one must be performed prior to randomization.

<sup>h</sup> A brief physical examination including a visual head-to-toe inspection of the subject's anterior and posterior torso and extremities.

<sup>i</sup> Prior medications includes all medications taken during pregnancy from the estimated date of confinement until study drug is randomly assigned.

<sup>j</sup> Concomitant medications must be recorded in the case report form through the End of Study Visit.

<sup>k</sup> Between 16<sup>0</sup> and 20<sup>6</sup> weeks of gestation.

<sup>l</sup> Three blood samples will be drawn from the PK population at the following times: (1) Before study drug dosing at either Visit 7 or 8 (ie, dose 5 or 6). (2) Before dosing at either Visit 9 or 10 (ie, Dose 7 or 8). (3) After dosing at a separate, non-dosing visit 1 to 4 days after Visit 10, 11, or 12 (ie, 1 to 4 days after Doses 8, 9, or 10).

<sup>m</sup> Study drug will be administered weekly (once every 7 ± 2 days) from randomization (Visit 3) through 36<sup>6</sup> weeks of gestation or delivery, whichever occurs first.

<sup>n</sup> All subjects, regardless of when they deliver, should be contacted for an End of Study Visit to obtain AE information including medications to treat AE(s). The contact can be either in person or by telephone and should occur 30 ± 7 days after the last dose of study drug or 30 ± 7 days after delivery, whichever occurs later.

<sup>o</sup> AEs are recorded from administration of the trial injection through the End of Study Visit including medications to treat the AE. Preterm birth is an anticipated outcome and is not considered an AE.

<sup>p</sup> Neonates will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first.

### **Study drug:**

The study drug is 250 mg of 17-HPC given by the study site personnel as a 1 mL intramuscular injection (or 1 mL of placebo inert oil). The study drug will be dispensed by the study coordinator at each site and stored as multiple-dose vials containing 17-HPC or a placebo of inert oil.

### **Prior medications**

Prior medications, defined as all medications taken during pregnancy from the date of conception until study drug is randomly assigned will be recorded in the subject's case report form (CRF) at Baseline (Visit 1), Initial Evaluation (Visit 2), and Randomization Visit (Visit 3). This will include all prescription drugs, herbal products, vitamins (including prenatal vitamins), minerals, and other over-the-counter (OTC) medications.

### **Concomitant Medications**

All concomitant medications will be recorded in the subject's CRF from the time the subject is randomly assigned at Visit 3 through the End of Study Visit. This will include all prescription drugs, herbal products, vitamins (including prenatal vitamins), minerals, and OTC medications. Any changes in concomitant medications will also be recorded in the subject's CRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator.

### **Inclusion and exclusion criteria:**

One PK related exclusion criterion was included in the protocol:

- Progesterone treatment in any form (i.e., vaginal, oral, intramuscular) during current pregnancy.

### **PK samplings:**

Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) to analyze the dose-plasma concentration-time relationship of 17P. Participation in the PK substudy will be stratified by BMI ( $\leq 28$  and  $> 28$ ),

such that approximately 40% and 60% of subjects are in each BMI category, respectively. All subjects randomized into the clinical trial will participate in the PK substudy until the necessary number of subjects in each treatment group and BMI category are enrolled. Enrollment into the PK substudy within each treatment group and BMI strata will be monitored by unblinded site personnel.

A total of 3 blood samples will be drawn from each subject in the PK substudy:

1. Before study drug dosing at either Visit 7 or 8 (i.e., Dose 5 or 6).
2. Before study drug dosing at either Visit 9 or 10 (i.e., Dose 7 or 8).
3. At a separate, non-dosing visit 1 to 4 days after Visit 10, 11, or 12 (i.e., 1 to 4 days after Doses 8, 9, or 10).

#### **PK/PD analysis:**

PK/PD analysis will be conducted in the PK Population. Nonlinear mixed effects modeling will be used to analyze the dose-plasma concentration-time data of 17-HPC using a population PK approach and the NONMEM software (Icon Development Solutions, Ellicott City, MD).

As a starting point for the sparse data to be collected in the study, a structural PK model will be initially developed. The structural PK model will contain PK parameters such as clearance and volume as fixed-effect parameters. The dependence of apparent clearances and volumes on BMI will be examined as primary covariate. The sponsor anticipated that a two-compartment model with first order absorption and elimination rates will be adequate to describe this data. In addition, the between-subject (inter-subject) variability in the parameter estimates and the random residual error in the data will be estimated with an appropriate error model. The best base model will be selected based on the standard criteria such as minimum objective function value and diagnostic plots.

The relationship of 17-HPC steady-state exposure with the PD response markers will be defined using an appropriate PK/PD model such as an inhibitory maximum observed effect ( $E_{max}$ ) model. The selection of a starting base PD model will be based on graphical evaluation of the exposure-response data as well as biological meaningfulness.

The PK Population will be stratified by BMI at the time of randomization. Body mass index will be investigated as the primary covariate for its potential influence on the volume of distribution and clearance of 17-HPC through its formal inclusion in the NONMEM models. Statistical significance will be concluded by suitable reduction in the objective function.

Other factors including gender, race, and number of previous preterm delivery(ies) may be considered as covariates. Findings of a clinical relevant magnitude will be investigated further.

PK/PD models to evaluate effects on concomitant medications that may effect the inhibition or induction of 17-HPC will be evaluated and modeled as data permit.

#### **Reviewer's comments:**

1. *The study design is generally acceptable. Based on the 2 trough samplings and the post dose sampling focusing on the early part of the PK profile (i.e., Days 1 – 4 post pose), estimation of clearance (CL) and volume of distribution (V) should be feasible. Good estimation of CL and V would fulfill the main objectives of estimating exposure-response and testing for effect of BMI on drug exposure. A determination of one-compartment or two-compartment model structure may not be achieved. However, this is not a priority objective.*
2. *The sponsor is stratifying the subject based on BMI at time of randomization. It is not known if a patient's body weight at randomization would be reflective of her body weight later in pregnancy during the time of PK samplings. However, body weight will also be collected at each injection visit and be available for modeling if needed.*

3. *The 3<sup>rd</sup> PK sampling at 1 to 4 days post dose in one interval without specific stratification does not ensure an even distribution of patients over the time interval. Even distribution is essential to obtain a good fitting of the structural model. In addition, PK samplings during the latter half of the dosing interval (i.e., days 5 – 7) would be useful to better describe the PK model structure. This reviewer recommends that the 3<sup>rd</sup> PK sampling be stratified such that an equal number of samples is obtained in each of the following sampling intervals: 1 day, 2 days, 3 days, 4 days, and 5 – 7 day after Doses 8, 9, or 10). Each subject would be stratified to obtain the 3<sup>rd</sup> PK sample in one of the 5 sampling time intervals, thus ensuring there would be appropriate data for PK modeling without the burden of additional samplings. [This comment was conveyed to sponsor in an Advice letter dated 8/21/2008]*
4. *Only 17-HPC will be measured. Sponsor should consider storing a separate aliquot of PK blood samples for potential analysis in the future of any important metabolite(s) that may be identified following completion of the Phase 1 PK study (i.e., the Caritis/NIH study or a separate study by Sponsor). [This comment was conveyed to sponsor in an Advice letter dated 8/6/2008]*
5. *The clearance and volume of distribution of 17-HPC may change with progression of pregnancy and may need to be incorporated into the population PK model.*

2.6 In the resubmission of NDA 21-945, did the sponsor adequately address Clinical Pharmacology comment #3 in the Approvable letter?

Clinical Pharmacology comment #3 requested the sponsor to collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17-HPC pharmacokinetics.

The sponsor indicated that concomitant medication information will be collected throughout the efficacy and safety study. Effects of known strong inducers or inhibitors of metabolizing enzymes on pharmacokinetics of 17-HPC will be examined by inclusion as covariates in the population PK model, if feasible.

*Reviewer's comments:*

1. *The sponsor's proposal is acceptable.*

### **3 Detailed Labeling Recommendations**

Please see attached Sponsor's proposed label with recommended revisions from Clinical Pharmacology in Appendix 4.2.

## **4 Appendices**

- 4.1 Clinical Pharmacology review of original NDA 21-945.
- 4.2 Proposed labeling (Original with Clinical Pharmacology's recommended revisions)
- 4.3 Clinical Pharmacology memo at time of resubmission

**Appendix 4.1:**

**Clinical Pharmacology review of the original NDA 21-945**

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

---

NDA: 21-945	Submission Date(s): 04/20/2006
Brand Name	Gestiva™
Generic Name	17 alpha-Hydroxyprogesterone caproate
Reviewer	Doanh Tran, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
ORM division	Division of Reproductive and Urology Products
Sponsor	Adeza Biomedical
Relevant IND(s)	68-108
Submission Type; Code	Original; N (Priority review)
Formulation; Strength(s)	Solution for injection; 250 mg/mL
Indication	Prevention of recurrent preterm birth

---

### Table of Contents

Table of Contents .....	1
1 Executive Summary .....	2
1.1 Recommendation .....	2
1.2 Phase IV Commitments .....	2
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings .....	2
2 Question Based Review .....	4
2.1 General Attributes .....	4
2.2 General Clinical Pharmacology.....	5
2.3 Intrinsic Factors .....	13
2.4 Extrinsic Factors.....	13
2.5 General Biopharmaceutics.....	15
2.6 Analytical Section.....	16
3 Detailed Labeling Recommendations .....	19
4 Appendices.....	19
4.1 Proposed labeling .....	19

## 1 Executive Summary

This NDA for 17 alpha-hydroxyprogesterone caproate (17-HPC) contains very limited pharmacokinetic and clinical pharmacology information in non-pregnant and pregnant women. Additional drug metabolism and drug interaction information would have been useful in providing clearer directions to optimize therapy. Despite these limitations, the final formulation, the labeled dose and duration of use are identical to those used in the Phase 3 safety and efficacy trial. The Phase 3 trial allowed normal medical care including other concomitant treatments. Additionally, the medical need for effective prevention of preterm birth should be considered.

### 1.1 Recommendation

This reviewer finds NDA 21-945 acceptable from a clinical pharmacology perspective provided the labeling comments are adequately addressed.

In the event that there are additional clinical trials planned or requested the following pharmacokinetic elements are recommended to be included as part of those trials to allow for better understanding of 17-HPC pharmacokinetics and optimal dosing:

1. Characterize the pharmacokinetics of 17 alpha-hydroxyprogesterone (17-OHP), 17-HPC and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy.
2. Assess the 17-HPC exposure response relationship and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling of all subjects.
3. Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17-HPC PK.

The Division is prepared to work with Sponsor to design trials that would incorporate these elements.

### 1.2 Post Marketing Commitments

None

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- Limited pharmacokinetics (PK) information in pregnant women is derived from a published report (DAVIS et al. 1960) where single doses of Carbon-14 labeled 17-HPC were given to 4 pregnant women at 10 to 12 weeks gestation. The data showed that approximately 50% of radioactivity was excreted in the feces and an average of 29.7% of radioactivity was excreted in urine over 12 - 15 days. Maximum total plasma radioactivity was reached 5 days following IM injection followed by a slow decline. The dose in mg and formulation were not specified.
- PK information in non-pregnant women is derived from a literature report by Onsrud et al. (1985) using a formulation that is very similar to the to-be-marketed formulation. In this report, single dose of 1000 mg 17-HPC in endometrial cancer patients (n=5) resulted in a mean serum  $C_{max}$  of 65 nM,  $T_{max}$  of 4.6 days, and terminal half-life of 7.8 days. The same report also contained trough serum 17-HPC at weeks 1, 2, 3, 4, 5, and 13 after 5 daily loading doses of 1000 mg each followed by weekly or bi-weekly administration of 1000 mg 17-HPC (n = 6 – 9). The serum trough 17-HPC levels at week 13 were approximately 130 nM and 70 nM for the weekly and bi-weekly doses, respectively.
- Sponsor provided a preliminary in vitro metabolic profile study in human hepatocytes. About 70% was metabolized in 3 hours and there was no additional metabolism by 4 hour. Metabolism in the first 3 hours was apparently linear with half-life of 1.56 hr. The

main metabolic reactions were reduction, hydroxylation, and conjugation. 17-HPC appeared to be metabolized by both phase I and phase II reactions. The study was not designed to determine the specific enzyme(s) responsible for 17-HPC metabolism. The major metabolites identified with LC/MS/MS were all acetyl conjugates with the caproate group retained. Report by Davis et al. (1960) suggested that in humans the majority of 17-HPC metabolizes into glucuronide, sulfate, and an unknown conjugate, as measured in urine and feces.

- In vitro enzyme inhibition study using human liver microsomes showed that 17-HPC slightly inhibited (15.5 – 37.7% inhibition at 20  $\mu$ M) CYP2C8, 2C9, and 2C19 with  $IC_{50}$  values  $>20 \mu$ M. 17-HPC inhibited CYP3A4 by 49.4% at 20  $\mu$ M. These  $IC_{50}$  values are much higher than the 17-HPC concentrations observed in non-pregnant women (Onsrud, 1985).

Data not available in the NDA:

- In vivo drug interaction studies
- Quantitative in vivo metabolism
- Enzyme induction studies
- Studies examining the effect of intrinsic factors such as age, hepatic impairment, and renal impairment

The formulation in the phase 3 clinical trial is the same as the proposed commercial formulation. Sponsor provided comparability data between the commercial manufacturer and the 2 manufacturers of the clinical lots and they were found acceptable.

#### 1.4 Rationale for recommendations

1. Characterize the pharmacokinetics of 17-OHP, 17-HPC and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy. (The periods should be spaced out evenly to allow assessment of PK changes as a pregnancy progresses. For example, a 3-period study design may include assessments at 16 – 20, 24 – 28, and 32 – 34 weeks gestation.)

*This would provide an understanding of the pharmacokinetic properties of 17-HPC in the target population. The metabolite characterization would provide more clarity to the in vivo metabolic fate of 17-HPC that showed inconsistency between in vivo and in vitro in the currently available data. Steady state concentration in target population would also aid in assessing potential drug interactions. Consistent with the usefulness of PK information, several members of the Reproductive and Urology Product Advisory Committee suggested the need to understand 17-HPC PK in pregnant women.*

*The 17-OHP concentrations would help determine the effect of 17-HPC administration on the endogenous 17-OHP (if any) and may aid in a better understanding the mechanism of 17-HPC action.*

2. Assess the 17-HPC exposure response relationship and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling of all subjects.

*Sparse serum levels of 17-HPC would allow an analysis of exposure-response relationship that may be helpful in optimizing therapy. Exposure response data is also useful in assessing the effect of any changes in PK due to intrinsic or extrinsic factors. This valuable data can be obtained from blood collections at some of the scheduled weekly injection visits or other office visits and should not substantially increase burden on enrolled patients or the sponsor.*

Varied body weight may affect the pharmacokinetic of 17-HPC. 17-HPC serum levels collected for exposure response analysis can be used to determine the effect (if any) of body weight on 17-HPC exposure. The AC committee rightfully pointed out that the large range of body mass index (BMI) may lead to different individual drug concentrations and that it should be evaluated.

3. Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17-HPC PK.

This information may be helpful in assessing the need for dosing restriction or indicate the need for drug interaction studies.

