

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 21057**

**ADMINISTRATIVE DOCUMENTS**

21-057 July 29, 1999

JUL 29 1999

Division Director Memo  
New Drug Application

**NDA:** 21-057  
**Sponsor:** Organon, Inc.  
**Drug:** Antagon (ganirelix acetate) 250 ug per 0.5mL injection  
**Indication:** Inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation  
**Date received:** January 29, 1999  
**Date of Memo:** July 29, 1999

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This application presents data to establish and support the use of Antagon (Ganirelix acetate), a new molecular entity, for the indication of inhibition of premature Luteinizing Hormone (LH) surges in women undergoing controlled ovarian hyperstimulation.

The sponsor has presented two completed controlled clinical studies to support the use of this gonadotropin-releasing hormone (GnRH) antagonist in women undergoing controlled ovarian stimulation as part of assisted reproductive strategies such as in-vitro fertilization (IVF).

The study of IVF techniques and the use of pharmaceuticals in IVF are difficult as the analyses and results are complicated by many factors. Many pharmaceutical agents (some that carry approved indications as part of ovarian stimulation strategies and some "off-label") are used concomitantly in highly titrated and tightly monitored protocol settings.

IVF protocols have evolved over the last decade with development and refinement of a spectrum of regimens and opportunities for oocyte retrieval ranging from natural cycle conditions to highly controlled ovarian hyperstimulation settings.

In the world of controlled ovarian hyperstimulation leading to oocyte retrieval in IVF settings, many products have been tested and various "standard" regimens have developed in the hopes of generating the best possible outcomes. Outcomes in the IVF world are measured in terms of number of follicles developed, number of mature oocytes retrieved, manner and number of embryos transferred and implanted: all leading to the ultimate anticipated outcome—number of healthy pregnancies and deliveries.

Many factors are thus important in analyzing improvements in care for the IVF patient undergoing controlled ovarian hyperstimulation. One hurdle in the path to success in controlled hyperstimulation settings involves the need to decrease the chance of premature ovulation due to spontaneous LH surges. When a woman is found to have such premature ovulation, she is no longer a candidate to complete IVF procedures during that cycle of therapy. Instead, she must abandon her hoped-for pregnancy as a result of IVF or must wait to begin the strenuous regimen of controlled hyperstimulation during a future cycle (with the continued risk during each attempted cycle for discontinuation due to premature ovulation resulting from spontaneous LH surge).

Ganirelix, a GnRH antagonist, is a logical pharmaceutical choice for inhibition of premature LH surges leading to inappropriate timing of ovulation. Gonadotropin-releasing hormone stimulates pituitary secretion of both Follicle Stimulating Hormone (FSH) and LH. Thus, a pure antagonist of the releasing hormone should allow for inhibition of the release of both FSH and LH.

The underlying premise of highly controlled ovarian hyperstimulation involves use of multiple pharmaceutical products and reproductive techniques. Candidates often undergo advance ablation of GnRH activity (usually through the use of a GnRH agonist) followed by the "controlled" stimulation of ovulation through multiple manipulations. Urinary menopausal or recombinant gonadotropins (FSH and sometimes LH) are used to stimulate follicle development. Intensive monitoring of end organ response—through serum estradiol levels as well as vaginal/pelvic ultrasound—is used to assess response, adjust dosing and proceed to an injection of human chorionic gonadotropin (hCG) in order to trigger ovulation. Following oocyte retrieval and appropriate incubation, embryos are then transferred to the patient and luteal and sometimes early pregnancy supportive measures (progesterone supplementation) are often instituted.

The evaluation of just one aspect of these complicated techniques is therefore a major regulatory/scientific challenge. The review team has done an excellent job and their results are summarized here.

### Clinical/Statistical

The Medical Officer and Group leader describe the two controlled safety and efficacy studies of ganirelix as well as one pregnancy follow-up study.

One of the randomized and blinded studies served as a dose-finding study in 342 women and supports the assertion of a minimally effective dose. Six dosage groups were evaluated. Selection of the optimal dose was ultimately based on the ability of ganirelix to prevent LH surges. The 0.25 mg (subcutaneous) per day dose was appropriately selected as the optimal minimal effective dose.

The pregnant subjects from the dose finding study were followed for pregnancy outcomes. In the evaluation of the resulting 73 infants, no obvious risks to the offspring of ganirelix subjects were seen. Further discussion of the follow-up of infant outcome for the entire clinical trial program is discussed below.

The third study presented constitutes the major establishment of safety and efficacy of ganirelix at the chosen dose. Clinical trial design for this Phase 3 study included randomization of 730 subjects to an IVF protocol involving the inclusion of either ganirelix (a GnRH antagonist) versus Buserelin (an unapproved GnRH agonist used commonly in Europe in this setting).

Because no direct comparison to a group using no antagonist or agonist could be made, the reviewers considered the comparison to historical controls. Historical controls for this review were developed by evaluating known results for IVF therapies over the last decade. Both the Medical Officer and Team Leader describe the expected results without the use of a GnRH agonist or antagonist through evaluation of a national registry. This registry is a collaborative effort by the Society of Assisted Reproductive Technology. Through the registry records review, the reviewers are comfortable that IVF success rates have improved when comparing results over times when GnRH agonists or antagonists were not employed to the current study.

The safety review of these studies revealed no unexpected findings. Ovarian hyperstimulation syndrome—a major and potentially dangerous concern during controlled stimulation—did not occur at any higher rate than expected and was similar to the known risk of this syndrome in this setting (<5%).

Several other studies are presented. Each provides supportive evidence that the use of an agonist or antagonist contributes to improved pregnancy rates.

In terms of pregnancy follow-up, the infant study described above (73 infants) is the one completed pregnancy and delivery follow-up study. A complete report of all pregnancies from ongoing (both US and European) clinical trials was expected within the next year. In all, new information on the outcome of over

21-057 July 29, 1999

200 pregnancies amongst women treated with Antagon was anticipated. After a phone discussion with the sponsor on July 26<sup>th</sup>, Organon was able to provide follow-up data on 199 further infants resulting from the clinical trial program for Antagon. The safety update also included 11 infant outcomes. Thus a total of more than 280 infant outcomes are known from the development program.

For these 280 live born infants, 3 were born with major malformations. These include one case of omphalocele, one case of hydrocephalus/meningocele and one Beckwith-Wiedemann syndrome (BWS). The case of BWS involved an infant with exomphalos and macroglossia. This infant underwent repair of his abdominal wall and required no other intervention.

The team reviewed information on infant outcome for other approved products used in controlled ovarian stimulation. Results for other products yield similar findings in terms of rate of malformations in offspring. The sponsor was asked to include the infant outcome data in their product labeling.

#### Clinical Pharmacology and Biopharmaceutics

Dr. Jarugula presents a clear description of the human pharmacokinetics in his review. This application was the subject of an Office of Clinical Pharmacology and Biopharmaceutics (OCPB) briefing. OCPB agrees that the application is acceptable and can be approved.

#### Pharmacology/Toxicology

I agree with Dr. Raheja's conclusion that the submitted preclinical data is sufficient to support the proposed use in controlled ovarian hyperstimulation. As is described, the mouse micronucleus assay (one assessment in the standard mutagenicity battery of tests) is to be repeated in order to assure that adequate doses are tested. This study is underway and will be submitted later this year. The submission and review of the results post-approval is acceptable to the pharmacology/toxicology team.

I agree with the team's determination that carcinogenicity studies are not required for this short-term indication. If this drug is developed for other indications, carcinogenicity studies may be needed.

Dr. DeGeorge provided senior level comments for the pharm/tox package. His comments were reviewed. With the following outcomes: The infertility information in the labeling is captured in the pregnancy section. Dr. Raheja has added a memo to the file confirming that no further pharm/tox studies are needed to evaluate impurities. Dr. DeGeorge had suggested a change in the units used to express relative exposures in the animals. The data submitted does not lend itself to this conversion so has not been done. The pharm/tox team has confirmed that the genotoxicity and reproductive toxicity data do not suggest any increased risk of birth defects and specifically do not point to BWS as a risk. The labeling suggestion for the pregnancy section is no longer relevant as the wording has been changed and is consistent with Dr. DeGeorge's comment.

#### Chemistry/Microbiology

As can be seen, several information requests were generated to both the NDA and Drug Master File (DMF) holders for this application. All issues have been resolved and the application is considered sufficient for approval.

Some members of the review team for ganirelix voiced concern over the name "Antagon". The concern was based on the concept that the name indicates the mechanism of action that is common to many drugs and could be misleading. After review and discussion with the labeling and nomenclature committee as well as my consideration of the level of concern, the name has been accepted.

21-057 July 29, 1999

**Labeling**

Several labeling comments were conveyed as a consequence of each discipline review as well as after Dr. Houn's as well as my reviews. These comments are captured in the "meeting minutes" section of the action package. The labeling submitted on July 29, 1999 is accepted.