## 2 Question Based Review

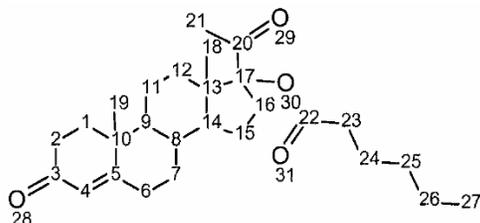
### 2.1 General Attributes

#### 2.1.1 What is 17 alpha-Hydroxyprogesterone caproate?

17 alpha-Hydroxyprogesterone caproate (17-HPC) is a synthetic progestin hormone, which is an esterified derivative of 17 alpha-hydroxyprogesterone. 17-HPC has a molecular formula  $C_{27}H_{40}O_4$  and an average molecular weight of 428.6. It has stronger progestational activity and a prolonged duration of action in a female rabbit model (JUNKMANN 1954).

17-HPC was a previously approved product Delalutin (NDA 10-347 and NDA 16-911). Delalutin was withdrawn by FDA in year 2000 following discontinuation of marketing by the NDAs' sponsor.

The molecular structure is indicated below.



#### 2.1.2 What is the proposed indication?

Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

17-HPC is not currently the subject of any approved NDA.

#### 2.1.3 What is the proposed dose and route of administration?

The proposed therapeutic dose of Gestiva™ for prevention of recurrent preterm birth is 250 mg intramuscularly once weekly at a dose of 250 mg (1 mL) beginning at 16 weeks 0 days to 20 weeks 6 days of gestation to week 37 of gestation or until birth. This dosage schedule is identical to that used in the phase 3 clinical efficacy trial. Different doses and dosing schedules such as one with a loading dose was not available for review to determine if better efficacy can be obtained.

#### 2.1.4 What is preterm birth?

Preterm birth is defined as birth occurring before 37 weeks gestation. It affects approximately 12.5% of all live births in the US. It is a leading cause of infant death and long-term disability. The risk of severe complications increases with younger preterm infants, particularly those born at less than 32 weeks gestation. Consequently, treatments that can decrease preterm delivery at less than 32 weeks in addition to a reduction at less than 37 weeks are valued.

The etiology of spontaneous preterm birth is not well understood but likely involves many factors. It was suggested in a recent report by the Institute of Medicine that preterm birth should be described as a “syndrome of multiple pathophysiological pathways”. A number of factors have been identified placing women at risk for preterm birth including low pre-pregnancy weight, drug and alcohol abuse, African American race, lower socioeconomic status, medical complication during pregnancy, multifetal gestation, cervical structural abnormality, and previous pregnancy history. Among these, a history of spontaneous preterm birth is one of the strongest predictors (17 – 40%) for a preterm birth in a subsequent pregnancy (Goldenberg 2002).

#### 2.1.5 What are the current treatments for prevention of preterm birth?

There are no approved treatments for prevention of preterm birth. According to a press release in January 2005 by the American College of Obstetricians and Gynecologists (ACOG), there are no widely established treatments to prevent preterm birth. There is a need for safe and effective treatments to prevent preterm birth.

According to a recent review (Vidaeff and Ramin 2006), some of the current interventions being used for preventions of preterm birth include cervical cerclage, antimicrobial therapy, and progesterone supplementation. However, there are mixed results reported with all of these intervention methods. Additionally, cervical cerclage and antimicrobial therapy may only be used in specific conditions (e.g., patients with cervical insufficiency or identified infection).

Previous interventions such as enhanced prenatal care, patient education, cessation of work, bed rest, home uterine monitoring, prophylactic tocolytics, nutritional supplements, and social support had been advanced as prophylactic interventions but eventually could not be associated with any consistent evidence of benefits (Vidaeff and Ramin, 2006).

## 2.2 General Clinical Pharmacology

### 2.2.1 What is the pharmacokinetics of 17-HPC following intramuscular (IM) injection?

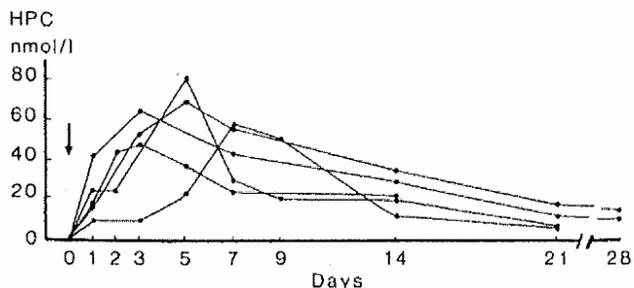
#### **Single-dose PK:**

A paper published by Onsrud et al. (1985) described the PK of 17-HPC in 5 non-pregnant female endometrial carcinoma patients receiving single dose of 1000 mg 17-HPC intramuscularly. The formulation was not indicated but it was assumed that the commercial product available in Norway in 1985, namely Primolut-Depot®, was used. Primolut-Depot® formulation was similar to the phase 3 clinical trial for prevention of preterm labor formulation except the omission of 2% benzyl alcohol as a preservative.

Figure 1 shows the PK profile of 17-HPC as reported by Onsrud et al. (1985). Adeza extracted data points from the graph and calculated PK parameters (Table 1). Adeza determined that only 4 of 5 subjects had enough data for calculation of  $t_{1/2}$ . The excluded profile (Subject 3) only had data up to 14 days. The data show that 17-HPC was bioavailable with a mean  $T_{max}$  of 4.6 days and prolonged half-life of approximately 7.8 days in non-pregnant female subjects. The average  $C_{max}$  following a single dose of 1000 mg IM was  $27.8 \pm 5.3$  ng/mL (i.e.,  $64.9 \pm 12.4$  nM).

Upon examination of the data, it is debatable that only 3 subjects had reliable  $t_{1/2}$  estimates. Subject 5 had data up to 21 days but the absorption phase was prolonged and of the 3 data points used for  $t_{1/2}$  calculation, one was very close to the  $C_{max}$  making it unreliable for use in  $t_{1/2}$  calculation. If that subject was also excluded the  $t_{1/2}$  estimates would be  $9.1 \pm 1.8$  days. The difference between the estimates is small and should not significantly affect the weekly dosing schedule of this drug. Therefore, this reviewer accepts the calculations by sponsor.

**Figure 1: Individual serum concentrations of 17-HPC in 5 endometrial cancer patients after intramuscular administration of a single dose of 1000 mg (arrow).**



**Table 1: PK parameters for single dose of 1000 mg 17-HPC in non-pregnant endometrial cancer patients (calculated from data extracted from figure 1).**

Parameter	Mean $\pm$ SD	n
$C_{max}$ (ng/mL)	27.8 $\pm$ 5.3	5
$T_{max}$ (days)	4.6 $\pm$ 1.7	5
AUC <sub>0-7</sub> (ng•day/mL)	118 $\pm$ 36	5
AUC <sub>0-14</sub> (ng•day/mL)	217 $\pm$ 49	5
$t_{1/2}$ (days)	7.8 $\pm$ 3.0	4
AUC <sub>0-∞</sub> (ng•day/mL)	355 $\pm$ 136	4

Some PK information is available in foreign labels of Proluton Depot, 250 mg/ml 17-HPC by Schering AG, a product that is said to be the same as Primalut Depot, the formulation that Onsrud likely used. The label for Austria, dated 1998, stated that elimination half-life is 6 days and the label for Turkey, also dated 1998, stated “Hydroxyprogesterone caproate is found in the blood only 2 hours after intramuscular administration. Maximum plasma levels are reached on the second day after injection. After that the concentration decreased slowly. 14 days after injection 60% of the maximum value can still be found. The elimination is protracted.” The elimination half-life of 6 days or “elimination is protracted” is consistent with Onsrud’s mean half-life of 7.8 days. The  $T_{max}$  of 2 days is shorter than observed in Onsrud’s study and is not clear if it is due to data variability ( $T_{max}$  range of 3 – 7 days) or perhaps a higher dose in Onsrud’s study. If a higher dose was used, such dose would require higher volume of injection and may reduce the rate of transfer of the fat soluble 17-HPC out of its oil formulation into the circulation. If the latter is true, the lower dose of 250 mg in this NDA may result in shorter  $T_{max}$  that is closer to 2 days than 4.6 days.

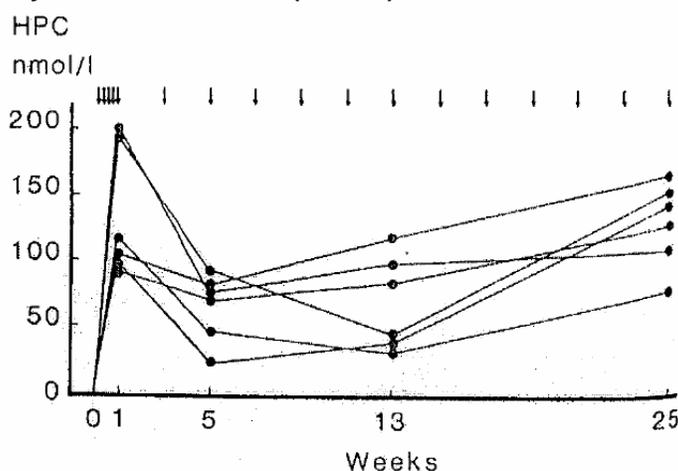
In support of the PK results by Onsrud et al. (1985), the sponsor submitted a publication by Davis et al. (DAVIS et al. 1960) where they reported that after administration of [C14]-17-HPC to 4 pregnant women (three were at 10-12 week gestation, the 4th was not specified, dose in mg and vehicle not specified), the highest level of radioactivity, which would be a combination of unchanged 17-HPC and metabolites, in the plasma occurred at the fifth day after intramuscular

injection, similar to the 4.6 days estimate from Onsrud's data. The total plasma radioactivity declined slowly over the next 6 days of measurement. However, this data is of limited usefulness due to the many unknowns (e.g., dose, formulation, and metabolite PK).

### Multiple-dose PK:

Onsrud's study also included a multiple dose portion where six non-pregnant subjects received 1000 mg 17-HPC daily for 5 days followed by 12 injections of 1000 mg once every two weeks for a total duration of 25 weeks. The results are shown in figure 2. The high serum concentration achieved after 5 loading doses in the first week declined then appeared to rise slowly from 5 to 25 weeks with the bi-weekly dosing. The timing of samples at weeks 5, 13 and 25 were not specified but assumed to be  $C_{trough}$ . These data show a trend of increasing concentration from week 13 to 25, indicating steady state was not reached by 13 weeks. Additionally, due to the expected long  $t_{1/2}$ , the concentration at week 5 might be lower had there been no loading doses (as proposed in this NDA), further suggesting the presence of increasing trough levels from week 5 to week 13.

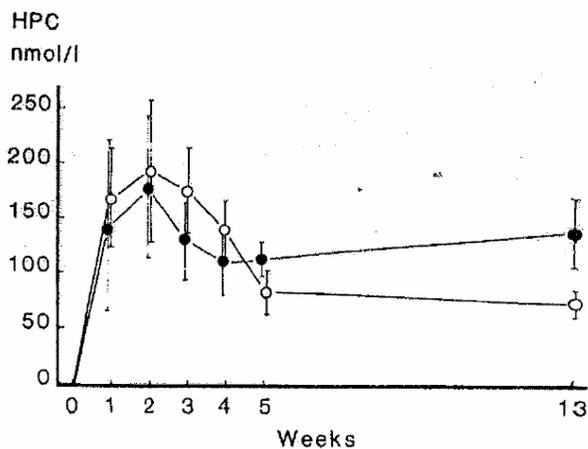
**Figure 2: Individual serum concentrations of 17-HPC in 6 non-pregnant female patients treated with IM injection for 25 weeks. 1000 mg 17-HPC was given daily for 5 days, and every 2 weeks thereafter (arrows).**



Separately, there were 2 cohorts of subjects both receiving five daily doses of 1000 mg 17-HPC. One cohort then received 1,000 mg 17-HPC weekly, and the other cohort received 1,000 mg biweekly. The mean concentrations for 6 - 9 subjects are shown in Figure 3 (also taken directly from Onsrud 1985). The  $C_{trough}$  at week 13 in women receiving weekly injection of 1000 mg 17-HPC was  $58.2 \pm 13.3$  ng/mL (or  $136 \pm 31$  nM). The sponsor pointed out that between 5 and 13 weeks, there was no apparent change in serum concentrations for the group receiving 1,000 mg 17-HPC bi-weekly, but there was a possible increase for the group receiving 1,000 mg weekly although the error bars indicate similar concentrations at both times.

To this reviewer, it is not clear if steady state was reached by week 13 if the loading doses were not present. In figure 3, serum 17-HPC level declines from week 2 to 5 even though a dose was given at week 3, suggesting that the trough value at week 5 may be significantly influenced by the loading doses and would be lower if the 5 loading doses were not present. A similar trend is also observed with the weekly dosing group, except that week 5 concentration appeared to hold steady with a slight rise by week 13. In addition, figure 2 shows a trend of increasing concentration from week 5 to week 13 and week 25. These data suggests that weekly dosing of 17-HPC without loading dose may result in drug accumulation with increase in serum 17-HPC concentration for at least 13 weeks.

**Figure 3: Serum concentration of 17-HPC in endometrial cancer patients who after a loading dose of 1000 mg daily for 5 days were treated with either 1000 mg 17-HPC every week (solid circles) or with 1000 mg every 2 weeks (open circles). Each point on the curves represents the mean  $\pm$  SE from 6 – 9 patients.**



In summary, there is limited PK information in non-pregnant females to show that 17-HPC is bioavailable following IM injection. The  $t_{1/2}$  is sufficiently long such that once weekly dosing interval would unlikely result in substantial minima in serum level of 17-HPC in non-pregnant females. Based on the single dose  $t_{1/2}$ , steady state may be reached by 39 - 46 days. However, trough data suggest that slight increase in concentration may continue for at least 13 weeks of dosing. The concentration data at 13 and 25 weeks should provide good estimates of concentration using a protocol without loading dose, as by that time the effect of loading dose should be minimal.

#### 2.2.2 What is the pharmacokinetics of 17-HPC in pregnant women?

Limited pharmacokinetics (PK) information in pregnant women is derived from a published report (DAVIS et al. 1960) where single doses of [ $C^{14}$ ] labeled 17-HPC were given as IM injections to 4 pregnant women (three were at 10-12 week gestation, the 4th was not specified) and urine and feces samples were collected for 7, 12, 14, and 15 days, respectively. The doses of radioactivity administered ranged from 25.9 to 28.8 microcuries. The doses in mg and formulation were not specified.

Maximum total plasma radioactivity was reached 5 days following IM injection followed by a slow decline (figure 4). The data showed that approximately 50% of radioactivity was excreted in the feces and an average of 29.7% (range 27.6 to 29.8%) of radioactivity was excreted in urine over 12 - 15 days (figure 5). The 4<sup>th</sup> patient excreted 15.3% of the injected radioactivity in urine during a collection period of 7 days. A plateau in daily urinary excretion curve was reached within 36 to 48 hours after the injection and maintained for the next 5 to 6 days (figure 6). The largest amounts of radioactivity were found in the feces expelled between 48 and 142 hours following injection.

Figure 4: Radioactivity in total plasma volume and daily urinary output at various time interval following IM of 4-C<sup>14</sup>-17-alpha-hydroxyprogesterone caproate.

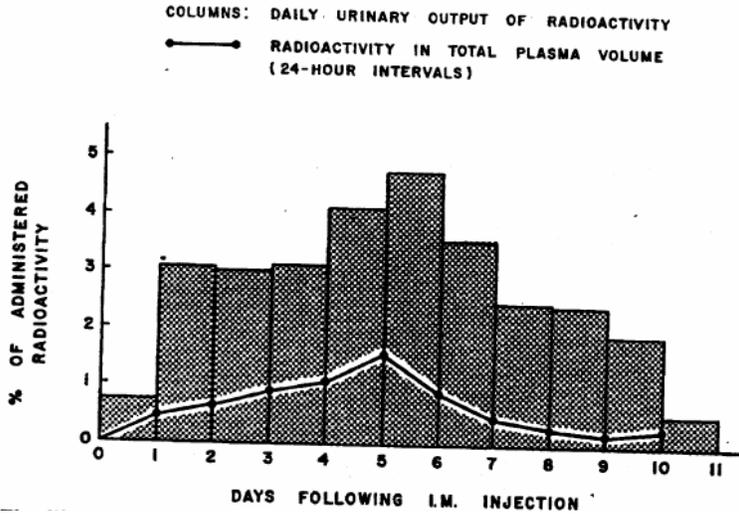
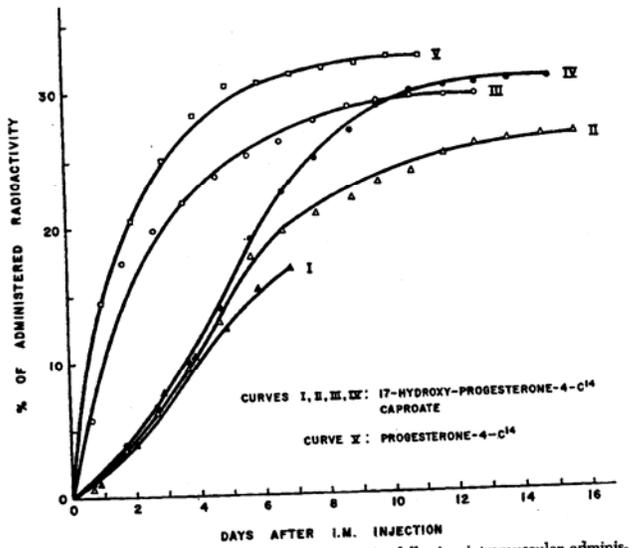
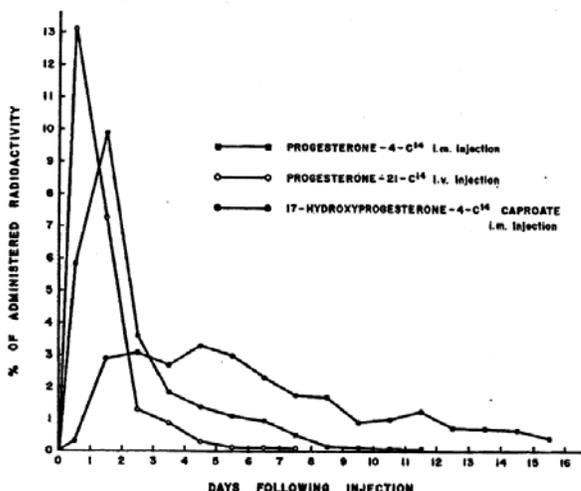


Figure 5: Cumulative excretion of radioactivity following intramuscular administration of [C14]-labeled 17-HPC (curves I – IV) and progesterone (curve V) to pregnant patients. Progesterone excretion is more rapid.



**Figure 6: Pattern of urinary excretion of radioactivity following administration of [C14]-labeled progestins.**



In summary, following IM injection of 17-HPC (formulation and dose in mg not specified) there is a delay of about 36 hours for maximum urinary excretion and 48 hours for fecal excretion. Maximum total plasma radioactivity was reached 5 days after injection and approximately 80% of radioactivity was excreted in urine and feces within 15 days after injection. As will be discussed in the metabolism section, the metabolites were suggested to be mainly conjugates, including glucuronide, sulfate and an unknown conjugate.

### 2.2.3 What is the metabolic pathway for 17-HPC?

17-HPC was shown to be metabolized by human hepatocytes in vitro (report 304-1176-01). Under sponsor's experimental conditions, the elimination was via an apparent first order process during the first 3 hours of incubation with an in vitro half-life of 1.56 hr. No further metabolism was present beyond 3 hr during the 4-hour incubations.

17-HPC metabolic profile was assessed in an in vitro hepatocyte study (report 304-1176-01) with tentative metabolite structure determination by LC/MS and Metabolynx software. LC/MS identified 22 putative metabolites. Further structural elucidation of five selected metabolites was done by LC/MS/MS analysis. The structural prediction of the Metabolynx software using mass ratio alone was not accurate since 3 of the 5 metabolites chosen for further elucidation by LC/MS/MS contradict earlier prediction by Metabolynx. The 5 metabolites chosen for further analysis were based on being the largest peaks and were predicted to be acetyl conjugates (H-6 and H-13), sulfate conjugate (H-2 and H-5), or a minor metabolite that was thought to have the caproate removed (H-14).

LC/MS/MS analysis indicated that all five were acetyl conjugates with the caproate group remain attached (figures 7 - 11). The data indicate the presence of reduction, hydroxylation, and conjugation. Of the 4 major metabolites, the phase 2 acetyl conjugation could theoretically proceed directly in the 3-carbon position ketone group (following CYP-independent reduction). In the case of the minor metabolite H-14, addition of a functional group containing oxygen by phase 1 metabolism must precede the conjugation reaction. Direct conjugation would represent the major elimination pathway for 17-HPC if in vivo metabolism parallels that observed in vitro. It should be noted that the structural elucidation by LC/MS/MS method is also not definitive.

Figure 7: metabolite H-2

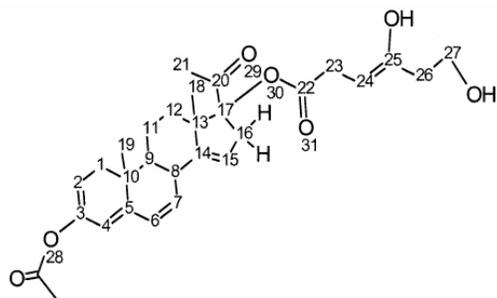


Figure 8: metabolite H-5

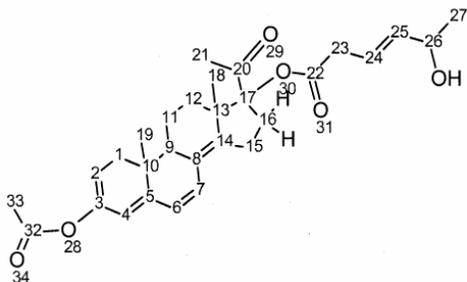


Figure 9: metabolite H-6

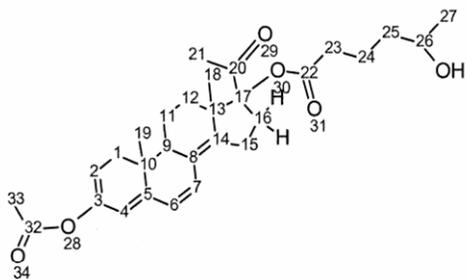


Figure 10: metabolite H-13

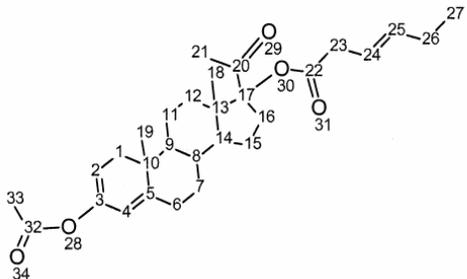
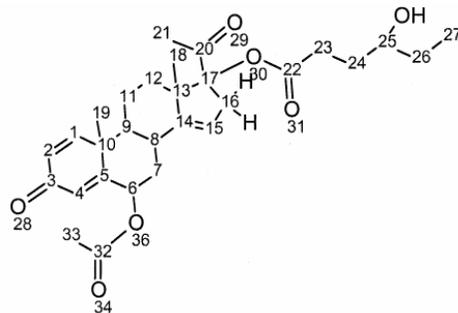


Figure 11: metabolite H-14



Davis et al. (1960) analyzed the urine from 3 subjects given ring labeled [C<sup>14</sup>]-17-HPC by extracting the free steroids in chloroform from a 10% sodium carbonate medium that would be expected to retain the hydrophilic conjugated metabolites. In each case, the sodium carbonate fraction retained the majority (75 – 81%) of the radioactivity, indicating that most of the metabolites excreted in the urine are conjugates or other polar metabolites. This finding may also indicate the presence of unchanged 17-HPC in the chloroform fraction but the authors indicated they were unable to find unchanged 17-HPC in urine or feces.

They reported that in one patient, treatment of urine with beta-glucuronidase before extraction indicated that some (about 20 to 25 % of total urine radioactivity), but not all the conjugates were glucuronides (DAVIS et al. 1960). Subsequent extraction with ether after hydrolysis at pH 1 indicated the possible presence of sulfate conjugates (about 15 – 22 of total urine radioactivity). The amount of conjugates hydrolyzable by hot acid ranged from 1.5 to 11% of total radioactivity. Thus in this particular patient, only 57 to 83% of the urinary radioactivity was extractable following all the hydrolytic procedures. Only 67% and 39% were extractable in 2 other patients, respectively, using the same procedures. The authors of the report suggested the presence of metabolites that are formed by “an unknown mode of conjugation”.

In summary, 17-HPC can be metabolized by human hepatocytes in vitro. The major metabolites found in vitro were all acetyl conjugates, while an in vivo literature report suggested that 17-HPC metabolizes into glucuronide, sulfate, and an unknown conjugate. The reason for in vitro and in vivo inconsistency is not known.

#### 2.2.4 What is the support that the caproate ester remained attached?

There are several pieces of evidence that suggest the caproate ester are not hydrolysed and remain attached following 17-HPC administration.

- 1.) The in vitro study mentioned above showed that all major metabolites retained the caproate. There were two minor metabolites that were suggested by LC/MS to have the caproate removed. However, further analysis using LC/MS/MS of one metabolite showed that the caproate was actually not removed.
- 2.) In a study by Wiener et al. (WIENER et al. 1961), following a 2-hour incubation in rat liver homogenate, they found 2 metabolites representing about 25 and 2% of starting 17-HPC amount, respectively, and both metabolites retained the caproate ester.
- 3.) The report by Wiener also included unpublished report by one co-author, Lupu, where [C<sup>14</sup>]-17-HPC labeled on one of the ring was given to 2 subjects and [C<sup>14</sup>]-17-HPC labeled on the caproate was given to a third subject and elimination of radioactivity was measured in the urine for 6 or 10 days. The result showed that the amounts of free and total 17-HPC radioactivity in the urine for the subject receiving the caproate-labeled 17-HPC were slightly higher than the amounts for the two that received the ring-labeled 17-HPC. If the caproate, and its associated radioactivity, were released from 17-HPC by metabolism, one would expect lower level of radioactivity to associate with steroids in urine. This data suggest that the caproate ester bond is not cleaved during metabolism.
- 4.) Sponsor suggested that the position of the caproate group at C-17 of the HPC molecule is not readily available for biochemical degradation by esterases due to steric hindrance.

The data is not conclusive, however they all suggest that the caproate ester is not removed during in vivo metabolism of 17-HPC.

#### 2.2.5 What are the protein binding properties of 17-HPC?

It has been shown that 17-HPC binds weakly to corticosteroid binding globulins ( $K_a = 4.3 \times 10^{-10} \pm 3 \times 10^{-11} \text{ M}^{-1}$ ) (Westphal 1986). Since steroids are bound by corticosteroid binding globulins and

albumin, this suggests that most of 17-HPC are bound to albumin in blood. Albumin generally binds steroids weakly and may be anticipated here with 17-HPC.

A label for 17-HPC injection (Proluton Depot, 1998) in Austria indicates that "[t]he active ingredient is 95% bound to plasma protein in vitro (human plasma)".

It appears that 17-HPC is extensively bound to plasma protein (95%) including albumin and corticosteroid binding globulins.

## 2.3 Intrinsic Factors

### 2.3.1 What are the effects of intrinsic factors on 17-HPC pharmacokinetics?

There is no submitted information on the effect of age, hepatic impairment, renal impairment, or any other intrinsic factors on the PK of 17-HPC. The sponsor indicated that they have done a current literature search and did not find any relevant information.

In general, as this drug is expected to be metabolized by hydroxylation and conjugation, likely by the liver, hepatic impairment may decrease the clearance of this drug. Urinary excretion of radio labeled 17-HPC over 15 days was approximately 30% (DAVIS et al. 1960) indicating that renal clearance may account for 30% or more of the excretion of 17-HPC. Thus renal impairment may also decrease clearance to some extent. However, since the conjugate metabolites may also be excreted in feces, which accounted for 50% of the excretion of 17-HPC, the effect of renal impairment may not be significant if there is compensatory excretion via biliary excretion.

## 2.4 Extrinsic Factors

### 2.4.1 What are the effects of other drugs on the PK of 17-HPC?

There is no submitted data to assess the potential effect of concomitant administration of other drugs on the PK of 17-HPC. Based on the in vitro metabolism study, which suggests that 17-HPC may be partly metabolized by phase 1 metabolism, there is potential for drug interactions with inhibitors and inducers of CYP enzymes. However, for purpose of drug elimination, there is potential for direct conjugation at the C-3 ketone position and therefore elimination of 17-HPC without the need for CYP enzymes. The reliability of these in vitro data to predict in vivo metabolism is not clear as there were conflicting results as to which conjugate(s) are formed. For example, in vivo data suggest the formation of glucuronide, sulfate and an unknown conjugate. Whereas the in vitro data only found acetyl conjugate in a system capable of forming glucuronide and sulfate conjugates of the positive control 7-ethoxycoumarin. Additional detailed studies of 17-HPC metabolic pathway in vitro and in vivo are needed for a clearer conclusion.

### 2.4.2 What are the effects of 17-HPC on the metabolism of other drugs?

There was an in vitro inhibition study examining the effect of 17-HPC on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 enzyme activity using CYP isoform-specific substrates in human liver microsomes (report 304-1177-02). The substrates used and the corresponding isoforms were: phenacetin (CYP1A2), coumarin (CYP2A6), S-mephenytoin (CYP2B6), paclitaxel (CYP2C8), tolbutamide (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), chloroxazone (CYP2E1), and testosterone (CYP3A4). The substrates used are the preferred substrates as listed in FDA guidance on in vitro metabolism. Ketoconazole was used as positive control. The results are listed in Table 2.

The results showed that 17-HPC could inhibit some CYP enzymes in vitro but due to the estimated low therapeutic concentration of less than 0.2  $\mu\text{M}$ , it is unlikely to have significant effect

in vivo. 17-HPC slightly inhibited (15.5 – 37.7% inhibition at 20 µM) CYP2C8, 2C9, and 2C19 with IC<sub>50</sub> values >20 µM. 17-HPC inhibited CYP3A4 by 49.4% at 20 µM, indicating an IC<sub>50</sub> of approximately 20 µM. No inhibition of other tested isoforms was observed. Since the estimated 17-HPC level is less than 0.2 µM during weekly administration of 250 mg 17-HPC (based on results of Onsrud's study in non-pregnant females), the use of the proposed regimen is not likely to inhibit the metabolism of other drugs metabolized by the CYP isoforms. However, since the concentrations of 17-HPC in pregnant women after therapeutic doses are not known, the potential for inhibition when used by pregnant women is not completely clear.