**Phase 4 Commitments**

**Recommendations**

Approval with labeling as submitted July 29, 1999.

LS/ 7/29/99  
Lisa Rarick, MD  
Director  
DRUDP, HFD-580

cc: NDA 21-057  
HFD-580/Bennett/Slaughter/Mann/Moore/Rumble  
HFD-103/Houn/Collier

**CONFIDENTIAL**

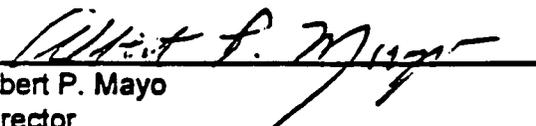
**Org 37462 Injection  
Debarment Certification**

1

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**CERTIFICATION**

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subscriptions (a) or (b) [Section 306 (a) or (b)], in connection with the New Drug Application for Org 37462 Injection NDA 21-057.

  
\_\_\_\_\_  
Albert P. Mayo  
Director  
Regulatory Affairs

05 NOV 98  
Date

NDA 21-057

Antagon™ (ganirelix acetate) 250 µg/mL injection  
Organon, Inc.

**Advisory Committee Meeting Minutes**

This application was not the subject of an Advisory Committee Meeting.

NDA 21-057

Antagon™ (ganirelix acetate) 250 µg/mL injection

Organon, Inc.

**CAC/Executive Committee Report**

No carcinogenicity studies are required for this short-term indication per Dr. Raheja, June 4, 1999. No CAC Executive Committee meeting was held.

NDA 21-057

Antagon™ (ganirelix acetate) 250 µg/mL injection

Organon, Inc.

**Carcinogenicity Studies**

No carcinogenicity studies are required for this indication per Dr. Raheja, June 4, 1999.

NDA 21-057  
Antagon™ (ganirelix acetate) 250 µg/mL injection  
Organon, Inc.

**Methods Validation**

The Methods Validation is pending. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated

NDA 21-057

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**Abuse Liability Review**

This product does not require an abuse liability review.

NDA 21-057

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Organon, Inc.

**Safety Update Review**

The safety update review is included in the Medical Officer's review dated June 15, 1999  
(see Tab B-1, p. 36).

NDA 21-057

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Organon, Inc.

**Labeling: FDA Reviews**

Labeling reviews are incorporated in the respective reviews.

NDA 21-057

Antagon™ (ganirelix acetate) 250 µg/mL injection  
Organon, Inc.

**Foreign Labeling**

This product has not been approved in any foreign country. There is no foreign market labeling for this product.

MEMO  
NDA 21-057

June 14, 1999

**Pediatric studies are not needed because the drug has little potential for use in pediatric patients.**

**/S/**

**Ridgely C. Bennett, M.D.**

NDA 21-057

Antagon™ (ganirelix acetate) 250 µg/mL injection  
Organon, Inc.

**Statistical Review of drug stability**

~~No statistical review of drug stability was performed for this product.~~

*addressed in chem reviews dated 5/25/99  
and 7/15/99.*

NDA 21-057

Antagon™ (ganirelix acetate) 250 µg/mL injection  
Organon, Inc.

**Statistical Review**

No statistical review is required per the attached memorandum from Dr. David Hoberman dated June 15, 1999.

Memorandum

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

Date: ~~May~~ June 15, 1999

From: David Hoberman, Ph.D., HFD-715

Subject: Ganirelix Injection for the prevention of LH surges

To: File (NDA# 21-057)

The data in this NDA was largely descriptive in nature. The Medical Division (DRUDP) decided that the most important evaluations of the drug would be made using historical experience. As such, no formal statistical review was deemed necessary.

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David Hoberman, Ph.D.

Concur: Dr. Kammerman *gok 6/15/99*

Dr. Nevius *gmv 6/15/99*

cc:

Arch NDA# 20-057

HFD-580

HFD-580/SSlaughter, MMann

HFD-715/DHoberman, DOB2, Chron

## PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

<b>NDA/BLA Number:</b>	<u>21057</u>	<b>Trade Name:</b>	<u>ORG37462(GANIRELIX ACETATE)250UG/0.5ML</u>
<b>Supplement Number:</b>	<u>0</u>	<b>Generic Name:</b>	<u>ORG37462(GANIRELIX ACETATE)250UG/0.5ML</u>
<b>Supplement Type:</b>		<b>Dosage Form:</b>	<u>FU</u>
<b>Regulatory Action:</b>	<u>PN</u>	<b>Proposed Indication:</b>	<u>The inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation.</u>

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, Pediatric content not necessary because of pediatric waiver

**What are the INTENDED Pediatric Age Groups for this submission?**

NeoNates (0-30 Days )     Children (25 Months-12 years)  
 Infants (1-24 Months)     Adolescents (13-16 Years)

<b>Label Adequacy</b>	<u>Does Not Apply</u>
<b>Formulation Status</b>	.....
<b>Studies Needed</b>	.....
<b>Study Status</b>	.....

**Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?** NO

**COMMENTS & RECOMMENDATIONS:**

This Page was completed based on information from a Project Manager/Consumer Safety Officer, DIANE MOORE

JSI  
 \_\_\_\_\_  
 Signature

7/22/99  
 \_\_\_\_\_  
 Date

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

TE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # NDA 21057 Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE6

HFD-580 \_\_\_\_\_ Trade and generic names/dosage form: Antagon™ (ganirelix acetate) 250 µg/0.5 mL injection Action: AP/AE/NA

Applicant Organon, Inc. Therapeutic Class IP

Indication(s) previously approved none

Pediatric information in labeling of approved indication(s) is adequate X inadequate \_\_\_\_\_

Proposed indication in this application reduction of premature LH surges in women undergoing controlled ovarian hyperstimulation

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1 month) Infants (1month-2yrs) Children (2-12yrs) Adolescents (12-16 yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing.

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from the Medical Officer (see attached)

Signature of Preparer and Title SI

Regulatory Project  
Manager Date 6/2/99

ORIG NDA/BLA # NDA 21-057

HFD-580 /DIV FILE

NDA/BLA ACTION PACKAGE

HFD-006/ KROBERTS

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

**PATENT INFORMATION AND ORIGINAL DECLARATION**

**PATENT INFORMATION**

21 CFR §314.53(c)(1)

(i) U.S. Patent No. 4,801,577  
Expiration Date - February 5, 2007

(ii) Type of Patent - Composition

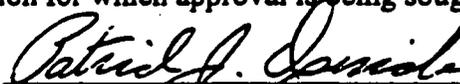
(iii) Name of Patent Owner of Record

Syntex (U.S.A.) Inc.  
3401 Hillview Ave.  
P.O. Box 10850  
Palo Alto, CA 94303

**ORIGINAL DECLARATION**

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 4,801,577 covers the formulation, composition and/or method of use of ganirelix acetate. This product is the subject of the application for which approval is being sought.



Patrick J. Osinski  
Vice President  
Organon Inc.

**PATENT INFORMATION AND ORIGINAL DECLARATION**

**PATENT INFORMATION**

21 CFR §314.53(c)(1)

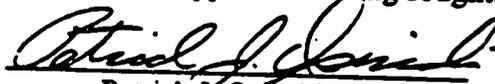
- (i) U.S. Patent No. 5,767,082  
Expiration Date - June 16, 2015
- (ii) Type of Patent - Method of Use
- (iii) Name of Patent Owner of Record

Syntex (U.S.A.) Inc.  
3401 Hillview Ave.  
P.O. Box 10850  
Palo Alto, CA 94303

**ORIGINAL DECLARATION**

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 5,767,082 covers the formulation, composition and/or method of use of ganirelix acetate. This product is the subject of the application for which approval is being sought.



Patrick J. Osinski  
Vice President  
Organon Inc.



d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /  / NO /  / OTC Switch /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_ / NO /\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.**

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS -**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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YES /  / NO /  /

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain:

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- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / \_\_\_ /      NO / \_\_\_ /

If yes, explain:

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- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:
- 
- 

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES / \_\_\_ /                      NO / \_\_\_ /

Investigation #2                      YES / \_\_\_ /                      NO / \_\_\_ /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____	_____
_____	_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____	_____
_____	_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	IND # _____	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> / Explain: _____
Investigation #2	IND # _____	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> / Explain: _____



## **CLAIMED EXCLUSIVITY**

**21 CFR §314.50 (j)(1) and (2) and (3)**

**In the opinion of Organon Inc., and to the best of its knowledge and belief, no other drug product containing ganirelix acetate, the active ingredient in ORG 37462 Injection (the subject of NDA 21-057), has been previously approved under section 505 (b) of the Federal Food, Drug and Cosmetic Act (as evidenced by information published in the FDA list of "Approved Drug Products with Therapeutic Equivalence Evaluations") or has been previously marketed in the United States. Accordingly, Organon Inc. claims, and is entitled to, the exclusivity set forth in 21 CFR §314.108 (b) (2) and 505 (c) (3) (D) (ii) of the Federal Food, Drug and Cosmetic Act.**

MEMO TO THE FILE

NDA 21-057

Drug product: Antagon (Ganirelix acetate) injection

Sponsor: Organon Inc. West Orange, NJ

This is in response to Dr. Joseph DeGeorge comment regarding a statement in the Pharmacology review that "depending upon the Chemist review of the submission with regards to the impurity profile, more toxicity studies may be requested with the new drug substance produced by

The review chemist, Dr. De Swapan has stated that the impurity profile of the present drug substance is equivalent to the previous product and as such no more toxicity studies were required.