**Table 2: Activity of Cytochrome P450 isoforms in Presence of 17-HPC**

Isoform	Metabolic Activity (% of Vehicle Control) in Presence of 17-HPC				
	0.02 µM 17-HPC	0.06 µM 17-HPC	0.2 µM 17-HPC	2.0 µM 17-HPC	20 µM 17-HPC
CYP1A2	185%	183%	172%	167%	123%
CYP2A6	253%	246%	229%	246%	200%
CYP2B6	167%	170%	179%	165%	140%
CYP2C8	130%	141%	120%	109%	75.7%
CYP2C9	101%	115%	110%	121%	62.3%
CYP2C19	95.9%	103%	95.8%	110%	84.5%
CYP2D6	98.6%	121%	118%	125%	106%
CYP2E1	103%	114%	111%	124%	117%
CYP3A4	99.2%	123%	118%	112%	50.6%

The sponsor also noted 17-HPC caused acceleration of the activity of some CYP isoforms (e.g., CYP2A6, 2B6, 1A2) in this in vitro microsome system. However, the linkage between in vitro acceleration and in vivo metabolism interaction is not established in the literature. Therefore, this in vitro acceleration data has little value to predict in vivo activity.

There were no in vivo drug interaction studies examining the effect of 17-HPC on the PK of other drug. Furthermore, neither in vitro nor in vivo enzyme induction studies were submitted.

2.4.3 What is the effect of 17-HPC administration on serum level of 17-hydroxyprogesterone (17-OHP) concentrations and its implication on the mechanism of 17-HPC action or on clinical test for congenital adrenal hyperplasia?

17-OHP does not appear to be a metabolite of 17-HPC. However, higher levels of 17-OHP in maternal serum between 7 and 17 weeks gestation have been reported with administration of 17-HPC to pregnant women than with placebo (Reijnders et al. 1988). The mean serum 17-OHP levels in the 17-HPC group during this period ranged from about 12 to 22 nM.

It is not known what is the effect of weekly administration of 17-HPC will have on concentration of endogenous 17-OHP level at later times during the pregnancy. Since 17-OHP also has progestational activity and there are some indications that 17-HPC might increase levels of 17-OHP, an understanding the concentration profile of 17-OHP during pregnancy in the presence or absence of 17-HPC administration may be helpful in determining whether the action of 17-HPC is mediated in part via 17-OHP.

It is also not known if the increase in 17-OHP observed by Reijnders et al. would persist at birth and whether fetal/neonatal serum levels of 17-OHP are also elevated due to 17-HPC administration to the mother.

Measurement of neonatal serum 17-OHP is used to screen for congenital adrenal hyperplasia, a condition characterized by an impaired biosynthesis of cortisol and aldosterone and an increased secretion of 17-OHP and androgens (van der Kamp et al. 2005). The median serum 17-OHP levels in neonates without this condition range from 99 nM to 21 nM for neonates born at  $\leq$  28 weeks and 37 weeks of gestation, respectively.

## 2.5 General Biopharmaceutics

### 2.5.1 What is the formulation for 17-HPC in this NDA?

Gestiva is supplied as a sterile solution of hydroxyprogesterone caproate for injection USP, 250 mg/mL, in benzyl benzoate USP (46% v/v) and castor oil USP (28.6% v/v), with the preservative benzyl alcohol NF (2% v/v). The formulation is identical to that used in clinical trial 17P-CT-002 (Table 3). Additionally, it is also similar to the previously approved drug product, Delalutin (Hydroxyprogesterone caproate injection USP) at the 250 mg/mL concentration. Table 3 also includes formulation information for Primalut, the product marketed in Europe and probably used by Onsrud (1985).

**Table 3: Composition of formulation of injectable 17-HPC**

Component	Adeza Product 250 mg/mL	Study 17P-CT-002 250 mg/mL	Delalutin <sup>b</sup> 250 mg/mL	Primalut/ Proluton Depot <sup>c</sup> 250 mg/mL
17-HPC	250 mg/mL	250 mg/mL	250 mg/mL	250 mg/mL
Benzyl benzoate, USP <sup>a</sup>	514.3 mg/mL 46% (v/v)	514.3 mg/mL 46% (v/v)	46%	517.7 mg/mL
Benzyl alcohol, NF <sup>a</sup>	21.92 mg/mL 2% (v/v)	21.92 mg/mL 2% (v/v)	2% (w/v)	None
Castor oil, USP <sup>a</sup>	277.8 mg/mL 28.6% (v/v)	277.8 mg/mL 28.6% (v/v)	q.s to volume	297.3 mg/mL

a Formulary designations are for the Adeza Product 17P and for the formulation used for Study 17P-CT-002 only.

b Delalutin Package Insert (1979). Type of percentage not reported for benzyl benzoate, but assumed to be v/v according to Chemist Review (1970).

c Information taken from Proluton Depot package insert for Turkey (1998b). Percentages not reported.

### 2.5.2 Is the Clinical trial formulation the same as the to-be-marketed formulation?

As indicated above the formulation used in the phase 3 clinical trial and the proposed commercial formulation are identical. However, two different manufacturers (b) (4) (b) (4) supplied the study drug for study 17P-CT-HPC and these manufacturers are different than the proposed commercial product manufacturer (Baxter). Table 4 shows the results from the Certificates of Analysis for a current lot of Adeza product (Lot No. 901379) manufactured by Baxter Pharmaceutical Solutions, LLC (Bloomington, IN) and two lots from (b) (4) that were evaluated in the NICHD Study 17P-CT-002. Lot No. EPC001 was manufactured for (b) (4) and was used for about 83% of the subjects in Study 17P-CT -002. Lot No. 7101831 was manufactured at the (b) (4) and was used for the remaining 17% of the subjects.

Dr. Monica Cooper from ONDQA has reviewed the data and commented that they are comparable. This formulation is a sterile solution for injection and no additional bioequivalent study is needed. **Table 4: Results from certificate of analysis comparing the lots used in phase 3 trial and a lot from Adeza's proposed to-be-marketed product.**

Test	Current Specification	Adeza Product Lot # 901379	(b) (4)		
			Lot #EPC001	Lot #7101831	
Physical examination	Clear, yellow color, essentially free of foreign particulate matter, viscous and oily solution with organic odor	Clear, yellow color, essentially free of foreign particulate matter, viscous and oily solution with an organic odor	Clear, yellow, viscous, oily liquid with organic odor	Clear, yellow, viscous, oily liquid with organic odor	
Volume recovery, USP<1>	(b) (4)				
Specific gravity, USP<841>					
Identification, HPLC	(b) (4)				
Assay, USP spectrophotometric assay or HPLC					
Purity, HPLC assay 1. 17 $\alpha$ -hydroxyprogesterone 2. Other					
Benzyl alcohol assay, GC assay					
Benzyl alcohol, HPLC assay					
Sterility, USP<7> membrane filtration					
Bacterial Endotoxins, USP<85>					
Particulate matter, USP<788>					(b) (4)

<sup>1</sup> Final product test result provided in (b) (4) certificate of analysis for information only.

<sup>2</sup> Results provided in Section 3.2.R.3, Comparability Protocols (Equivalence Between Clinical and Commercial Formulations) in Submission 3, Chemistry, Manufacturing and Controls, Volume 2, page 89.

## 2.6 Analytical Section

Table 5 shows a summary of the analytical methods used for the pharmacokinetic and metabolism studies.

**Table 5: Analytical method summary**

Study No. or Reference	Matrix	Method Type	Sensitivity	Specificity (parent/metabolites)
Onsrud 1985a	Serum	RIA	5 nmol/L or 2.15 ng/mL	No cross-reactivity with 17-hydroxyprogesterone or cortisol
In Vitro Study 304-1176-01	Hepatocytes in suspension	LC/MS/MS	Not applicable	Molecular weight based separation and identification of parent drug and 5 metabolites
Wiener 1961	Aqueous buffer plus drug in propylene glycol	Scintillation counting of carbon-14	Not reported	All molecules containing carbon-14
	Chloroform extracts	Paper and silica gel chromatography	Not applicable	Molecules with carbon-14 separated by chromatography
Davis 1960	Urine, feces, fat, plasma	Combustion plus counting in ionization chamber	Not reported	All molecules containing carbon-14
	Extracts of urine, feces, fat	Chromatographic separation and crystallization	Not applicable	Molecules with carbon-14 separated by chromatography

No validation data were provided for literature reports and relied entirely on the journal peer review process. In the human PK study, Onsrud et al. mentioned that their RIA assay for 17-HPC did not cross-react with 17-hydroxyprogesterone or cortisol but did not provide any additional supporting data. They also stated that the assay had a sensitivity of 5 nmol/l (2.14 ng/ml) and the inter-assay coefficient of variation (CV) was 7% at 50 nmol/l (214 ng/ml).

## Reference List

- DAVIS ME, PLOTZ EJ, LUPU CI, and EJARQUE PM (1960) The metabolism of progesterone and its related compounds in human pregnancy. *Fertil Steril* 11: 18-48
- Goldenberg RL (2002) The management of preterm labor. *Obstet Gynecol* 100: 1020-1037
- JUNKMANN K (1954) [Retard effect of gestagens.]. *Naunyn Schmiedebergs Arch Exp Pathol Pharmacol* 223: 244-253
- Onsrud M, Paus E, Haug E, and Kjorstad K (1985) Intramuscular administration of hydroxyprogesterone caproate in patients with endometrial carcinoma. Pharmacokinetics and effects on adrenal function. *Acta Obstet Gynecol Scand* 64: 519-523
- Reijnders FJ, Thomas CM, Doesburg WH, Rolland R, and Eskes TK (1988) Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial. *Br J Obstet Gynaecol* 95: 462-468
- van der Kamp HJ, Oudshoorn CG, Elvers BH, van BM, Otten BJ, Wit JM, and Verkerk PH (2005) Cutoff levels of 17-alpha-hydroxyprogesterone in neonatal screening for congenital adrenal hyperplasia should be based on gestational age rather than on birth weight. *J Clin Endocrinol Metab* 90: 3904-3907
- Vidaeff AC and Ramin SM (2006) From concept to practice: the recent history of preterm delivery prevention. Part II: Subclinical infection and hormonal effects. *Am J Perinatol* 23: 75-84
- Westphal U (1986) *Steroid-Protein Interactions II*. Springer-Verlag, Berlin, Germany.,
- WIENER M, LUPU CI, and PLOTZ EJ (1961) Metabolism of 17 alpha-hydroxyprogesterone-4-C14-17 alpha-caproate by homogenates of rat liver and human placenta. *Acta Endocrinol (Copenh)* 36: 511-519

### 3 Detailed Labeling Recommendations

See attached labeling for labeling recommendations.

### 4 Appendices

4.1 Proposed labeling (**Note: contains only OCP recommendations**)

Note: deletions are indicated by ~~strike through~~ and additions are indicated by underline.

(b) (4)



9/21/2006

8 Pages 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/

-----  
Doanh Tran  
9/21/2006 04:33:26 PM  
PHARMACOLOGIST

Ameeta Parekh  
9/21/2006 04:48:09 PM  
BIOPHARMACEUTICS

**Appendix 4.2:**

**Proposed labeling (Original with Clinical Pharmacology's recommended revisions)**

11 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately  
Following This Page

**Appendix 4.3:**

**Clinical Pharmacology memo at time of resubmission**

## OFFICE OF CLINICAL PHARMACOLOGY MEMO

---

---

NDA: 21-945	Submission Date(s): 4/24/2008
Brand Name	Gestiva
Generic Name	17 $\alpha$ -Hydroxyprogesterone Caproate (HPC)
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Cytc
Submission Type	Resubmission
Formulation; Strength(s)	Solution for injection, 250 mg/mL
Indication	Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth

---

---

This is a memo acknowledging the receipt of the resubmission for NDA 21-945 and provides a brief summary of Sponsor's responses to Clinical Pharmacology comments in the Approvable letter.

This NDA was originally submitted on 4/20/2006. It received an Approvable action on 10/20/2006. The Clinical Pharmacology review of the original submission indicated that it was acceptable. However, additional pharmacokinetic information should be obtained if future clinical trials are conducted. The Approvable letter requested, among other things, that Sponsor provide draft protocol for additional clinical study(ies) of efficacy and safety to be conducted post-approval if the product were to be approved.

The following Clinical Pharmacology comments were included in the Approvable letter:

### Clinical Pharmacology

In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.
- Assess the HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.
- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on HPC pharmacokinetics.

In this resubmission, the sponsor did not provide any new Clinical Pharmacology information. The sponsor proposed to address the Clinical Pharmacology comments the following way:

1. The sponsor indicated that a study evaluating the pharmacology of HPC in pregnant women with a previous history of preterm birth (ClinicalTrials.gov identifier: NCT00409825) is being conducted by the University of Pittsburgh and NIH (Principal investigator: Steve Caritis, MD). Sponsor indicated that it had spoken with Dr. Caritis and the trial is expected to be completed in December 2008. The sponsor proposed to provide a literature summary of the data that emerge from this study to address the first Clinical Pharmacology request to characterize the pharmacokinetics (PK) of HPC in pregnant women.
2. To address the issue of exposure-response relationship and effects of body weight on the PK of HPC, the sponsor proposed to use a population pharmacokinetic/pharmacodynamic (PK/PD) approach. The sponsor incorporated a population PK substudy into the efficacy and safety study. Pharmacokinetic assessments will be made on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) enrolled in the PK substudy stratified according to BMI in order to analyze the dose-plasma concentration-time relationship of 17P. Three blood samples will be drawn:
  - Before study drug dosing at either Visit 7 or 8 (i.e., Dose 5 or 6).
  - Before study drug dosing at either Visit 9 or 10 (i.e., Dose 7 or 8).
  - At a separate, non-dosing visit 1 to 4 days after Visit 10, 11, or 12 (i.e., 1 to 4 days after Dose 8, 9, or 10).

The HPC exposure-response relationship will be explored by a population PK/PD approach using a nonlinear mixed effect model. The dependence of apparent clearances and volumes on BMI will be examined as the primary covariate.

3. To address the issue concomitant administration of strong inducers and inhibitors of drug metabolizing enzymes on the PK of HPC, the sponsor proposed that concomitant medication information will be collected throughout the efficacy and safety study and tested as covariates in the population PK model.

Reviewer's comments:

1. The resubmission discussed the Clinical Pharmacology comments in the Approvable letter. The acceptability of the sponsor's proposal will be reviewed.
2. Some issues to be considered during the review include:
  - i. Is the literature report of the study by Dr. Caritis adequate with respect to the scope of the PK investigation as well as FDA's access to the raw data and bioanalytical method validation?
  - ii. Is the design of the proposed population PK study acceptable?

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

/s/

-----  
Doanh Tran  
8/21/2008 01:43:54 PM  
BIOPHARMACEUTICS

Please note Phase 4 Commitments in signature block

Sandhya Apparaju  
8/21/2008 04:15:06 PM  
BIOPHARMACEUTICS

Hae-Young Ahn  
8/26/2008 09:18:26 AM  
BIOPHARMACEUTICS

The division agrees with Phase 4 commitments. I am  
signing it out for Dennis Bashaw.

## OFFICE OF CLINICAL PHARMACOLOGY MEMO

---

NDA: 21-945	Submission Date(s): 4/24/2008
Brand Name	Gestiva
Generic Name	17 $\alpha$ -Hydroxyprogesterone Caproate (HPC)
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Cytyc
Submission Type	Resubmission
Formulation; Strength(s)	Solution for injection, 250 mg/mL
Indication	Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth

---

This is a memo acknowledging the receipt of the resubmission for NDA 21-945 and provides a brief summary of Sponsor's responses to Clinical Pharmacology comments in the Approvable letter.

This NDA was originally submitted on 4/20/2006. It received an Approvable action on 10/20/2006. The Clinical Pharmacology review of the original submission indicated that it was acceptable. However, additional pharmacokinetic information should be obtained if future clinical trials are conducted. The Approvable letter requested, among other things, that Sponsor provide draft protocol for additional clinical study(ies) of efficacy and safety to be conducted post-approval if the product were to be approved.