/S/

7/28/99

Krishan Raheja, Review Pharmacologist

CC: A.Jordan  
D.Moore

/S/

/S/

9/28

Memo to the file

Topic: Pharmacology recommendations for labeling changes

NDA No. 21-057

Sponsor: Organon Inc. West Orange, NJ

Drug name: Ganirelix acetate

Indication: Prevention of premature surges in women undergoing controlled ovarian hyperstimulation.

Under NDA review dated 6-7-99, pharmacology had requested that 1) the sponsor conduct a mouse micronucleus assay according to ICH guidelines and 2) the doses used in the reproductive toxicity studies be expressed as multiples of the human therapeutic dose on body surface area basis.

Sponsor has agreed to conduct the mouse micronucleus assay and also has made other necessary changes as requested.

Pharmacology now considers the labeling adequate.

HFD-580

HFD-580/A.Jordan/D.Moore

1S/ 7/18/99  
Krishan L. Raheja, DVM, PhD

1S/ 7/16

July 16, 1999  
~~JUN 16 1999~~

MEMORANDUM

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

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DATE: July 15, 1999

FROM: Venkateswar R. Jarugula, Ph.D. (HFD-870) /S/ 7/15/99

THROUGH: Amecta Parekh, Ph.D., Team Leader (HFD-870) /S/

TO: HFD-580

RE: Labeling for NDA 21-057 (Ganirelix Acetate SC injection)

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Organon, Inc. submitted a revised labeling for Antagon ( NDA 21-057) on July 11, 1999, in response to the comments noted in Clinical Pharmacology and Biopharmaceutics review dated 06/25/99. The revised labeling is adequate from Clinical Pharmacology and Biopharmaceutics perspective.

cc: NDA 21-057, HFD-580 (Bennett, Moore), HFD-870 (M.Chen, Parekh), CDR (B.Murphy for Drug)

Memo to NDA 21-057 Ganirelix acetate  
Florence Houn MD MPH FACP  
July 29, 1999

JUL 29 1999

IS/ 7/29/99

This application supports the approval of ganirelix acetate for the inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation as part of assisted reproductive technologies. Ganirelix is a gonadotropin releasing hormone (GnRH) antagonist. This is the first GnRH antagonist that will be approved by the Food and Drug Administration. The sponsor will need to conduct the mouse micronucleus assay as part of its phase 4 pharm-tox commitment to FDA.

The GnRH agonists control LH surges by first binding to pituitary receptors which causes the release of gonadotropins (FSH and LH). After continued administration of GnRH agonists, there is down-regulation of the receptors and eventual suppression of endogenous LH and FSH production. Thus, a logical and physiologic mechanism for primary blockade of GnRH by a GnRH antagonist is supported.

The efficacy trials are well described by the medical officer, team leader, and division director. Of note, the first trial is a phase 2 double blind, randomized, dose-finding study conducted in 13 centers to select the minimal effective dose of ganirelix that would prevent premature surges of LH. There were 342 subjects randomized to one of six dose groups. The second trial is a phase 3, multi-centered, open-labeled, non-inferiority study using buserelin as an active control which not approved for use in the US (but approved in Europe). There were 486 subjects randomized using 2:1 randomization pattern to receive 0.25 mg of ganirelix and 244 subjects randomized to receive buserelin. The goal of the study was to demonstrate the mean number of cumulus-oocyte complexes and the pregnancy rates with ganirelix were comparable or better to standard of care in Europe using buserelin. Finally, FDA had the sponsor submit historical data from the medical literature supporting the role of GnRH agonists, which are currently used off-label for the same indication as ganirelix.

The initial safety database included a follow-up of pregnancies from the phase 2 study. A total of 68 pregnancies resulted in 73 infants, one having Beckwith Wiedemann Syndrome. There were also minor abnormalities including two with fetal maturation impaired and two born pre-maturely with abruptio placenta. FDA then asked and received follow up of roughly 200 infants (practically the entire clinical trials' database of pregnancies), revealing no further cases of BWS.

This application raises several points related to drug development policy and review for FDA: a non-inferiority trial based on an active control product approved by European authorities, but not by FDA; use of historical data of a GnRH agonist to support the role of a GnRH antagonist; and the presence of a very rare congenital abnormality that resulted from a pregnancy that was assisted by study drug. In addition, no FDA statistical review was performed because of the descriptive nature of the studies. The clinical relevance of findings was interpreted by the medical review staff.

Non-inferiority trials test whether the effectiveness of a new technology is no worse than that of an existing technology. The lower boundary of outcome difference between or among study arms needs to be specified a priori. For ganirelix, the numbers of cumulus-oocyte complexes and pregnancy rate were endpoints. Differences of less than 3 oocytes and 5% pregnancy rate were stated as clinically acceptable. The study resulted in an estimated treatment mean of number of cumulus-oocyte complexes for ganirelix of 8.3 and 9.3 for buserelin. For on going pregnancies, the estimated treatment rate was 20.3% for ganirelix and 25.7% for buserelin. The lower limits for the 97.5% confidence interval of the difference between ganirelix and buserelin for oocytes was -1.8 and for pregnancy rates was -11.9%. While "winning" on oocyte complex, pregnancy rate was not equivalent. However, the effectiveness standard as outlined by the Food Drug and Cosmetic Act requires the sponsor to provide substantial evidence that the drug does what its sponsors purport it can to do under labeled conditions. The sponsor's indication for the drug does not include a relative efficacy claim. Given this, historical data could be used to support the hypothesis that ganirelix is more effective than placebo. (The sponsor and FDA agreed that for this study

placebo trials would be difficult in this population of women, although patients were only subject to one IVF cycle. Future drug sponsors and FDA may agree to have placebo-controlled cycle or cycles.) The sponsor submitted publications from 1990 through 1995 that report the pregnancy rate for in-vitro fertilization (IVF) cycles without GnRH agonists ranged from 0-25%. With GnRH agonists, the rates from 1994-97 were from 19-45%. There are no historical data with GnRH antagonists, like ganirelix. Previous antagonists had serious histamine-type allergic reactions that thwarted their development. The mechanism of action for ganirelix, a GnRH antagonist, is believed to be more direct than GnRH agonists (as mentioned above), thereby providing the rationale to support approval.

With respect to infant outcomes, Beckwith Wiedemann Syndrome (BWS) is a rare event, occurring at a rate of 1 per 15,000. It is sometimes related to inheritance, but most cases are spontaneous. Some cases have chromosomal abnormalities identified. From a pharm-tox perspective, there is no data to suggest genotoxicity of ganirelix, but the mouse micronucleus assay will be completed to have the full pharm-tox battery of tests available for assessment. The case report on this infant states there is no chromosomal testing data and the child is reported as having moved away and is lost to follow up. To address concerns about this event, FDA asked the sponsor to follow up the case to see if there is family history of this disorder. FDA also asked for follow up on all pregnancies assisted by ganirelix in the sponsor's clinical trials to see infant outcomes, in particular the presence of BWS. A second case of BWS would have been very worrisome, but this was not present. The division and office discussed the possibility of a pregnancy registry, either for drug-assisted pregnancies or inadvertent fetal exposure. The use of pregnancy registries has limitations and requires careful planning and thoughtful procedures in order to gather useful surveillance data. It was decided that advisory committee discussion, possibly later this year, on the indications and appropriateness of pregnancy registries for drugs assisting reproduction would be useful. The labeling of ganirelix will have this event identified as an adverse event as well as include the other adverse outcomes for infants. In general, labeling of reproductive drugs should contain such information as the ultimate clinical endpoint for drugs assisting reproduction (and what patients are most concerned about) is the newborn and it's outcome.

APPEARS THIS WAY  
ON ORIGINAL

# REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee  
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Reproductive and Urologic Drug Products	HFD-580
Attention: Moo-Jhong Rhee, Ph.D.	Phone: 827-4237
Date: September 29, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: ANTAGON	IND# 1
Established name, including dosage form: Ganirelix acetate	
Other trademarks by the same firm for companion products:	
Indications for Use (may be a summary if proposed statement is lengthy): Prevention of premature LH surges in women undergoing ovarian hyperstimulation	
Initial Comments from the submitter (concerns, observations, etc.): The dosage form is 0.5ml disposable, prefilled syringe affixed with 27 gauge 1/2inch needle And to be administered via SC. This drug is a GnRH antagonist and the trademark has that connotation.	

Note: Meetings of the Committee are scheduled for the 4<sup>th</sup> Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

# Minutes of Teleconference

**Date:** June 17, 1999      **Time:** 10:30 - 11:00 AM      **Place:** Parklawn; Room 17B-43

**NDA:** 21-057      **Drug Name:** Antagon (ganirelix acetate) for injection

**Type of Meeting:** Guidance (Labeling)

**Indication:** GnRH antagonist for the reduction of premature LH surges in women undergoing controlled ovarian hyperstimulation

**External Constituent:** Organon, Inc.

**FDA Lead:** Ms. Diane Moore

**External Participant Lead:** Mr. Albert Mayo

**Meeting Recorder:** Ms. Diane Moore

## **FDA Participants:**

Shelley Slaughter, M.D., Ph.D. - Team Leader, DRUDP (HFD-580)  
Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)  
Diane Moore - Regulatory Project Manager, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)

## **External Participants:**

Albert P. Mayo, Director, Regulatory Affairs, Organon, Inc.  
Eric Oriemans, Ph.D. International Project Manager, NV Organon  
Marjo Peters, Ph.D. Regulatory Affairs, NV Organon  
Joel Krasnow, M.D. Associate Director, Medical Services, Organon Inc.  
David Stern - Project Management, Marketing, Organon Inc.  
Dana Petro - Medical writer

**Meeting Objective:** To discuss Phase 4 commitment and further labeling comments for NDA 21-057.

**Background:** See teleconference minutes dated May 20, and June 7, and 10, 1999. On June 11, 1999, the sponsor sent a copy, via telefacsimile, of the combined revisions to the label for NDA 21-057. A hard copy will follow.

## **Discussion:**

- the final report for the mouse micronucleus assay will not be available by the User Fee Goal Date; the report is scheduled for completion in September 1999

## **Decisions:**

- the sponsor should submit the final report for the mouse micronucleus assay for review; if the report cannot be submitted during the review clock, a Phase 4 commitment should be made to submit the report in September 1999

**Action Items:**

- Item
- incorporate the above revisions to the labeling
- minutes to sponsor

**Responsible Person:**  
Organon, Inc.

**Date Due:**  
1-2 days

DRUDP

1 month

*/S/*

*8/3/99*

Signature, minutes preparer

*/S/*

*8/3/99*

Signature, Chair

drafted: dm/6.19.99/n21057TC61799.doc

**Concurrence:**

TRumble 07.20.99/SSlaughter 07.22.99/RBennett 08.02.99

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/LPauls/TRumble/AParekh/VJarugula/D Moore

HFD-580/KRaheja/AJordan/Rheem/SDes/KMeaker/DHoberman

# Minutes of Teleconference

**Date:** July 8, 1999

**Time:** 1:30 - 2:15 PM

**Place:** Parklawn; Room 17B-43

**NDA:** 21-057

**Drug Name:** Antagon (ganirelix acetate) for injection

**Type of Meeting:** Guidance (Chemistry)

**Indication:** GnRH antagonist for the reduction of premature LH surges in women undergoing controlled ovarian hyperstimulation

**External Constituent:** Organon, Inc.

**FDA Lead:** Dr. Moo-Jhong Rhee

**External Participant Lead:** Mr. Albert Mayo

**Meeting Recorder:** Ms. Diane Moore

## **FDA Participants:**

Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

## **External Participants:**

Albert P. Mayo - Director, Regulatory Affairs, Organon, Inc.

Henk Koops – Regulatory Affairs NV Organon

John Engelhart – Manager Pharmaceutical Development

Eric Orlemans, Ph.D. – Project Management, NV Organon

Peter Jansen – Manufacturing Technology

Jay Rheingold Director, Pharmaceutical Development

**Meeting Objective:** To discuss drug specifications and labeling comments for NDA 21-057.

## **Discussion:**

- the reference standard was tested at  $-20^{\circ}\text{C}$  for a 2-year retest period
- the amount of potency that is changed upon storage and the monitoring process should be clarified
- the sponsor explained that the standard was made by dissolving a defined quantity from Batch K in water and dispensing it into vials and freeze drying the vials; they are stored at  $-20^{\circ}\text{C}$
- determinations demonstrated that the standard was the same as the starting Batch K after 12-months storage at  $-5^{\circ}\text{C}$ ; the working standard, stored at  $-20^{\circ}\text{C}$  has an expiry date of two years
- the sponsor is requesting 24 months shelf life

## **Decisions:**

- the amount of glacial acetic acid in the product should be clarified in the DESCRIPTION section
- the sponsor must commit to provide data from 18 month stability study
- the end of shelf life specifications contains too high a level of impurities
- FDA proposed specifications are 18 months at  $25^{\circ}\text{C}$

- if original specifications are too tight for future batches to meet, the sponsor can file a post-approval supplement based on the data to revise the specifications
- the sponsor's proposal for the batches are too wide; FDA proposes <.1%

**Action items:**

<b>Item</b>	<b>Responsible Person:</b>	<b>Date Due:</b>
• convey decision to accept or reject FDA specifications proposal and follow-up with commitment letter	Organon, Inc.	July 9, 1999
• incorporate the above revisions to the labeling	Organon, Inc.	±2 days
• minutes to sponsor	DRUDP	1 month

\_\_\_\_\_  
Signature, minutes preparer

\_\_\_\_\_  
Signature, Chair

drafted: dm/6.19.99/n21057TC61799.doc

**Concurrences:**

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/LPauls/TRumble/AParekh/VJarugula/D Moore

HFD-580/KRaheja/AJordan/Rheem/SDes/KMeaker/DHoberman

# Teleconference Minutes

**Date:** June 25, 1999

**Time:** 2:30-2:45 p.m. **Location:** Parklawn; Rm. 17B-45

**NDA:** 21-057

**Drug:** Antagon™ (ganirelix acetate) Injection

**Indication:** Inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation

**Sponsor:** Organon Inc.

**Type of Meeting:** Information Request

**Meeting Chair:** Marianne Mann, MD

**External Lead:** Al Mayo

**Meeting Recorder:** Domette Spell-LeSane NP-C

**FDA Attendees:**

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products,  
(DRUDP HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacology Reviewer, DRUDP (HFD-580)

Terri Rumble, Chief, Project Management Staff, DRUDP (HFD-580)

Domette Spell-LeSane, Regulatory Project Manager, DRUDP (HFD-580)

**External Attendees:**

Al Mayo, Director Regulatory Affairs, Organon Inc.

**Meeting Objective:**

To discuss Pharmacology concerns discovered in the draft package insert (4<sup>th</sup> Revision) faxed to the division June 18, 1999.

**Background:**

This NDA is currently under review, draft labeling was faxed by the sponsor for review on June 18, 1999, FDA requested this T-con to discuss concerns regarding the pharmacology content of the label.

**Discussion:**

- teratogenicity studies performed for this NDA should be included in the Carcinogenesis and Mutagenesis, Impairment of Fertility section of the label; rabbit and mice doses in mg/kg should be expressed as multiples of the human therapeutic dose on a body surface area basis
- Pregnancy category is satisfactory as presented

NDA 21-057  
Teleconference minutes 6/25/99  
Page2

**Decisions made:**

- sponsor agrees with recommended changes

**Unresolved decisions:**

- None

**Action Items:**

- sponsor to fax changes to draft label by COB 6/29/99
- chemistry information requested by FDA is being finalized and will be faxed in one week
- Phase 4 commitment will be submitted in September or October 1999
- minutes will be exchanged with the sponsor within 30 days

Note: changes to draft label faxed by the sponsor July 1, 1999, was satisfactory

IS/

Minutes Preparer

IS/

Concurrence, Chair

7-13-99

cc:

Original NDA 21-057  
HFD-580/DivFile  
HFD-580/Moore/Rumble/  
HFD-580/Mann/Raheja/Slaughter/Bennett

drafted: dsl, 7/6/99

concurrence: LPauls, 7.8.99/Mann, 7.9.99/Raheja; 7.12.99/Rumble, 7.14.99/

final: 7/13/99

**TELECONFERENCE MINUTES**

# Minutes of Teleconference

**Date:** June 10, 1999      **Time:** 11:56 AM - 12:10 PM      **Place:** Parklawn; Ms. Moore's Office

**NDA:** 21-057

**Drug Name:** Antagon (ganirelix acetate) for injection

**Type of Meeting:** Guidance (Labeling)

**Indication:** GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

**External Constituent:** Organon, Inc.

**FDA Lead:** Ms. Diane Moore

**External Participant Lead:** Ms. Carole Ann Cartier

**Meeting Recorder:** Ms. Diane Moore

**FDA Participants:**

Diane Moore -- Regulatory Project Manager, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)

**External Participants:**

Carole Ann Cartier - Sr. Regulatory Associate, Regulatory Affairs, Organon, Inc.