The following Clinical Pharmacology comments were included in the Approvable letter:

### Clinical Pharmacology

In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.
- Assess the HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.
- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on HPC pharmacokinetics.

In this resubmission, the sponsor did not provide any new Clinical Pharmacology information. The sponsor proposed to address the Clinical Pharmacology comments the following way:

1. The sponsor indicated that a study evaluating the pharmacology of HPC in pregnant women with a previous history of preterm birth (ClinicalTrials.gov identifier:

- NCT00409825) is being conducted by the University of Pittsburgh and NIH (Principal investigator: Steve Caritis, MD). Sponsor indicated that it had spoken with Dr. Caritis and the trial is expected to be completed in December 2008. The sponsor proposed to provide a literature summary of the data that emerge from this study to address the first Clinical Pharmacology request to characterize the pharmacokinetics (PK) of HPC in pregnant women.
2. To address the issue of exposure-response relationship and effects of body weight on the PK of HPC, the sponsor proposed to use a population pharmacokinetic/pharmacodynamic (PK/PD) approach. The sponsor incorporated a population PK substudy into the efficacy and safety study. Pharmacokinetic assessments will be made on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) enrolled in the PK substudy stratified according to BMI in order to analyze the dose-plasma concentration-time relationship of 17P. Three blood samples will be drawn:
    - Before study drug dosing at either Visit 7 or 8 (i.e., Dose 5 or 6).
    - Before study drug dosing at either Visit 9 or 10 (i.e., Dose 7 or 8).
    - At a separate, non-dosing visit 1 to 4 days after Visit 10, 11, or 12 (i.e., 1 to 4 days after Dose 8, 9, or 10).

- The HPC exposure-response relationship will be explored by a population PK/PD approach using a nonlinear mixed effect model. The dependence of apparent clearances and volumes on BMI will be examined as the primary covariate.
3. To address the issue concomitant administration of strong inducers and inhibitors of drug metabolizing enzymes on the PK of HPC, the sponsor proposed that concomitant medication information will be collected throughout the efficacy and safety study and tested as covariates in the population PK model.

Reviewer's comments:

1. The resubmission discussed the Clinical Pharmacology comments in the Approvable letter. The acceptability of the sponsor's proposal will be reviewed.
2. Some issues to be considered during the review include:
  - i. Is the literature report of the study by Dr. Caritis adequate with respect to the scope of the PK investigation as well as FDA's access to the raw data and bioanalytical method validation?
  - ii. Is the design of the proposed population PK study acceptable?

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

/s/

-----  
Doanh Tran  
7/11/2008 12:55:08 PM  
BIOPHARMACEUTICS

Myong-Jin Kim  
7/14/2008 07:19:39 AM  
BIOPHARMACEUTICS

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

---

NDA: 21-945	Submission Date(s): 04/20/2006
Brand Name	Gestiva™
Generic Name	17 alpha-Hydroxyprogesterone caproate
Reviewer	Doanh Tran, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
ORM division	Division of Reproductive and Urology Products
Sponsor	Adeza Biomedical
Relevant IND(s)	68-108
Submission Type; Code	Original; N (Priority review)
Formulation; Strength(s)	Solution for injection; 250 mg/mL
Indication	Prevention of recurrent preterm birth

---

### Table of Contents

Table of Contents .....	1
1 Executive Summary .....	2
1.1 Recommendation .....	2
1.2 Phase IV Commitments .....	2
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings .....	2
2 Question Based Review .....	4
2.1 General Attributes .....	4
2.2 General Clinical Pharmacology.....	5
2.3 Intrinsic Factors .....	13
2.4 Extrinsic Factors.....	13
2.5 General Biopharmaceutics.....	15
2.6 Analytical Section.....	16
3 Detailed Labeling Recommendations .....	19
4 Appendices.....	19
4.1 Proposed labeling .....	19

## 1 Executive Summary

This NDA for 17 alpha-hydroxyprogesterone caproate (17-HPC) contains very limited pharmacokinetic and clinical pharmacology information in non-pregnant and pregnant women. Additional drug metabolism and drug interaction information would have been useful in providing clearer directions to optimize therapy. Despite these limitations, the final formulation, the labeled dose and duration of use are identical to those used in the Phase 3 safety and efficacy trial. The Phase 3 trial allowed normal medical care including other concomitant treatments. Additionally, the medical need for effective prevention of preterm birth should be considered.

### 1.1 Recommendation

This reviewer finds NDA 21-945 acceptable from a clinical pharmacology perspective provided the labeling comments are adequately addressed.

In the event that there are additional clinical trials planned or requested the following pharmacokinetic elements are recommended to be included as part of those trials to allow for better understanding of 17-HPC pharmacokinetics and optimal dosing:

1. Characterize the pharmacokinetics of 17 alpha-hydroxyprogesterone (17-OHP), 17-HPC and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy.
2. Assess the 17-HPC exposure response relationship and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling of all subjects.
3. Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17-HPC PK.

The Division is prepared to work with Sponsor to design trials that would incorporate these elements.

### 1.2 Post Marketing Commitments

None

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- Limited pharmacokinetics (PK) information in pregnant women is derived from a published report (DAVIS et al. 1960) where single doses of Carbon-14 labeled 17-HPC were given to 4 pregnant women at 10 to 12 weeks gestation. The data showed that approximately 50% of radioactivity was excreted in the feces and an average of 29.7% of radioactivity was excreted in urine over 12 - 15 days. Maximum total plasma radioactivity was reached 5 days following IM injection followed by a slow decline. The dose in mg and formulation were not specified.
- PK information in non-pregnant women is derived from a literature report by Onsrud et al. (1985) using a formulation that is very similar to the to-be-marketed formulation. In this report, single dose of 1000 mg 17-HPC in endometrial cancer patients (n=5) resulted in a mean serum  $C_{max}$  of 65 nM,  $T_{max}$  of 4.6 days, and terminal half-life of 7.8 days. The same report also contained trough serum 17-HPC at weeks 1, 2, 3, 4, 5, and 13 after 5 daily loading doses of 1000 mg each followed by weekly or bi-weekly administration of 1000 mg 17-HPC (n = 6 – 9). The serum trough 17-HPC levels at week 13 were approximately 130 nM and 70 nM for the weekly and bi-weekly doses, respectively.
- Sponsor provided a preliminary in vitro metabolic profile study in human hepatocytes. About 70% was metabolized in 3 hours and there was no additional metabolism by 4 hour. Metabolism in the first 3 hours was apparently linear with half-life of 1.56 hr. The

main metabolic reactions were reduction, hydroxylation, and conjugation. 17-HPC appeared to be metabolized by both phase I and phase II reactions. The study was not designed to determine the specific enzyme(s) responsible for 17-HPC metabolism. The major metabolites identified with LC/MS/MS were all acetyl conjugates with the caproate group retained. Report by Davis et al. (1960) suggested that in humans the majority of 17-HPC metabolizes into glucuronide, sulfate, and an unknown conjugate, as measured in urine and feces.

- In vitro enzyme inhibition study using human liver microsomes showed that 17-HPC slightly inhibited (15.5 – 37.7% inhibition at 20  $\mu\text{M}$ ) CYP2C8, 2C9, and 2C19 with  $\text{IC}_{50}$  values  $>20 \mu\text{M}$ . 17-HPC inhibited CYP3A4 by 49.4% at 20  $\mu\text{M}$ . These  $\text{IC}_{50}$  values are much higher than the 17-HPC concentrations observed in non-pregnant women (Onsrud, 1985).

Data not available in the NDA:

- In vivo drug interaction studies
- Quantitative in vivo metabolism
- Enzyme induction studies
- Studies examining the effect of intrinsic factors such as age, hepatic impairment, and renal impairment

The formulation in the phase 3 clinical trial is the same as the proposed commercial formulation. Sponsor provided comparability data between the commercial manufacturer and the 2 manufacturers of the clinical lots and they were found acceptable.

#### 1.4 Rationale for recommendations

1. Characterize the pharmacokinetics of 17-OHP, 17-HPC and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy. (The periods should be spaced out evenly to allow assessment of PK changes as a pregnancy progresses. For example, a 3-period study design may include assessments at 16 – 20, 24 – 28, and 32 – 34 weeks gestation.)

*This would provide an understanding of the pharmacokinetic properties of 17-HPC in the target population. The metabolite characterization would provide more clarity to the in vivo metabolic fate of 17-HPC that showed inconsistency between in vivo and in vitro in the currently available data. Steady state concentration in target population would also aid in assessing potential drug interactions. Consistent with the usefulness of PK information, several members of the Reproductive and Urology Product Advisory Committee suggested the need to understand 17-HPC PK in pregnant women.*

*The 17-OHP concentrations would help determine the effect of 17-HPC administration on the endogenous 17-OHP (if any) and may aid in a better understanding the mechanism of 17-HPC action.*

2. Assess the 17-HPC exposure response relationship and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling of all subjects.

*Sparse serum levels of 17-HPC would allow an analysis of exposure-response relationship that may be helpful in optimizing therapy. Exposure response data is also useful in assessing the effect of any changes in PK due to intrinsic or extrinsic factors. This valuable data can be obtained from blood collections at some of the scheduled weekly injection visits or other office visits and should not substantially increase burden on enrolled patients or the sponsor.*

Varied body weight may affect the pharmacokinetic of 17-HPC. 17-HPC serum levels collected for exposure response analysis can be used to determine the effect (if any) of body weight on 17-HPC exposure. The AC committee rightfully pointed out that the large range of body mass index (BMI) may lead to different individual drug concentrations and that it should be evaluated.

3. Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17-HPC PK.

This information may be helpful in assessing the need for dosing restriction or indicate the need for drug interaction studies.

## 2 Question Based Review

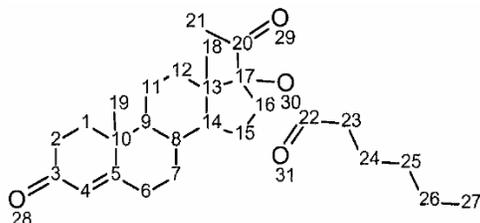
### 2.1 General Attributes

#### 2.1.1 What is 17 alpha-Hydroxyprogesterone caproate?

17 alpha-Hydroxyprogesterone caproate (17-HPC) is a synthetic progestin hormone, which is an esterified derivative of 17 alpha-hydroxyprogesterone. 17-HPC has a molecular formula  $C_{27}H_{40}O_4$  and an average molecular weight of 428.6. It has stronger progestational activity and a prolonged duration of action in a female rabbit model (JUNKMANN 1954).

17-HPC was a previously approved product Delalutin (NDA 10-347 and NDA 16-911). Delalutin was withdrawn by FDA in year 2000 following discontinuation of marketing by the NDAs' sponsor.

The molecular structure is indicated below.



#### 2.1.2 What is the proposed indication?

Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

17-HPC is not currently the subject of any approved NDA.

#### 2.1.3 What is the proposed dose and route of administration?

The proposed therapeutic dose of Gestiva™ for prevention of recurrent preterm birth is 250 mg intramuscularly once weekly at a dose of 250 mg (1 mL) beginning at 16 weeks 0 days to 20 weeks 6 days of gestation to week 37 of gestation or until birth. This dosage schedule is identical to that used in the phase 3 clinical efficacy trial. Different doses and dosing schedules such as one with a loading dose was not available for review to determine if better efficacy can be obtained.

#### 2.1.4 What is preterm birth?

Preterm birth is defined as birth occurring before 37 weeks gestation. It affects approximately 12.5% of all live births in the US. It is a leading cause of infant death and long-term disability. The risk of severe complications increases with younger preterm infants, particularly those born at less than 32 weeks gestation. Consequently, treatments that can decrease preterm delivery at less than 32 weeks in addition to a reduction at less than 37 weeks are valued.

The etiology of spontaneous preterm birth is not well understood but likely involves many factors. It was suggested in a recent report by the Institute of Medicine that preterm birth should be described as a “syndrome of multiple pathophysiological pathways”. A number of factors have been identified placing women at risk for preterm birth including low pre-pregnancy weight, drug and alcohol abuse, African American race, lower socioeconomic status, medical complication during pregnancy, multifetal gestation, cervical structural abnormality, and previous pregnancy history. Among these, a history of spontaneous preterm birth is one of the strongest predictors (17 – 40%) for a preterm birth in a subsequent pregnancy (Goldenberg 2002).

#### 2.1.5 What are the current treatments for prevention of preterm birth?

There are no approved treatments for prevention of preterm birth. According to a press release in January 2005 by the American College of Obstetricians and Gynecologists (ACOG), there are no widely established treatments to prevent preterm birth. There is a need for safe and effective treatments to prevent preterm birth.

According to a recent review (Vidaeff and Ramin 2006), some of the current interventions being used for preventions of preterm birth include cervical cerclage, antimicrobial therapy, and progesterone supplementation. However, there are mixed results reported with all of these intervention methods. Additionally, cervical cerclage and antimicrobial therapy may only be used in specific conditions (e.g., patients with cervical insufficiency or identified infection).

Previous interventions such as enhanced prenatal care, patient education, cessation of work, bed rest, home uterine monitoring, prophylactic tocolytics, nutritional supplements, and social support had been advanced as prophylactic interventions but eventually could not be associated with any consistent evidence of benefits (Vidaeff and Ramin, 2006).

### 2.2 General Clinical Pharmacology

#### 2.2.1 What is the pharmacokinetics of 17-HPC following intramuscular (IM) injection?

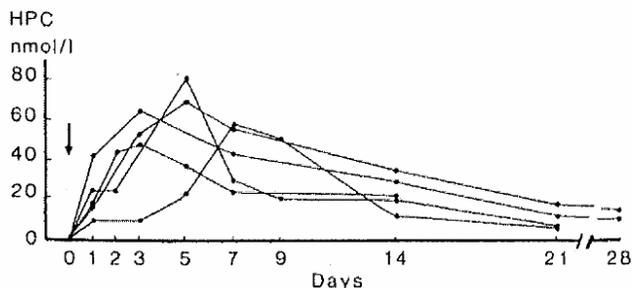
##### **Single-dose PK:**

A paper published by Onsrud et al. (1985) described the PK of 17-HPC in 5 non-pregnant female endometrial carcinoma patients receiving single dose of 1000 mg 17-HPC intramuscularly. The formulation was not indicated but it was assumed that the commercial product available in Norway in 1985, namely Primolut-Depot®, was used. Primolut-Depot® formulation was similar to the phase 3 clinical trial for prevention of preterm labor formulation except the omission of 2% benzyl alcohol as a preservative.

Figure 1 shows the PK profile of 17-HPC as reported by Onsrud et al. (1985). Adeza extracted data points from the graph and calculated PK parameters (Table 1). Adeza determined that only 4 of 5 subjects had enough data for calculation of  $t_{1/2}$ . The excluded profile (Subject 3) only had data up to 14 days. The data show that 17-HPC was bioavailable with a mean  $T_{max}$  of 4.6 days and prolonged half-life of approximately 7.8 days in non-pregnant female subjects. The average  $C_{max}$  following a single dose of 1000 mg IM was  $27.8 \pm 5.3$  ng/mL (i.e.,  $64.9 \pm 12.4$  nM).

Upon examination of the data, it is debatable that only 3 subjects had reliable  $t_{1/2}$  estimates. Subject 5 had data up to 21 days but the absorption phase was prolonged and of the 3 data points used for  $t_{1/2}$  calculation, one was very close to the  $C_{max}$  making it unreliable for use in  $t_{1/2}$  calculation. If that subject was also excluded the  $t_{1/2}$  estimates would be  $9.1 \pm 1.8$  days. The difference between the estimates is small and should not significantly affect the weekly dosing schedule of this drug. Therefore, this reviewer accepts the calculations by sponsor.