**Meeting Objective:** To discuss labeling comments for the **DOSAGE AND ADMINISTRATION** section and the **Directions for using Antagon (ganirelix acetate) Injection** subsection of the labeling for NDA 21-057.

**Background:** See teleconference minutes dated May 20, and June 7, 1999. On June 9, 1999, the sponsor sent a copy, via telefacsimile, of the combined revisions to the label for NDA 21-057, with a hard copy to follow.

**Discussion:**

- **CLINICAL PHARMACOLOGY** section, **Clinical Studies** subsection
  - the exclusion criteria was not included in this section in the June 9, 1999, revision

**Decisions:**

- **PRECAUTIONS** section, **Laboratory Tests** subsection
  - the designation ( $*10^9/L$ ) should be clarified
- **DOSAGE AND ADMINISTRATION** section
  - the instructions for use of the syringe appears to have a disconnection at item number 8; the following should be inserted in that item:

NDA 21-057  
Meeting Minutes - June 10, 1999

Action items:

- Item
- incorporate the above revisions to the labeling
- minutes to sponsor

Responsible Person:  
Organon, Inc.

Date Due:  
1 week

DRUDP

1 month

ISJ  
Signature, minutes preparer

6/18/99

drafted: dm/612.99/n21057TC61099.doc

Concurrences:

SSlaughter 06.17.99

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/LPauls/TRumble/AParekh/VJarugula/D Moore

HFD-580/KRaheja/AJordan/Rheem/SDes/KMeaker/DHoberman

# Minutes of Teleconference

**Date:** June 7, 1999      **Time:** 10:30 - 11:30 AM      **Place:** Parklawn; Rm. 17B-43

**NDA:** 21-057      **Drug Name:** Antagon™ (ganirelix acetate) for injection

**Type of Meeting:** Guidance (Labeling)

**Indication:** GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

**External Constituent:** Organon, Inc.

**FDA Lead:** Dr. Marianne Mann

**External Participant Lead:** Mr. Al Mayo

**Meeting Recorder:** Ms. Diane Moore

## **FDA Participants:**

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

Swapam De, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

## **External Participants:**

Albert P. Mayo, Director, Regulatory Affairs, Organon, Inc.

Carole Ann Cartier - Sr. Regulatory Associate, Regulatory Affairs, Organon, Inc.

Joel Krasnow, M.D. - Medical Services, Organon, Inc.

Dana Petro, Pharm. D. - Medical Services, Organon, Inc.

David Stern - Product Management, Organon, Inc.

Lynn Angell - Product Management, Organon, Inc.

Bernadette Mannaerts - International Clinical Development Team Leader, NV Organon

Eric Orlemans, Ph.D. - Project Management, NV Organon

Marjo Peters, Ph.D. - Regulatory Affairs, NV Organon

**Meeting Objective:** To discuss labeling comments from the teleconference held on May 20, 1999, the sponsor's telefacsimile sent on June 4, 1999, and the FDA telefacsimile sent on June 4, 1999, for NDA 21-057.

**Background:** Internal labeling discussions were held on May 18, May 25, and June 4, 1999. The sponsor sent a response to the May 26, 1999, teleconference between the Division and representatives of Organon, Inc. in a telefacsimile on June 4, 1999. FDA comments from the May 25, 1999, meeting were sent to the sponsor via telefacsimile on June 4, 1999.

**Discussion:**

- the plant inspections at GMBH feder, the manufacturing site facility, and NV Organon, for the drug substance, went well
- although it cannot be succinctly explained, the sponsor's rationale for the different ongoing pregnancy rates in the dose-finding study and the Phase 3 study was that changes in personnel at the various clinical sites caused variable levels of expertise regarding drug administration which affected the final outcome in the procedures (the dose-finding study had more pregnancies than the Phase 3 study)
- in the **CLINICAL PHARMACOLOGY** section, Pharmacokinetics subsection, the added sentence, \_\_\_\_\_ is relevant to the physiology of the drug; it brackets the to-be-marketed drug; additional FDA revisions to this section could be suggested after finalization of the Biopharmaceutics review

**Decisions:**

- Pharmacology information
    - the mouse micronucleus report should be submitted; a draft report would be acceptable at this time; a time commitment may be necessary to allow review of this report for the NDA
    - although previously requested, significant reproductive/toxicology findings have not been incorporated into the labeling; these findings should be included in the draft package insert; doses should be expressed as mg/kg, and the multiples of the human therapeutic doses should be based on actual systemic exposure or on body surface area
  - **DESCRIPTION SECTION**
    - the amount of Mannitol should be added in the carton and label whenever the sterile syringe is mentioned; the pH adjustment to 5.0 should also be added
  - **CLINICAL PHARMACOLOGY** section
    - the sponsor proposed that sentences 2 and 3 that read, \_\_\_\_\_ be retained in the label because they illustrate the fact that LH rises are transient, expected and not deleterious
      - the Division agrees that the sentences can be retained in the label
    - the sponsor feels that their previous term, \_\_\_\_\_ is a more appropriate term than the suggested term, \_\_\_\_\_ in the Clinical Studies section, fifth paragraph, second sentence, that begins, \_\_\_\_\_
      - the Division agrees to allow the word, \_\_\_\_\_ to remain in the labeling
    - the sponsor objected to the addition of parameters referring to patients with LH rises >10 mIU in Table 3 because the parameters were not based on the study protocol and the decision to include these subjects was at the discretion of the investigator. In addition, the numbers of patients with LH > 10 mIU were very small
      - three items that were suggested by the Division to be added to Table 3, but were not included in the sponsor's revisions to the label were:
        - the number of subjects with LH  $\geq$  10 mIU/mL
        - the number of subjects to reach retrieval with LH >10 mIU/mL
        - and the number of subjects with LH  $\geq$ 10 retrieval with no embryo transfer
- the Division feels strongly that the line that reads, \_\_\_\_\_ should be inserted; with an asterisk that corresponds to a footnote that reads, \_\_\_\_\_ this is relevant to the indications statement; the subsequent two items do not have to be added; the sponsor found this proposal acceptable

- **Clinical Studies subsection**
  - the sponsor proposed to include in the labeling the exclusion criteria for the studies; this includes women who had PCOS or no or low ovarian reserve
- **Pharmacokinetics (PK) subsection**
  - the doses referring to the PK parameters should be converted from mg to micrograms for consistency
- **INDICATIONS section**
  - the wording, \_\_\_\_\_ indicates that there is 100% success in reducing LH surges, when that is not the case in this situation; the term, \_\_\_\_\_ clarifies that this drug does not eliminate the incidence of LH surges in all cases; this is different from using prevention for a disease state; the sponsor can propose an alternative language to this section
- **PRECAUTIONS section**
  - **General**
    - the sentence that begins, \_\_\_\_\_ should be supported by data; a full bioanalysis report should be submitted for review
  - **Laboratory Tests subsection**
    - in the sentence that begins, \_\_\_\_\_ the laboratory cut-off of FSH should be clarified in the label with a definition of low or no reserve of FSH or estrogen levels defining the study population
    - the abnormal white blood cell (WBC) counts in this group of patients can be attributed to the neutrophil counts rising in patients undergoing ovulation induction; laboratory normal ranges should be clarified
- **HOW SUPPLIED section**
  - the sentence that reads, \_\_\_\_\_ can be deleted because the warning is in another section of the labeling and does not need to be duplicated
- **DOSAGE AND ADMINISTRATION section**
  - comments for this section will be conveyed at a later date
- the sponsor should submit a revised label based on the labeling comments from the May 20, 1999 teleconference and today's comments

**Action items:**

Item	Responsible Person:	Date Due:
• provide time table for mouse micronucleus report	Organon, Inc.	1 day
• discuss mouse micronucleus issue with supervisor	Dr. Raheja	1 week
• provide revised labeling based on these recommendations	Organon, Inc.	24-48 hours
• minutes to sponsor	DRUDP	1 month

ISI 7/13/99

Signature, minutes preparer

ISI M.D. 7/13/99

Signature, Chair

NDA 21-057

Meeting Minutes - June 7, 1999

Page 4

drafted: dm/5.28.99/n21057TC52099.doc

Concurrences:

RBennett, SDe 06.14.99/KRaheja 06.17.99/MMann 06.21.99

Concurrence not received from TRumble/VJarugula

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/LPauls/TRumble/AParekh/VJarugula/D Moore

HFD-580/KRaheja/AJordan/Rheem/SDes/KMeaker/DHoberman

# Meeting Minutes

Date: June 4, 1999

Time: 3:00 - 3:30 PM

Place: Parklawn; Rm 17B-43

NDA: 21-057

Drug Name: Antagon™ (ganirelix acetate) for injection

Type of Meeting: Third Labeling Meeting

Indication: GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

Sponsor: Organon, Inc.

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

## FDA Participants:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Shelley Slaughter, M.D. - Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective: To discuss the sponsor's June 9, 1999, response to the Division's labeling recommendations for NDA 21-057.

Background: Comments from the Division labeling discussions held on May 18, 1999, were conveyed to Organon, Inc. in a Teleconference on May 20, 1999. The sponsor responded to those comments in a telefacsimile dated June 4, 1999, which was followed by a June 8, 1999, submission to the file. A second Division labeling discussion was held on May 25, 1999. A teleconference is scheduled for June 7, 1999 to discuss the sponsor's June 4, 1999 response and the comments from the May 25, 1999, meeting.

## Discussion Items:

- the sponsor made most of the suggested revisions to the ANTAGON labeling; three comments in response to the FDA comments are delineated in the Decisions Reached section

## Decisions:

### Sponsor Comments

- CLINICAL PHARMACOLOGY section

- the sponsor proposed retaining sentences 2 and 3 that read,

\_\_\_\_\_ be retained in the label because they illustrate the fact that LH rises are transient, expected and not deleterious



# Meeting Minutes

Date: May 25, 1999

Time: 1:30 - 3:00 PM

Place: Parklawn; Rm 17B-43

NDA: 21-057

Drug Name: Org 37462 (ganirelix acetate) for injection

Type of Meeting: Labeling Meeting

Indication: GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

Sponsor: Organon, Inc.

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

## FDA Participants:

Florence Houn M.D., M.P.H. - Office Director, ODE III (HFD-103)

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Shelley Slaughter, M.D. - Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Jerry Willett, M.D. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective: To complete preliminary discussions regarding the labeling recommendations for NDA 21-057.

Background: This NDA was submitted on January 28, 1999; filing date is March 29, 1999; the to-be-marketed dose is 0.25 ng; target Division goal date is June 15, 1999.

## Discussion Items:

- Clinical
  - although hypersensitivity is not expected for a third generation agonist, the study duration lasted only one cycle; it may be warranted to include this information in the labeling
  - the labeling may need to include the fact that PCOS patients and patients with low or no ovarian response to FSH HMG were excluded from the trials
- Chemistry, Manufacturing and Quality Control
  - the stability of the product under extreme temperatures should be assessed

## Decisions:

- the CLINICAL PHARMACOLOGY section, including Pharmacokinetics, *Absorption*, *Distribution*, *Metabolism*, *Elimination*, Special Populations subsections, and the first paragraph of the Clinical Studies subsection, should be revised (see attached)
- in the third paragraph of the Clinical Studies subsection, High E<sub>2</sub> levels and high LH and FSH levels with low E<sub>2</sub> levels should be defined; the numbers of subjects in these categories should be included

- **INDICATIONS AND USAGE** section
  - the indication should be revised to read,
- **PRECAUTIONS** section
  - **General**
    - the labeling states
    - \_\_\_\_\_ should be deleted
    - delete the second and third sentences that begin, \_\_\_\_\_  
because the results of the antibody study requested by the FDA has not been completed
    - the sentence that reads, \_\_\_\_\_  
\_\_\_\_\_ should be deleted from the label
    - the sponsor should provide data to link allergic symptoms to GnRH analogs; the term, \_\_\_\_\_  
\_\_\_\_\_ should be more specific; if a type one hypersensitivity reaction  
has occurred, use should be cautioned against; if the risk is theoretical, then the statement  
can be included in the **Clinical Trials** subsection as an exclusion criterion
  - **Information for Patients** subsection
    - in the third sentence that begins, \_\_\_\_\_  
and the phrase, \_\_\_\_\_  
\_\_\_\_\_ should be deleted
    - \_\_\_\_\_ Org 37462 should be replaced by \_\_\_\_\_
  - **Laboratory Tests** subsection
    - the first sentence that begins, \_\_\_\_\_  
\_\_\_\_\_ should be revised to read, \_\_\_\_\_  
\_\_\_\_\_ the upper limits of normal and the \_\_\_\_\_  
normal WBC ranges should be defined in parenthesis; also, the range of the elevations in  
subjects should be given
  - **Pediatric Use** subsection
    - this section should be deleted
- **ADVERSE REACTIONS** section
  - second paragraph, in the sentence that begins, \_\_\_\_\_  
\_\_\_\_\_ the phrase, \_\_\_\_\_  
\_\_\_\_\_ should be deleted
- **DRUG ABUSE AND DEPENDENCE** section
  - this section should be deleted
- **DOSAGE AND ADMINISTRATION** section
  - in the first paragraph, fifth sentence that begins, \_\_\_\_\_  
\_\_\_\_\_ the phrase, \_\_\_\_\_  
should be replaced by the word, \_\_\_\_\_ and the sentence added to the previous sentence so that the  
sentence reads, \_\_\_\_\_
- **Directions for using Org 37462 (ganirelix acetate) injection** subsection
  - Item 5. second sentence that begins, \_\_\_\_\_  
\_\_\_\_\_ should be revised to read, \_\_\_\_\_
  - this section should be further revised
- **HOW SUPPLIED** section
  - the sentence, \_\_\_\_\_  
\_\_\_\_\_ should be deleted; this is already mentioned in the **PRECAUTIONS**  
section



# Minutes of Teleconference

Date: May 20, 1999 Time: 11:15 AM - 12:30 PM Place: Parklawn; Ms. Moore's Office

NDA: 21-057 Drug Name: Org 37462 (ganirelix acetate) for injection

Type of Meeting: Guidance (Labeling)

Indication: GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

External Constituent: Organon, Inc.

FDA Lead: Dr. Shelley Slaughter

External Participant Lead: Mr. Al Mayo

Meeting Recorder: Ms. Diane Moore

## FDA Participants:

Shelley Slaughter, M.D. - Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

## External Participants:

Albert P. Mayo, Director, Regulatory Affairs, Organon, Inc.

Carol Ann Cartier, Sr. Regulatory Associate, Regulatory Affairs, Organon, Inc.

Joel Krasnow, M.D. - Medical Services, Organon, Inc.

David Stern - Product Management, Organon, Inc.

Ellen Yetzer, D.O. - Medical Services Organon, Inc.

Bernadette Mannaerts - International, Clinical Development Team Leader, NV Organon

Eric Orlemans, Ph.D. - Project Management, NV Organon

Marjo Peters, Ph.D. - Regulatory Affairs, NV Organon

Meeting Objective: To convey labeling comments for NDA 21-057.

Background: Internal labeling discussions were held on May 18, 1999. More recommendations will be conveyed to the sponsor as the review continues.

## Decisions:

- the tradename, ANTAGON, should be inserted throughout the label where the drug is referenced
- CLINICAL PHARMACOLOGY section
  - in the first paragraph, the second and third sentences that begin with, /  
( ) should be deleted
  - the third paragraph that begins, ( ) should be deleted
  - the first two sentences in the fourth paragraph that begins, /  
should be deleted; the third sentence should be moved to the end of the second paragraph
  - the Pediatric, Geriatric, Gender, Race, Renal Insufficiency and Hepatic Insufficiency items in the Special Populations subsection should be consolidated into one sentence; a sentence should be proposed for the revised label