**Figure 1: Individual serum concentrations of 17-HPC in 5 endometrial cancer patients after intramuscular administration of a single dose of 1000 mg (arrow).**



**Table 1: PK parameters for single dose of 1000 mg 17-HPC in non-pregnant endometrial cancer patients (calculated from data extracted from figure 1).**

Parameter	Mean $\pm$ SD	n
$C_{max}$ (ng/mL)	27.8 $\pm$ 5.3	5
$T_{max}$ (days)	4.6 $\pm$ 1.7	5
AUC <sub>0-7</sub> (ng•day/mL)	118 $\pm$ 36	5
AUC <sub>0-14</sub> (ng•day/mL)	217 $\pm$ 49	5
$t_{1/2}$ (days)	7.8 $\pm$ 3.0	4
AUC <sub>0-∞</sub> (ng•day/mL)	355 $\pm$ 136	4

Some PK information is available in foreign labels of Proluton Depot, 250 mg/ml 17-HPC by Schering AG, a product that is said to be the same as Primalut Depot, the formulation that Onsrud likely used. The label for Austria, dated 1998, stated that elimination half-life is 6 days and the label for Turkey, also dated 1998, stated “Hydroxyprogesterone caproate is found in the blood only 2 hours after intramuscular administration. Maximum plasma levels are reached on the second day after injection. After that the concentration decreased slowly. 14 days after injection 60% of the maximum value can still be found. The elimination is protracted.” The elimination half-life of 6 days or “elimination is protracted” is consistent with Onsrud’s mean half-life of 7.8 days. The  $T_{max}$  of 2 days is shorter than observed in Onsrud’s study and is not clear if it is due to data variability ( $T_{max}$  range of 3 – 7 days) or perhaps a higher dose in Onsrud’s study. If a higher dose was used, such dose would require higher volume of injection and may reduce the rate of transfer of the fat soluble 17-HPC out of its oil formulation into the circulation. If the latter is true, the lower dose of 250 mg in this NDA may result in shorter  $T_{max}$  that is closer to 2 days than 4.6 days.

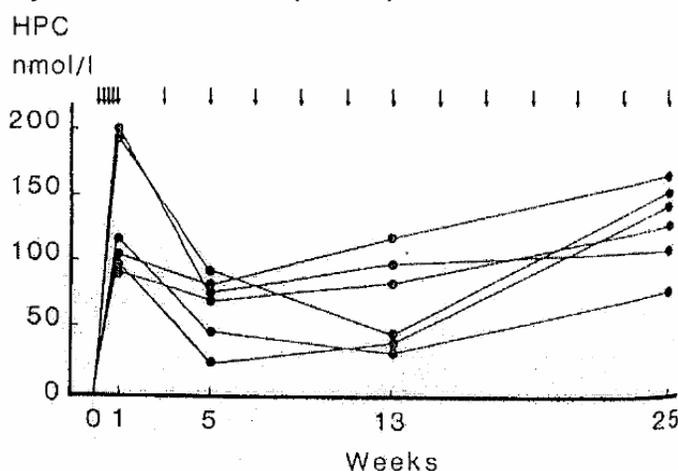
In support of the PK results by Onsrud et al. (1985), the sponsor submitted a publication by Davis et al. (DAVIS et al. 1960) where they reported that after administration of [C14]-17-HPC to 4 pregnant women (three were at 10-12 week gestation, the 4th was not specified, dose in mg and vehicle not specified), the highest level of radioactivity, which would be a combination of unchanged 17-HPC and metabolites, in the plasma occurred at the fifth day after intramuscular

injection, similar to the 4.6 days estimate from Onsrud's data. The total plasma radioactivity declined slowly over the next 6 days of measurement. However, this data is of limited usefulness due to the many unknowns (e.g., dose, formulation, and metabolite PK).

### Multiple-dose PK:

Onsrud's study also included a multiple dose portion where six non-pregnant subjects received 1000 mg 17-HPC daily for 5 days followed by 12 injections of 1000 mg once every two weeks for a total duration of 25 weeks. The results are shown in figure 2. The high serum concentration achieved after 5 loading doses in the first week declined then appeared to rise slowly from 5 to 25 weeks with the bi-weekly dosing. The timing of samples at weeks 5, 13 and 25 were not specified but assumed to be  $C_{trough}$ . These data show a trend of increasing concentration from week 13 to 25, indicating steady state was not reached by 13 weeks. Additionally, due to the expected long  $t_{1/2}$ , the concentration at week 5 might be lower had there been no loading doses (as proposed in this NDA), further suggesting the presence of increasing trough levels from week 5 to week 13.

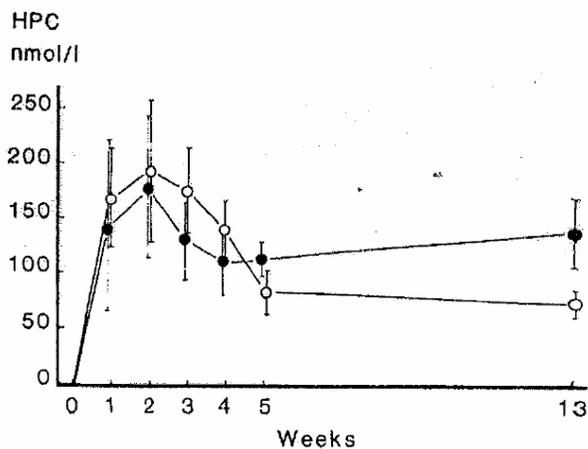
**Figure 2: Individual serum concentrations of 17-HPC in 6 non-pregnant female patients treated with IM injection for 25 weeks. 1000 mg 17-HPC was given daily for 5 days, and every 2 weeks thereafter (arrows).**



Separately, there were 2 cohorts of subjects both receiving five daily doses of 1000 mg 17-HPC. One cohort then received 1,000 mg 17-HPC weekly, and the other cohort received 1,000 mg biweekly. The mean concentrations for 6 - 9 subjects are shown in Figure 3 (also taken directly from Onsrud 1985). The  $C_{trough}$  at week 13 in women receiving weekly injection of 1000 mg 17-HPC was  $58.2 \pm 13.3$  ng/mL (or  $136 \pm 31$  nM). The sponsor pointed out that between 5 and 13 weeks, there was no apparent change in serum concentrations for the group receiving 1,000 mg 17-HPC bi-weekly, but there was a possible increase for the group receiving 1,000 mg weekly although the error bars indicate similar concentrations at both times.

To this reviewer, it is not clear if steady state was reached by week 13 if the loading doses were not present. In figure 3, serum 17-HPC level declines from week 2 to 5 even though a dose was given at week 3, suggesting that the trough value at week 5 may be significantly influenced by the loading doses and would be lower if the 5 loading doses were not present. A similar trend is also observed with the weekly dosing group, except that week 5 concentration appeared to hold steady with a slight rise by week 13. In addition, figure 2 shows a trend of increasing concentration from week 5 to week 13 and week 25. These data suggests that weekly dosing of 17-HPC without loading dose may result in drug accumulation with increase in serum 17-HPC concentration for at least 13 weeks.

**Figure 3: Serum concentration of 17-HPC in endometrial cancer patients who after a loading dose of 1000 mg daily for 5 days were treated with either 1000 mg 17-HPC every week (solid circles) or with 1000 mg every 2 weeks (open circles). Each point on the curves represents the mean  $\pm$  SE from 6 – 9 patients.**



In summary, there is limited PK information in non-pregnant females to show that 17-HPC is bioavailable following IM injection. The  $t_{1/2}$  is sufficiently long such that once weekly dosing interval would unlikely result in substantial minima in serum level of 17-HPC in non-pregnant females. Based on the single dose  $t_{1/2}$ , steady state may be reached by 39 - 46 days. However, trough data suggest that slight increase in concentration may continue for at least 13 weeks of dosing. The concentration data at 13 and 25 weeks should provide good estimates of concentration using a protocol without loading dose, as by that time the effect of loading dose should be minimal.

#### 2.2.2 What is the pharmacokinetics of 17-HPC in pregnant women?

Limited pharmacokinetics (PK) information in pregnant women is derived from a published report (DAVIS et al. 1960) where single doses of [ $C^{14}$ ] labeled 17-HPC were given as IM injections to 4 pregnant women (three were at 10-12 week gestation, the 4th was not specified) and urine and feces samples were collected for 7, 12, 14, and 15 days, respectively. The doses of radioactivity administered ranged from 25.9 to 28.8 microcuries. The doses in mg and formulation were not specified.

Maximum total plasma radioactivity was reached 5 days following IM injection followed by a slow decline (figure 4). The data showed that approximately 50% of radioactivity was excreted in the feces and an average of 29.7% (range 27.6 to 29.8%) of radioactivity was excreted in urine over 12 - 15 days (figure 5). The 4<sup>th</sup> patient excreted 15.3% of the injected radioactivity in urine during a collection period of 7 days. A plateau in daily urinary excretion curve was reached within 36 to 48 hours after the injection and maintained for the next 5 to 6 days (figure 6). The largest amounts of radioactivity were found in the feces expelled between 48 and 142 hours following injection.

Figure 4: Radioactivity in total plasma volume and daily urinary output at various time interval following IM of 4-C<sup>14</sup>-17-alpha-hydroxyprogesterone caproate.

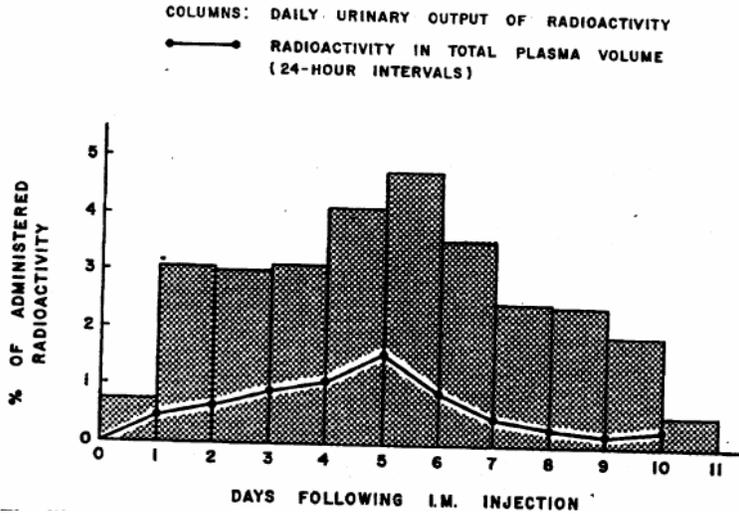
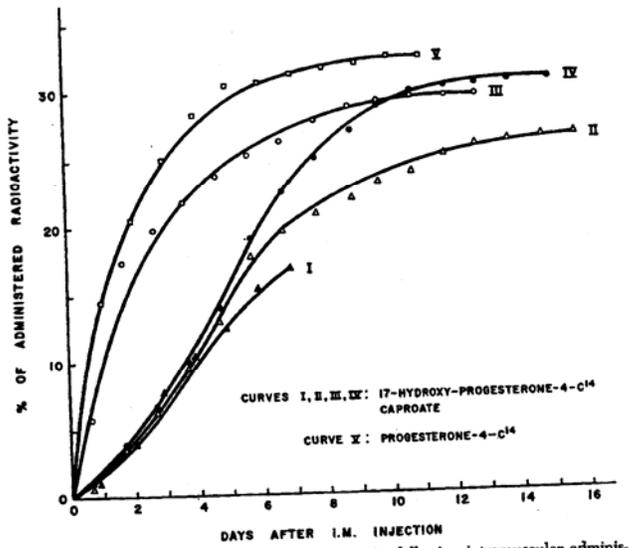
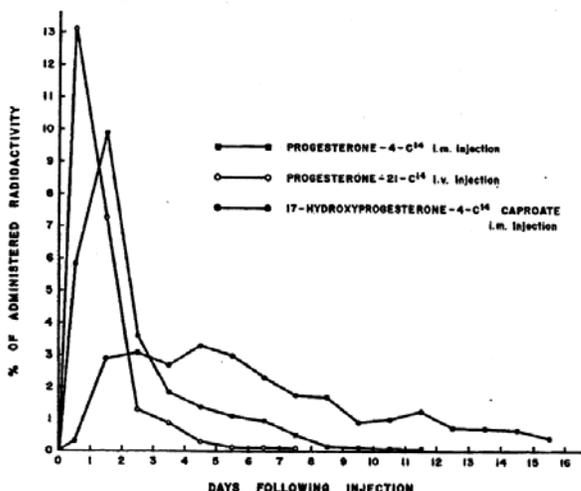


Figure 5: Cumulative excretion of radioactivity following intramuscular administration of [C14]-labeled 17-HPC (curves I – IV) and progesterone (curve V) to pregnant patients. Progesterone excretion is more rapid.



**Figure 6: Pattern of urinary excretion of radioactivity following administration of [C14]-labeled progestins.**



In summary, following IM injection of 17-HPC (formulation and dose in mg not specified) there is a delay of about 36 hours for maximum urinary excretion and 48 hours for fecal excretion. Maximum total plasma radioactivity was reached 5 days after injection and approximately 80% of radioactivity was excreted in urine and feces within 15 days after injection. As will be discussed in the metabolism section, the metabolites were suggested to be mainly conjugates, including glucuronide, sulfate and an unknown conjugate.

### 2.2.3 What is the metabolic pathway for 17-HPC?

17-HPC was shown to be metabolized by human hepatocytes in vitro (report 304-1176-01). Under sponsor's experimental conditions, the elimination was via an apparent first order process during the first 3 hours of incubation with an in vitro half-life of 1.56 hr. No further metabolism was present beyond 3 hr during the 4-hour incubations.

17-HPC metabolic profile was assessed in an in vitro hepatocyte study (report 304-1176-01) with tentative metabolite structure determination by LC/MS and Metabolynx software. LC/MS identified 22 putative metabolites. Further structural elucidation of five selected metabolites was done by LC/MS/MS analysis. The structural prediction of the Metabolynx software using mass ratio alone was not accurate since 3 of the 5 metabolites chosen for further elucidation by LC/MS/MS contradict earlier prediction by Metabolynx. The 5 metabolites chosen for further analysis were based on being the largest peaks and were predicted to be acetyl conjugates (H-6 and H-13), sulfate conjugate (H-2 and H-5), or a minor metabolite that was thought to have the caproate removed (H-14).

LC/MS/MS analysis indicated that all five were acetyl conjugates with the caproate group remain attached (figures 7 - 11). The data indicate the presence of reduction, hydroxylation, and conjugation. Of the 4 major metabolites, the phase 2 acetyl conjugation could theoretically proceed directly in the 3-carbon position ketone group (following CYP-independent reduction). In the case of the minor metabolite H-14, addition of a functional group containing oxygen by phase 1 metabolism must precede the conjugation reaction. Direct conjugation would represent the major elimination pathway for 17-HPC if in vivo metabolism parallels that observed in vitro. It should be noted that the structural elucidation by LC/MS/MS method is also not definitive.

Figure 7: metabolite H-2

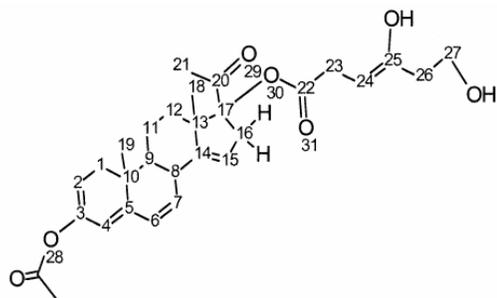


Figure 8: metabolite H-5

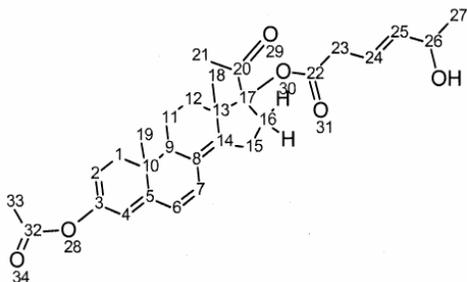


Figure 9: metabolite H-6

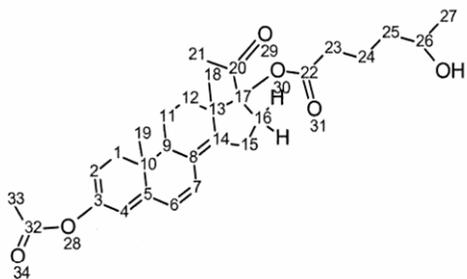


Figure 10: metabolite H-13

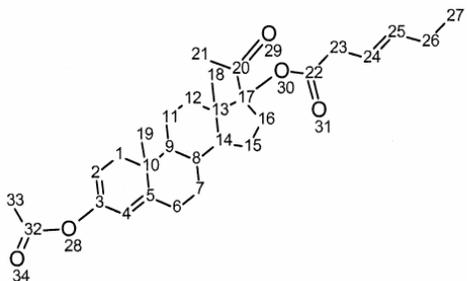
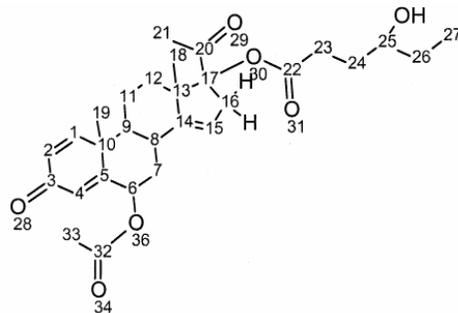


Figure 11: metabolite H-14



Davis et al. (1960) analyzed the urine from 3 subjects given ring labeled [C<sup>14</sup>]-17-HPC by extracting the free steroids in chloroform from a 10% sodium carbonate medium that would be expected to retain the hydrophilic conjugated metabolites. In each case, the sodium carbonate fraction retained the majority (75 – 81%) of the radioactivity, indicating that most of the metabolites excreted in the urine are conjugates or other polar metabolites. This finding may also indicate the presence of unchanged 17-HPC in the chloroform fraction but the authors indicated they were unable to find unchanged 17-HPC in urine or feces.

They reported that in one patient, treatment of urine with beta-glucuronidase before extraction indicated that some (about 20 to 25 % of total urine radioactivity), but not all the conjugates were glucuronides (DAVIS et al. 1960). Subsequent extraction with ether after hydrolysis at pH 1 indicated the possible presence of sulfate conjugates (about 15 – 22 of total urine radioactivity). The amount of conjugates hydrolyzable by hot acid ranged from 1.5 to 11% of total radioactivity. Thus in this particular patient, only 57 to 83% of the urinary radioactivity was extractable following all the hydrolytic procedures. Only 67% and 39% were extractable in 2 other patients, respectively, using the same procedures. The authors of the report suggested the presence of metabolites that are formed by “an unknown mode of conjugation”.

In summary, 17-HPC can be metabolized by human hepatocytes in vitro. The major metabolites found in vitro were all acetyl conjugates, while an in vivo literature report suggested that 17-HPC metabolizes into glucuronide, sulfate, and an unknown conjugate. The reason for in vitro and in vivo inconsistency is not known.

#### 2.2.4 What is the support that the caproate ester remained attached?

There are several pieces of evidence that suggest the caproate ester are not hydrolysed and remain attached following 17-HPC administration.

- 1.) The in vitro study mentioned above showed that all major metabolites retained the caproate. There were two minor metabolites that were suggested by LC/MS to have the caproate removed. However, further analysis using LC/MS/MS of one metabolite showed that the caproate was actually not removed.
- 2.) In a study by Wiener et al. (WIENER et al. 1961), following a 2-hour incubation in rat liver homogenate, they found 2 metabolites representing about 25 and 2% of starting 17-HPC amount, respectively, and both metabolites retained the caproate ester.
- 3.) The report by Wiener also included unpublished report by one co-author, Lupu, where [C<sup>14</sup>]-17-HPC labeled on one of the ring was given to 2 subjects and [C<sup>14</sup>]-17-HPC labeled on the caproate was given to a third subject and elimination of radioactivity was measured in the urine for 6 or 10 days. The result showed that the amounts of free and total 17-HPC radioactivity in the urine for the subject receiving the caproate-labeled 17-HPC were slightly higher than the amounts for the two that received the ring-labeled 17-HPC. If the caproate, and its associated radioactivity, were released from 17-HPC by metabolism, one would expect lower level of radioactivity to associate with steroids in urine. This data suggest that the caproate ester bond is not cleaved during metabolism.
- 4.) Sponsor suggested that the position of the caproate group at C-17 of the HPC molecule is not readily available for biochemical degradation by esterases due to steric hindrance.

The data is not conclusive, however they all suggest that the caproate ester is not removed during in vivo metabolism of 17-HPC.

#### 2.2.5 What are the protein binding properties of 17-HPC?

It has been shown that 17-HPC binds weakly to corticosteroid binding globulins ( $K_a = 4.3 \times 10^{-10} \pm 3 \times 10^{-11} \text{ M}^{-1}$ ) (Westphal 1986). Since steroids are bound by corticosteroid binding globulins and

albumin, this suggests that most of 17-HPC are bound to albumin in blood. Albumin generally binds steroids weakly and may be anticipated here with 17-HPC.

A label for 17-HPC injection (Proluton Depot, 1998) in Austria indicates that “[t]he active ingredient is 95% bound to plasma protein in vitro (human plasma)”.

It appears that 17-HPC is extensively bound to plasma protein (95%) including albumin and corticosteroid binding globulins.

## 2.3 Intrinsic Factors

### 2.3.1 What are the effects of intrinsic factors on 17-HPC pharmacokinetics?

There is no submitted information on the effect of age, hepatic impairment, renal impairment, or any other intrinsic factors on the PK of 17-HPC. The sponsor indicated that they have done a current literature search and did not find any relevant information.

In general, as this drug is expected to be metabolized by hydroxylation and conjugation, likely by the liver, hepatic impairment may decrease the clearance of this drug. Urinary excretion of radio labeled 17-HPC over 15 days was approximately 30% (DAVIS et al. 1960) indicating that renal clearance may account for 30% or more of the excretion of 17-HPC. Thus renal impairment may also decrease clearance to some extent. However, since the conjugate metabolites may also be excreted in feces, which accounted for 50% of the excretion of 17-HPC, the effect of renal impairment may not be significant if there is compensatory excretion via biliary excretion.

## 2.4 Extrinsic Factors

### 2.4.1 What are the effects of other drugs on the PK of 17-HPC?

There is no submitted data to assess the potential effect of concomitant administration of other drugs on the PK of 17-HPC. Based on the in vitro metabolism study, which suggests that 17-HPC may be partly metabolized by phase 1 metabolism, there is potential for drug interactions with inhibitors and inducers of CYP enzymes. However, for purpose of drug elimination, there is potential for direct conjugation at the C-3 ketone position and therefore elimination of 17-HPC without the need for CYP enzymes. The reliability of these in vitro data to predict in vivo metabolism is not clear as there were conflicting results as to which conjugate(s) are formed. For example, in vivo data suggest the formation of glucuronide, sulfate and an unknown conjugate. Whereas the in vitro data only found acetyl conjugate in a system capable of forming glucuronide and sulfate conjugates of the positive control 7-ethoxycoumarin. Additional detailed studies of 17-HPC metabolic pathway in vitro and in vivo are needed for a clearer conclusion.

### 2.4.2 What are the effects of 17-HPC on the metabolism of other drugs?

There was an in vitro inhibition study examining the effect of 17-HPC on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 enzyme activity using CYP isoform-specific substrates in human liver microsomes (report 304-1177-02). The substrates used and the corresponding isoforms were: phenacetin (CYP1A2), coumarin (CYP2A6), S-mephenytoin (CYP2B6), paclitaxel (CYP2C8), tolbutamide (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), chloroxazone (CYP2E1), and testosterone (CYP3A4). The substrates used are the preferred substrates as listed in FDA guidance on in vitro metabolism. Ketoconazole was used as positive control. The results are listed in Table 2.

The results showed that 17-HPC could inhibit some CYP enzymes in vitro but due to the estimated low therapeutic concentration of less than 0.2  $\mu$ M, it is unlikely to have significant effect

in vivo. 17-HPC slightly inhibited (15.5 – 37.7% inhibition at 20  $\mu$ M) CYP2C8, 2C9, and 2C19 with  $IC_{50}$  values  $>20$   $\mu$ M. 17-HPC inhibited CYP3A4 by 49.4% at 20  $\mu$ M, indicating an  $IC_{50}$  of approximately 20  $\mu$ M. No inhibition of other tested isoforms was observed. Since the estimated 17-HPC level is less than 0.2  $\mu$ M during weekly administration of 250 mg 17-HPC (based on results of Onsrud's study in non-pregnant females), the use of the proposed regimen is not likely to inhibit the metabolism of other drugs metabolized by the CYP isoforms. However, since the concentrations of 17-HPC in pregnant women after therapeutic doses are not known, the potential for inhibition when used by pregnant women is not completely clear.

**Table 2: Activity of Cytochrome P450 isoforms in Presence of 17-HPC**

Isoform	Metabolic Activity (% of Vehicle Control) in Presence of 17-HPC				
	0.02 $\mu$ M 17-HPC	0.06 $\mu$ M 17-HPC	0.2 $\mu$ M 17-HPC	2.0 $\mu$ M 17-HPC	20 $\mu$ M 17-HPC
CYP1A2	185%	183%	172%	167%	123%
CYP2A6	253%	246%	229%	246%	200%
CYP2B6	167%	170%	179%	165%	140%
CYP2C8	130%	141%	120%	109%	75.7%
CYP2C9	101%	115%	110%	121%	62.3%
CYP2C19	95.9%	103%	95.8%	110%	84.5%
CYP2D6	98.6%	121%	118%	125%	106%
CYP2E1	103%	114%	111%	124%	117%
CYP3A4	99.2%	123%	118%	112%	50.6%

The sponsor also noted 17-HPC caused acceleration of the activity of some CYP isoforms (e.g., CYP2A6, 2B6, 1A2) in this in vitro microsome system. However, the linkage between in vitro acceleration and in vivo metabolism interaction is not established in the literature. Therefore, this in vitro acceleration data has little value to predict in vivo activity.

There were no in vivo drug interaction studies examining the effect of 17-HPC on the PK of other drug. Furthermore, neither in vitro nor in vivo enzyme induction studies were submitted.

#### 2.4.3 What is the effect of 17-HPC administration on serum level of 17-hydroxyprogesterone (17-OHP) concentrations and its implication on the mechanism of 17-HPC action or on clinical test for congenital adrenal hyperplasia?

17-OHP does not appear to be a metabolite of 17-HPC. However, higher levels of 17-OHP in maternal serum between 7 and 17 weeks gestation have been reported with administration of 17-HPC to pregnant women than with placebo (Reijnders et al. 1988). The mean serum 17-OHP levels in the 17-HPC group during this period ranged from about 12 to 22 nM.

It is not known what is the effect of weekly administration of 17-HPC will have on concentration of endogenous 17-OHP level at later times during the pregnancy. Since 17-OHP also has progestational activity and there are some indications that 17-HPC might increase levels of 17-OHP, an understanding the concentration profile of 17-OHP during pregnancy in the presence or absence of 17-HPC administration may be helpful in determining whether the action of 17-HPC is mediated in part via 17-OHP.

It is also not known if the increase in 17-OHP observed by Reijnders et al. would persist at birth and whether fetal/neonatal serum levels of 17-OHP are also elevated due to 17-HPC administration to the mother.

Measurement of neonatal serum 17-OHP is used to screen for congenital adrenal hyperplasia, a condition characterized by an impaired biosynthesis of cortisol and aldosterone and an increased secretion of 17-OHP and androgens (van der Kamp et al. 2005). The median serum 17-OHP levels in neonates without this condition range from 99 nM to 21 nM for neonates born at  $\leq$  28 weeks and 37 weeks of gestation, respectively.

## 2.5 General Biopharmaceutics

### 2.5.1 What is the formulation for 17-HPC in this NDA?

Gestiva is supplied as a sterile solution of hydroxyprogesterone caproate for injection USP, 250 mg/mL, in benzyl benzoate USP (46% v/v) and castor oil USP (28.6% v/v), with the preservative benzyl alcohol NF (2% v/v). The formulation is identical to that used in clinical trial 17P-CT-002 (Table 3). Additionally, it is also similar to the previously approved drug product, Delalutin (Hydroxyprogesterone caproate injection USP) at the 250 mg/mL concentration. Table 3 also includes formulation information for Primalut, the product marketed in Europe and probably used by Onsrud (1985).

**Table 3: Composition of formulation of injectable 17-HPC**

Component	Adeza Product 250 mg/mL	Study 17P-CT-002 250 mg/mL	Delalutin <sup>b</sup> 250 mg/mL	Primalut/ Proluton Depot <sup>c</sup> 250 mg/mL
17-HPC	250 mg/mL	250 mg/mL	250 mg/mL	250 mg/mL
Benzyl benzoate, USP <sup>a</sup>	514.3 mg/mL 46% (v/v)	514.3 mg/mL 46% (v/v)	46%	517.7 mg/mL
Benzyl alcohol, NF <sup>a</sup>	21.92 mg/mL 2% (v/v)	21.92 mg/mL 2% (v/v)	2% (w/v)	None
Castor oil, USP <sup>a</sup>	277.8 mg/mL 28.6% (v/v)	277.8 mg/mL 28.6% (v/v)	q.s to volume	297.3 mg/mL

a Formulary designations are for the Adeza Product 17P and for the formulation used for Study 17P-CT-002 only.

b Delalutin Package Insert (1979). Type of percentage not reported for benzyl benzoate, but assumed to be v/v according to Chemist Review (1970).

c Information taken from Proluton Depot package insert for Turkey (1998b). Percentages not reported.

### 2.5.2 Is the Clinical trial formulation the same as the to-be-marketed formulation?

As indicated above the formulation used in the phase 3 clinical trial and the proposed commercial formulation are identical. However, two different manufacturers (b) (4) (b) (4) supplied the study drug for study 17P-CT-HPC and these manufacturers are different than the proposed commercial product manufacturer (Baxter). Table 4 shows the results from the Certificates of Analysis for a current lot of Adeza product (Lot No. 901379) manufactured by Baxter Pharmaceutical Solutions, LLC (Bloomington, IN) and two lots from (b) (4) that were evaluated in the NICHD Study 17P-CT-002. Lot No. EPC001 was manufactured for (b) (4) and was used for about 83% of the subjects in Study 17P-CT -002. Lot No. 7101831 was manufactured at the (b) (4) and was used for the remaining 17% of the subjects.

Dr. Monica Cooper from ONDQA has reviewed the data and commented that they are comparable. This formulation is a sterile solution for injection and no additional bioequivalent study is needed.