- **DRUG-DRUG INTERACTIONS** section
  - the abbreviation \_\_\_\_\_ should be prefaced by the entire phrase, \_\_\_\_\_
- **Clinical Studies** subsection
  - the first paragraph, fifth sentence that begins, \_\_\_\_\_ should be revised to read, \_\_\_\_\_
- **Table 2: "Results from the multicenter, double-blind, randomized, dose-finding study to assess the efficacy of Org 37462 to prevent premature LH surges in women undergoing COH with recombinant FSH"**
  - the phrase in column one, row three, should read/ \_\_\_\_\_
  - the information in rows five and six should be combined as was done in Serum E<sub>2</sub> \_\_\_\_\_
  - in the second column, fourth row entitled, LH rise  $\geq 10$  mIU.mL, the \_\_\_\_\_ should be revised to read \_\_\_\_\_
  - rows 7-10 beginning with, \_\_\_\_\_ should be deleted
  - in the third paragraph, first sentence, the phrase that reads, \_\_\_\_\_ should be deleted; it is \_\_\_\_\_ redundant \_\_\_\_\_
  - in the fourth paragraph that begins, \_\_\_\_\_ the high and low \_\_\_\_\_ estradiol levels and high LH and FSH levels should be defined \_\_\_\_\_
  - in the fifth paragraph, second sentence, that begins, \_\_\_\_\_ the \_\_\_\_\_ word, \_\_\_\_\_ should be replaced by the word, \_\_\_\_\_
  - in the fifth paragraph, fifth sentence that begins, \_\_\_\_\_ should be \_\_\_\_\_ revised to read, \_\_\_\_\_
- **Table 3**
  - in column 2, row 5, a less than sign \_\_\_\_\_ should precede 0.6-6.9 \_\_\_\_\_
  - \_\_\_\_\_ should be inserted between rows three and four (after Duration of recombinant FSH); the asterisk should correspond to a footnote that reads, \_\_\_\_\_
  - additional rows should be inserted entitled/ \_\_\_\_\_
- the sixth paragraph should be deleted and replaced with the sentence, \_\_\_\_\_ (the range should be added in the- \_\_\_\_\_ parenthesis) \_\_\_\_\_
- in the seventh paragraph that begins, \_\_\_\_\_ the data information should \_\_\_\_\_ not be pooled; only data from Study 30607 should be included \_\_\_\_\_
- **CONTRAINDICATIONS** section
  - the fourth and fifth sentences in the third paragraph that begins, \_\_\_\_\_
  - the seventh sentence in the third paragraph that begins, \_\_\_\_\_ should be moved to the **CARCINOGENICITY** section \_\_\_\_\_
  - the sentence, \_\_\_\_\_ should be moved to the **REPRODUCTION** section \_\_\_\_\_
- **PRECAUTIONS** section
  - **General** \_\_\_\_\_ should be deleted \_\_\_\_\_
  - the second and third sentences that begin, \_\_\_\_\_ " should be \_\_\_\_\_ deleted \_\_\_\_\_
- **Carcinogenesis and Mutagenesis, Impairment of Fertility** subsection

- in the second sentence that begins, [redacted] the phrase, [redacted] should be deleted
- significant reproductive/toxicology findings should be included in the draft package insert; doses should be expressed as mg/kg and the multiple of the human therapeutic dose should be based on actual systemic exposure basis
- ADVERSE REACTIONS section
  - TABLE 4
    - the title in the first row that reads, [redacted] should be revised to read, [redacted]
    - the adverse event, [redacted] should have [redacted] added to the term [redacted]
    - another row should be added entitled, [redacted] the %(n) should be 1.5%
    - this table should only include data from the open-label study 30607
    - data less than 1% should not be included in the table
- the phrase, [redacted] should be included in the HOW SUPPLIED section of the package insert and on the carton and blister package of the labeling
- the amount of Mannitol in the 0.5 mg dose should be clarified in the labeling
- requested text items should be provided in WORD on electronic disk and paper copy

Action items:

Item	Responsible Person:	Date Due:
• provide information regarding LH surges	Organon, Inc.	1-2 weeks
• provide a list of countries where Buserelin is approved and the summary basis of effectiveness from the sponsor	Organon, Inc.	1-2 weeks
• clarify the location of the identification report for the metabolic profile	Organon, Inc.	one week
• provide PK data using non MEM analysis for study 38602 on diskette	Organon, Inc.	1-2 weeks
• provide revised labeling based on these recommendations	Organon, Inc.	1 week
• minutes to sponsor	DRUDP	1 month

IS/

6/14/99

Signature, minutes preparer

IS/

Signature, Chair

M.D., Ph.D.

drafted: dm/5.28.99/n21057TC52099.doc

Concurrences:

TRumble 06.03.99/SSlaughter 06.09.99

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/LPauls/TRumble/AParekh/VJarugula/D Moore

HFD-580/KRaheja/AJordan/Rheem/SDes/KMeaker/DHoberman

# Meeting Minutes

Date: May 18, 1999

Time: 3:00 - 4:30 PM

Place: Parklawn; Rm 17B-43

NDA: 21-057

Drug Name: Org 37462 (ganirelix acetate) for injection

Type of Meeting: 4-month Labeling and Status Meeting

Indication: GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

Sponsor: Organon, Inc.

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

## FDA Participants:

Florence Houn M.D., M.P.H. - Office Director, ODE III (HFD-103)

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Shelley Slaughter, M.D. - Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

Swapan De, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)

Venkateswar R. Jarugula; Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

David Hoberman - Statistician - @DRUDP (HFD-580)

Meeting Objective: To discuss the labeling and status of NDA 21-057 at month 4 of the review.

Background: the NDA was submitted on January 28, 1999; filing date is March 29, 1999; the to-be-marketed dose is 0.25 mg; target Division completion date is June 15, 1999.

## Decisions:

- Status Reports
  - Clinical
    - review underway; target completion date is June 1, 1999
    - the basis of efficacy is the historical data dose-finding study, and the Phase 3 clinical trial
  - DSI sites
    - one clinical audit is completed; one is pending
  - Chemistry, Manufacturing and Quality Control
    - chemistry review will be completed this week
    - the Tradename, "ANTAGON" was found to be acceptable by the Division
  - Pharmacology
    - review to be completed this week
    - references are required to support the sponsor's assertion that anaphylaxis is not a problem with this drug

- **Biometrics:**
  - no formal statistical review will be performed; the clinical review will utilize an historical comparison
  - in the ITT analysis, there were (15/463) failures after Ganirelix was given; patients who had LH surges should be reviewed for statistical relevance
- **Clinical Pharmacology and Biopharmaceutics**
  - a draft of the NDA review is targeted for May 28, 1999; the Biopharmaceutics NDA review will be briefed in the Clinical Pharmacology and Biopharmaceutics Division the first week in June; finalization of the review is targeted for June 15, 1999
- **Microbiology**
  - completion of review is expected in May
- **Labeling comments**
  - the tradename, ANTAGON should be inserted throughout the label where the drug is referenced
  - the word, "sterile" should be included on the carton labeling
  - the amount of Mannitol in the 0.5 mg dose should be clarified
  - PK values can be included in either the text or table, the values are not needed in both places
  - the Pediatric, Geriatric, Gender, Race, Renal Insufficiency and Hepatic Insufficiency items in the Special Populations should be consolidated into one sentence saying that  
or  
; rather than having the same statement duplicated for each population
  - the mean number of treatment days can be included in the text, they are not needed in the table; the data should not be pooled; the significant end points in Tables 2 and 3 should be similar
  - **CLINICAL PHARMACOLOGY** section
    - in the first paragraph, the second and third sentences that begin, [ ] should be deleted
    - the third paragraph that begins, [ ] should be deleted
    - the first two sentences in the fourth paragraph that begins, [ ] should be deleted; the third sentence should be moved to the end of the second paragraph
- **DRUG-DRUG INTERACTIONS** section
  - the abbreviation [ ] should be prefaced by the entire phrase, [ ]
- **Clinical Studies** subsection
  - first paragraph, fifth sentence that begins, [ ] should be revised to read, [ ]
- **Table 2: "Results from the multicenter, double-blind, randomized, dose-finding study to assess the efficacy of Org 37462 to prevent premature LH surges in women undergoing COH with recombinant FSH"**
  - the phrase in column one, row three, should read, [ ]
  - rows six and seven (5<sup>th</sup> -95<sup>th</sup> percentiles) should be combined
  - in the second column, fourth row entitled, LH rise > 10 mIU/mL, the 5 should be replaced by a number 4
  - rows 7-10 beginning with, [ ] should be deleted
  - in the third paragraph, first sentence, the phrase that reads, [ ] should be deleted

- in the fourth paragraph, the high and low estradiol levels and high LH and FSH levels should be defined
- in the fifth paragraph, second sentence, that begins, / word, / should be replaced by the word, / the
- in the fifth paragraph, fifth sentence that begins, / revised to read, / should be
- Table 3
  - in column 2, row 5, a less than sign / should precede 0.6-6.9
  - / should be inserted between rows five and six; the asterisk should correspond to a footnote that reads, /
- the sixth paragraph should be deleted and replaced with the sentence, / the range should be added in the parenthesis)
- in the seventh paragraph that begins, / the data information should not be pooled
- CONTRAINDICATIONS section
  - the fourth and fifth sentences in the third paragraph that begins, / should be moved to the CARCINOGENICITY section
  - the seventh sentence in the third paragraph that begins, / should be moved to the REPRODUCTION section
- PRECAUTIONS section
  - General
    - the second and third sentences that begin, / should be deleted; otherwise, the analogs must be specifically defined
  - Carcinogenesis and Mutagenesis, Impairment of Fertility subsection
    - in the second sentence that begins, / the phrase, / should be deleted
    - the sponsor should include significant reproductive/toxicology findings in the draft package insert; doses should be expressed as mg/kg and the multiple of the human therapeutic dose should be based on actual systemic exposure basis
- ADVERSE REACTIONS section
  - TABLE 4
    - the title in the first row that reads, / should be revised to read,
    - the adverse event, / should have / added to the term
    - another row should be added entitled, / the %(n) should be 1.5%
    - this table should include data from the open-label study 30607 only

Action items:

- | Item  | Responsible Person:         | Date Due:             |
|---|-----------------------------|-----------------------|
| • convey to sponsor labeling comments                                       | Dr. Slaughter and Ms. Moore | one week              |
| • edit the Pharmacokinetics section of the label                            | Dr. Jarugulav               | prior to next meeting |
| • set up additional labeling meeting to complete first label review session | Ms. Moore                   | one week              |
| • request information regarding LH surges                                   | Ms. Moore                   | one week              |



# Meeting Minutes

Date: April 21, 1999

Time: 1:00 - 1:30 PM

Place: Parklawn; Rm 17B-43

NDA: 21-057

Drug Name: Org 37462 (ganirelix acetate) for injection

Type of Meeting: 3-Month Status

Indication: GnRH antagonist for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation

Sponsor: Organon, Inc.