**Table 4: Results from certificate of analysis comparing the lots used in phase 3 trial and a lot from Adeza's proposed to-be-marketed product.**

Test	Current Specification	Adeza Product Lot # 901379	(b) (4)	
			Lot #EPC001	Lot #7101831
Physical examination	Clear, yellow color, essentially free of foreign particulate matter, viscous and oily solution with organic odor	Clear, yellow color, essentially free of foreign particulate matter, viscous and oily solution with an organic odor	Clear, yellow, viscous, oily liquid with organic odor	Clear, yellow, viscous, oily liquid with organic odor
Volume recovery, USP<1>	(b) (4)			
Specific gravity, USP<841>				
Identification, HPLC				
Assay, USP spectrophotometric assay or HPLC				
Purity, HPLC assay 1. 17 $\alpha$ -hydroxyprogesterone 2. Other				
Benzyl alcohol assay, GC assay				
Benzyl alcohol, HPLC assay				
Sterility, USP<7> membrane filtration				
Bacterial Endotoxins, USP<85>				
Particulate matter, USP<788>				

<sup>1</sup> Final product test result provided in (b) (4) certificate of analysis for information only.

<sup>2</sup> Results provided in Section 3.2.R.3, Comparability Protocols (Equivalence Between Clinical and Commercial Formulations) in Submission 3, Chemistry, Manufacturing and Controls, Volume 2, page 89.

## 2.6 Analytical Section

Table 5 shows a summary of the analytical methods used for the pharmacokinetic and metabolism studies.

**Table 5: Analytical method summary**

Study No. or Reference	Matrix	Method Type	Sensitivity	Specificity (parent/metabolites)
Onsrud 1985a	Serum	RIA	5 nmol/L or 2.15 ng/mL	No cross-reactivity with 17-hydroxyprogesterone or cortisol
In Vitro Study 304-1176-01	Hepatocytes in suspension	LC/MS/MS	Not applicable	Molecular weight based separation and identification of parent drug and 5 metabolites
Wiener 1961	Aqueous buffer plus drug in propylene glycol	Scintillation counting of carbon-14	Not reported	All molecules containing carbon-14
	Chloroform extracts	Paper and silica gel chromatography	Not applicable	Molecules with carbon-14 separated by chromatography
Davis 1960	Urine, feces, fat, plasma	Combustion plus counting in ionization chamber	Not reported	All molecules containing carbon-14
	Extracts of urine, feces, fat	Chromatographic separation and crystallization	Not applicable	Molecules with carbon-14 separated by chromatography

No validation data were provided for literature reports and relied entirely on the journal peer review process. In the human PK study, Onsrud et al. mentioned that their RIA assay for 17-HPC did not cross-react with 17-hydroxyprogesterone or cortisol but did not provide any additional supporting data. They also stated that the assay had a sensitivity of 5 nmol/l (2.14 ng/ml) and the inter-assay coefficient of variation (CV) was 7% at 50 nmol/l (214 ng/ml).

## Reference List

- DAVIS ME, PLOTZ EJ, LUPU CI, and EJARQUE PM (1960) The metabolism of progesterone and its related compounds in human pregnancy. *Fertil Steril* 11: 18-48
- Goldenberg RL (2002) The management of preterm labor. *Obstet Gynecol* 100: 1020-1037
- JUNKMANN K (1954) [Retard effect of gestagens.]. *Naunyn Schmiedebergs Arch Exp Pathol Pharmacol* 223: 244-253
- Onsrud M, Paus E, Haug E, and Kjorstad K (1985) Intramuscular administration of hydroxyprogesterone caproate in patients with endometrial carcinoma. Pharmacokinetics and effects on adrenal function. *Acta Obstet Gynecol Scand* 64: 519-523
- Reijnders FJ, Thomas CM, Doesburg WH, Rolland R, and Eskes TK (1988) Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial. *Br J Obstet Gynaecol* 95: 462-468
- van der Kamp HJ, Oudshoorn CG, Elvers BH, van BM, Otten BJ, Wit JM, and Verkerk PH (2005) Cutoff levels of 17-alpha-hydroxyprogesterone in neonatal screening for congenital adrenal hyperplasia should be based on gestational age rather than on birth weight. *J Clin Endocrinol Metab* 90: 3904-3907
- Vidaeff AC and Ramin SM (2006) From concept to practice: the recent history of preterm delivery prevention. Part II: Subclinical infection and hormonal effects. *Am J Perinatol* 23: 75-84
- Westphal U (1986) *Steroid-Protein Interactions II*. Springer-Verlag, Berlin, Germany.,
- WIENER M, LUPU CI, and PLOTZ EJ (1961) Metabolism of 17 alpha-hydroxyprogesterone-4-C14-17 alpha-caproate by homogenates of rat liver and human placenta. *Acta Endocrinol (Copenh)* 36: 511-519

### 3 Detailed Labeling Recommendations

See attached labeling for labeling recommendations.

### 4 Appendices

#### 4.1 Proposed labeling (**Note: contains only OCP recommendations**)

Note: deletions are indicated by ~~strike through~~ and additions are indicated by underline.

(b) (4)



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

/s/

-----  
Doanh Tran  
9/21/2006 04:33:26 PM  
PHARMACOLOGIST

Ameeta Parekh  
9/21/2006 04:48:09 PM  
BIOPHARMACEUTICS

*Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form*

**General Information About the Submission**

	Information		Information
NDA Number	21-945	Brand Name	Gestiva™
OCP Division	DCP3	Generic Name	17 alpha-Hydroxyprogesterone Caproate
Medical Division	DRUP	Drug Class	Hormone
OCPB Reviewer	Doanh Tran, Ph.D	Indication(s)	Prevention of recurrent preterm birth
OCPB Team Leader	Ameeta Parekh, Ph.D	Dosage Form	Sterile solution for injection
		Dosing Regimen	250 mg once weekly
Date of Submission	4/20/2006	Route of Administration	Intramuscular
Estimated Due Date of OCPB Review	7/15/2006	Sponsor	Adeza Biomedical
PDUFA Due Date	10/20/2006	Priority Classification	Priority
Division Due Date	9/20/2006		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			Analytical assays for 17-HPC and the 17-P drug product are located in section 3 of the NDA (i.e., chemistry section).
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1		Published paper and Adeza's PK analysis of literature report by Onsrud, 1985 of 1000 mg dose (PK-01-05)
multiple dose:	x			Same paper as single dose (i.e., Onsrud's paper). Loading dose was used.
<i>Patients-</i>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:	x	2		17P-IF-001 and 17P-CT-002
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>	x	2		Onsrud 1985 and Davis 1960
<b>Total Number of Studies</b>		5		
<b>Filability and QBR comments</b>				
	<b>"X" if yes</b>	<b>Comments</b>		
<b>Application filable ?</b>	x	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>	1. Is additional PK data needed for safe and effective use of 17 alpha-Hydroxyprogesterone Caproate?			
<b>Other comments or information not included above</b>	Sponsor also included 3 in vitro studies, Reports 303-1177-02, 304-1176-01, and Wiener 1961 (the latter one was a literature reference), examining potential CYP inhibitions and metabolic stability and profiling.			

<b>Primary reviewer Signature and Date</b>	
<b>Secondary reviewer Signature and Date</b>	

## Filing Memo

---

### Clinical Pharmacology Review

**NDA:** 21-945  
**Compound:** 17 alpha-Hydroxyprogesterone Caproate (17-HPC) Injection, 250 mg/mL  
**Sponsor:** Adeza Biomedical

**Date:** 05/05/2006  
**Reviewer:** Doanh Tran

**Background:** 17 alpha-Hydroxyprogesterone Caproate (17-HPC) 250 mg/mL is the active ingredient in the previously approved product Delalutin (NDA 10-347 and NDA 16-911) at the same strength and formulation but for different indications. Delalutin was withdrawn by FDA in year 2000 following discontinuation of marketing by that NDA's sponsor. In this NDA the sponsor, Adeza Biochemical, is seeking an indication of prevention of recurrent preterm birth based on data obtained from a published study by Meis et al. (2003). Minimal pharmacokinetic information from literature and in vitro studies were submitted in the NDA. The following paragraphs describe pertinent information available for review that are related to key sections of the Clinical Pharmacology section of the label.

**Bioavailability:** a waiver of bioavailability requirement was requested based on 21 CFR 320.22(b)(1). This reviewer does not concur because 1) the Delalutin label did not contain any pharmacokinetic information that would help label Gestiva™, 2) in the latest label (revised 1979), Delalutin was not indicated for use in pregnant women (e.g., the indications [prevention of] "habitual and threatened abortion" were not present), and 3) a waiver is not needed since there is a submitted trial of efficacy and safety, which would satisfy the bioavailability requirement if the trial is found to establish safety and efficacy of Gestiva. Note: Delalutin label in 1972 had the indications [prevention of] habitual and threatened abortion listed as probably effective, which required further investigation. A 1979 version of Delalutin label did not list habitual and threatened abortion as part of the indications section.

**Absorption, distribution, metabolism, and excretion (ADME):** Adeza did not conduct any study to examine 17-HPC ADME properties. The only in vivo pharmacokinetic data were from analysis of published paper by Onsrud et al. (1985) where 17-HPC was given either as intramuscular 1000 mg single dose or 1000 mg weekly following 5 daily 1000 mg loading doses. This study used a different dose and population (endometrial carcinoma patients) than the proposed indication. The formulation of 17-HPC is presumed to be the commercial product available in Norway in 1985, namely Primalut-Depot®. Primalut-Depot® formulation is similar to the to-be-marketed Adeza product but without the 2% Benzyl alcohol.

The sponsor also submitted results from an in vitro study examining the elimination and metabolic profile of 17-HPC in human hepatocytes. The results showed that 17-HPC was metabolized by human hepatocytes via both phase 1 and phase 2 pathways.

Literature data (Wiener 1961 and Davis 1960) suggested that in vivo 17-HPC metabolizes mainly into conjugates including glucuronide, sulfate, and an unknown conjugate. However, recent in vitro study by the sponsor did confirm metabolism to conjugates but glucuronide and sulfate conjugates were not found among the 5 chosen for structure analysis (including 2 that were classified by metabolynx® as sulfates). Instead, the major conjugates found in vitro were acetylated conjugates. It is not clear the

reason for the discrepancy between the in vivo and in vitro data. There were additional minor metabolites that were classified as sulfate conjugates by Metabolyx® but these were not confirmed with LC/MS/MS.

**Drug interactions:** No drug interaction studies were conducted. The in vitro effect of 17-HPC (0.02, 0.06, 0.2, 2.0, and 20 uM) on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 metabolism was examined using human liver microsomes.

**Inhibition:** CYP2C8, 2C9, and 2C19 were unaffected at concentration up to 2.0 uM. Inhibition of 15.5% to 37.7% were observed at 20 uM for the 2C isoforms. No inhibition of CYP3A4 at concentration up to 2 uM; however, at 20 uM, there was 49.4% inhibition. No inhibition of other studied isoforms at concentration up to 20 uM. The observed inhibition are all at concentrations above 2 uM, whereas the therapeutic C<sub>max</sub> is predicted to be less than 0.2 uM, suggesting low probability of in vivo inhibition of CYP enzymes by 17-HPC. However, the predicted C<sub>max</sub> was derived from the limited data in non-pregnant cancer patients in the Onsrud's study (1985) and the true C<sub>max</sub> in pregnant women are not known.

17-HPC also accelerated (not induction) the metabolism of CYP1A2 (max 85% at 0.02uM), 2A6 (max 153% at 0.02uM), 2B6 (max 79% at 0.2 uM), and to a lesser extent 2C8 (max 41% at 0.06 uM) in same liver microsome system. Sponsor proposes caution with CYP2A6 substrates such as warfarin and valproic acid. Sponsor propose that the metabolism rate of CYP2B6 and 1A2 substrates may be increased 2-fold; but for substrates that also metabolized by other CYP isoforms the effect would be minimal and for physicians to consults other labels for drug interaction info. It is not clear if this accelerated in vitro metabolism would results in in vivo effects.

No enzyme induction studies were conducted.

**Special population:** No study was performed in renal and hepatic impaired subjects. Pediatric and geriatric populations were not examined since the proposed indication would likely exclude use in these populations.

**Clinical vs. to-be-marketed formulation:** The formulation of the to-be-marketed formulation is identical to the formulation used in the NICHD trial that is submitted as basis of efficacy and safety. It is also identical to the previously marketed product, Delalutin 250 mg/mL. The clinical trial product was manufactured by 2 different manufacturers (Lot no. ECP001 by (b) (4) and lot no 7101831 by (b) (4), both were for (b) (4) which is also different than the commercial product manufacturer (Baxter Pharmaceutical Solutions, LLC for Adeza). ONDQA has data for review to determine pharmaceutical equivalence.

**Method validation:** No method validation data was available for the PK study by Onsrud et al. (1985) other than a statement in the paper which stated that the assay had a sensitivity of 5 nmol/l (2.14 ng/ml) the inter-assay coefficient of variation (CV) was 7% at 50 nmol/l (214 ng/ml). The paper also stated that no cross-reaction was found with cortisol or with 17-alpha-hydroxyprogesterone. Submitted phase 3 trial did not contain PK data.

**QT effect:** the sponsor submitted an in vitro hERG assay indicating low hERG channel blocking activity at predicted therapeutic concentration (approximately 0.21 uM 17-HCP inhibited hERG

potassium current by  $15.5 \pm 0.5\%$ ). Sponsor proposes that based on the in vitro results and lack of reported cases in the literature to suggest that progesterone has an effect on QT prolongation and no further assessment of 17-HPC on QT interval is needed.

**Recommendation:**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-945 is fileable.

Even though this NDA does not have any PK data in the target pregnant population, there is one phase 3 clinical study available for efficacy and safety review. Although the phase 3 trial data is not an ideal method of demonstrating bioavailability, it is not a refuse-to-file issue.

**Comments for sponsor:**

The submitted literature data on 17-alpha-hydroxyprogesterone caproate (17-HPC) pharmacokinetics (PK) is limited and will present a challenge in our ability to adequately label Gestiva™ for safe and effective use.

1. The submitted in vivo PK study by Onsrud et al. (1985) was done in non-pregnant, endometrial carcinoma patients using a 4-fold higher dose of 1000 mg and in limited sample size. It is not known if 17-HPC PK in these patients can be used to estimate the PK in the targeted population of pregnant women.
2. The metabolic pathway for elimination of 17-HPC is not established either in vitro or in vivo. It appears that phase 1 reactions may take place in addition to the phase 2 reactions that resulted in the acetyl conjugates. Data from a drug metabolizing enzyme identification study will help to better label Gestiva for safe and effective use.
3. 17-HPC in vitro caused inhibition of several important CYP enzymes. Since 17-HPC PK in pregnant women is not known, the clinical significance of these finding is not clear. Therefore, the safety risk to both mother and fetus due to the potential drug interactions is also not known.
4. The effect of 17-HPC on induction of CYP enzyme activity was not examined.
5. Since exposure response data is not available, it is not clear if the current dose is an optimal dose for safe and effective use.
6. You requested a waiver for bioavailability requirements. One method to satisfy the requirement for evidence of bioavailability as listed in 21 CFR 320.24(b)(4) is to provide “well-controlled clinical trials that establish the safety and effectiveness of the drug product”. A waiver is not needed if the clinical trials submitted in the NDA are determined during the review to meet the above criteria.

---

Doanh Tran, Ph.D., Primary Reviewer

---

Date

---

Ameeta Parekh, Ph.D., Team Leader

---

Date

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

/s/

-----  
Doanh Tran  
6/1/2006 04:00:42 PM  
PHARMACOLOGIST

Ameeta Parekh  
6/1/2006 04:26:34 PM  
BIOPHARMACEUTICS