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

## FDA Participants:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective: To discuss the 3-month status of NDA 21-057.

Background: the NDA was submitted on January 28, 1999; filing date is March 29, 1999; the to-be-marketed dose is 0.25 ng

## Decisions:

- Clinical
  - review pending; proposed completion date is early June 1999
- DSI sites
  - clinical audit sites have been requested
- Chemistry, Manufacturing and Quality Control
  - chemistry review has been completed; secondary review by the Team Leader is pending
  - three manufacturing sites have passed inspection; results from the two other inspection sites are pending
  - the Tradename, "Antagon" was found to be unacceptable by the Labeling and Nomenclature Committee (LNC); DRUDP believes that this name infers the drug's activity as an antagonist; because many other drugs act in this way, however, the name, "Antagon" could be misleading and confusing

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- Pharmacology
  - a mutagenicity review issue has been identified; additional information has been requested and received from the sponsor; the additional information is under review; completion expected in one week
  - references to support their assertion that anaphylaxis is not a problem with this drug
- Biometrics:
  - no report for this meeting
- Clinical Pharmacology and Biopharmaceutics
  - synopsis of study reports should be submitted in electronic form
  - NDA review targeted for mid-June
- Microbiology
  - a new Microbiologist may be assigned; completion of review is expected in May

## Action items:

- | Item   | Responsible Person: | Date Due: |
|--|---------------------|-----------|
| • convey to sponsor that the Division and LNC do not accept the proposed Tradename | Ms. Moore           | one week  |
| • request review report from Statistician  | Ms. Moore           | one week  |

          |S|            
Signature, minutes preparer

5/10/99

          |S|            
Signature, Chair

5/10/99

drafted: dm/4.23.99/n21057SM42399.doc

## Concurrences:

TRumble 04.28.99/SDe, KRaheja 04.30.99/MMann, MRhee 05.03.99/RBennett 05.04.99  
VJarugula 05.10.99

## cc:

HFD-580  
HFD-580/LRarick/MMann/SSlaughter/RBennett/LPauls/TRumble/AParekh/VJarugula/D Moore  
HFD-580/KRaheja/AJordan/Rheem/SDes/STran/TRumble/KMeaker/EDegua/DHoberman  
HFD-40/LStockbridge

JUL 29 1999

Memo to NDA 21-057 Ganirelix acetate  
Florence Houn MD MPH FACP  
July 29, 1999

/S/ 7/29/99

This application supports the approval of ganirelix acetate for the inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation as part of assisted reproductive technologies. Ganirelix is a gonadotropin releasing hormone (GnRH) antagonist. This is the first GnRH antagonist that will be approved by the Food and Drug Administration. The sponsor will need to conduct the mouse micronucleus assay as part of its phase 4 pharm-tox commitment to FDA.

The GnRH agonists control LH surges by first binding to pituitary receptors which causes the release of gonadotropins (FSH and LH). After continued administration of GnRH agonists, there is down-regulation of the receptors and eventual suppression of endogenous LH and FSH production. Thus, a logical and physiologic mechanism for primary blockade of GnRH by a GnRH antagonist is supported.

The efficacy trials are well described by the medical officer, team leader, and division director. Of note, the first trial is a phase 2 double blind, randomized, dose-finding study conducted in 13 centers to select the minimal effective dose of ganirelix that would prevent premature surges of LH. There were 342 subjects randomized to one of six dose groups. The second trial is a phase 3, multi-centered, open-labeled, non-inferiority study using buserelin as an active control which not approved for use in the US (but approved in Europe). There were 486 subjects randomized using 2:1 randomization pattern to receive 0.25 mg of ganirelix and 244 subjects randomized to receive buserelin. The goal of the study was to demonstrate the mean number of cumulus-oocyte complexes and the pregnancy rates with ganirelix were comparable or better to standard of care in Europe using buserelin. Finally, FDA had the sponsor submit historical data from the medical literature supporting the role of GnRH agonists, which are currently used off-label for the same indication as ganirelix.

The initial safety database included a follow-up of pregnancies from the phase 2 study. A total of 68 pregnancies resulted in 73 infants, one having Beckwith Wiedemann Syndrome. There were also minor abnormalities including two with fetal maturation impaired and two born pre-maturely with abruptio placenta. FDA then asked and received follow up of roughly 200 infants (practically the entire clinical trials' database of pregnancies), revealing no further cases of BWS.

This application raises several points related to drug development policy and review for FDA: a non-inferiority trial based on an active control product approved by European authorities, but not by FDA; use of historical data of a GnRH agonist to support the role of a GnRH antagonist; and the presence of a very rare congenital abnormality that resulted from a pregnancy that was assisted by study drug. In addition, no FDA statistical review was performed because of the descriptive nature of the studies. The clinical relevance of findings was interpreted by the medical review staff.

Non-inferiority trials test whether the effectiveness of a new technology is no worse than that of an existing technology. The lower boundary of outcome difference between or among study arms needs to be specified a priori. For ganirelix, the numbers of cumulus-oocyte complexes and pregnancy rate were endpoints. Differences of less than 3 oocytes and 5% pregnancy rate were stated as clinically acceptable. The study resulted in an estimated treatment mean of number of cumulus-oocyte complexes for ganirelix of 8.3 and 9.3 for buserelin. For on going pregnancies, the estimated treatment rate was 20.3% for ganirelix and 25.7% for buserelin. The lower limits for the 97.5% confidence interval of the difference between ganirelix and buserelin for oocytes was -1.8 and for pregnancy rates was -11.9%. While "winning" on oocyte complexes, pregnancy rate was not equivalent. However, the effectiveness standard as outlined by the Food Drug and Cosmetic Act requires the sponsor to provide substantial evidence that the drug does what its sponsors purport it can to do under labeled conditions. The sponsor's indication for the drug does not include a relative efficacy claim. Given this, historical data could be used to support the hypothesis that ganirelix is more effective than placebo. (The sponsor and FDA agreed that for this study

placebo trials would be difficult in this population of women, although patients were only subject to one IVF cycle. Future drug sponsors and FDA may agree to have placebo-controlled cycle or cycles.) The sponsor submitted publications from 1990 through 1995 that report the pregnancy rate for in-vitro fertilization (IVF) cycles without GnRH agonists ranged from 0-25%. With GnRH agonists, the rates from 1994-97 were from 19-45%. There are no historical data with GnRH antagonists, like ganirelix. Previous antagonists had serious histamine-type allergic reactions that thwarted their development. The mechanism of action for ganirelix, a GnRH antagonist, is believed to be more direct than GnRH agonists (as mentioned above), thereby providing the rationale to support approval.

With respect to infant outcomes, Beckwith Wiedemann Syndrome (BWS) is a rare event, occurring at a rate of 1 per 15,000. It is sometimes related to inheritance, but most cases are spontaneous. Some cases have chromosomal abnormalities identified. From a pharm-tox perspective, there is no data to suggest genotoxicity of ganirelix, but the mouse micronucleus assay will be completed to have the full pharm-tox battery of tests available for assessment. The case report on this infant states there is no chromosomal testing data and the child is reported as having moved away and is lost to follow up. To address concerns about this event, FDA asked the sponsor to follow up the case to see if there is family history of this disorder. FDA also asked for follow up on all pregnancies assisted by ganirelix in the sponsor's clinical trials to see infant outcomes, in particular the presence of BWS. A second case of BWS would have been very worrisome, but this was not present. The division and office discussed the possibility of a pregnancy registry, either for drug-assisted pregnancies or inadvertent fetal exposure. The use of pregnancy registries has limitations and requires careful planning and thoughtful procedures in order to gather useful surveillance data. It was decided that advisory committee discussion, possibly later this year, on the indications and appropriateness of pregnancy registries for drugs assisting reproduction would be useful. The labeling of ganirelix will have this event identified as an adverse event as well as include the other adverse outcomes for infants. In general, labeling of reproductive drugs should contain such information as the ultimate clinical endpoint for drugs assisting reproduction (and what patients are most concerned about) is the newborn and it's outcome.

APPEARS THIS WAY  
ON ORIGINAL