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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-663**

**Pharmacology Review(s)**



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

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-663  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: December 29, 2003  
PRODUCT: Menopur® (gonadotropins FSH & LH)  
INTENDED CLINICAL POPULATION: [ ]  
SPONSOR: Ferring Pharmaceuticals, Inc.  
DOCUMENTS REVIEWED: NDA 21-663 (N000-C) dated 1/13/04; Label  
REVIEW DIVISION: Division of Reproductive and Urologic Drug  
Products (HFD-580)  
PHARM/TOX REVIEWER: Lynnda Reid, Ph.D., Supervisory Pharmacologist  
DIVISION DIRECTOR: Daniel Shames, M.D.  
PROJECT MANAGER: Martin Kaufman

Date of review submission to Division File System (DFS): September 13, 2004

## EXECUTIVE SUMMARY

### I. Recommendations

- A. Recommendation on approvability: From a Pharmacology/Toxicology perspective, we recommend approval of this NDA based on the established safety of FSH and LH.
- B. Recommendation for nonclinical studies: none
- C. Recommendations on labeling: Label is satisfactory.

### II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings: There have been no specific nonclinical studies performed using Menopur®. Nonclinical data to support the safety of Menopur® and Repronex® were cross-referenced to Bravelle® (Bravelle®), NDA 21-289. Acute administration of Bravelle® containing doses up to 400 IU FSH/kg resulted in an increase in number and size of ovarian vesicular follicles in female rats and dogs. No evidence of toxicity was observed at this dose.
- B. Pharmacologic activity: stimulation of follicular growth and maturation
- C. Nonclinical safety issues relevant to clinical use: FSH and LH have a long history of human use. From a toxicological standpoint, there are no new safety issues associated with the described use of the gonadotropins in Menopur® described in this submission.

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## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-663

**Review number:** 1

**Sequence number/date/type of submission:** N000 dated December 29, 2004

**Information to sponsor:** Yes ( ) No ( x )

**Sponsor and/or agent:** Ferring Pharmaceuticals, Inc.  
400 Rella Boulevard, Suite 300  
Suffern, NY 10901

**Manufacturer for drug substance:** ☐

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**Reviewer name:** Lynnda Reid, Ph.D.

**Division name:** Reproductive and Urologic Drugs

**HFD #:** 580

**Review completion date:** September 10, 2004

**Drug:**

Trade name: Menopur®

Generic name: Menotropins for Injection, USP

Chemical name(s): follicle-stimulating hormone (FSH) and luteinizing hormone (LH)

**Relevant INDs/NDAs/DMFs:** Repronex® - NDA 21-047/IND 53,954  
Bravelle® - NDAs 21-289 and 21-484

**Drug class:** gonadotropins

**Intended clinical population:**

- 1) multifollicular development and pregnancy in women seeking assisted reproductive therapy (ART)
- 2) ☐

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**Clinical formulation:** Menopur® (menotropins for injection, USP) is a preparation of gonadotropins extracted and purified from the urine of postmenopausal women. Each vial of Menopur contains 75 IU each of FSH and LH activity, plus 21 mg lactose monohydrate and 0.005 mg Polysorbate 20 and Sodium Phosphate Buffer (USP) in a sterile, lyophilized form intended for reconstitution with sterile 0.9% Sodium Chloride for Injection (USP).

**Route of administration:** subcutaneous (SC)

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-663 are owned by Ferring Pharmaceuticals or are data for which Ferring Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 21-663 that Ferring Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Ferring Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-663.

**Studies reviewed within this submission:** There were no nonclinical studies submitted to NDA 21-663. All nonclinical data was cross-referenced to NDA 21-289 for Bravelle® approved in May 2002.

**Drug History:** Menopur® is a highly purified preparation of Repronex®. The active ingredients, menotropins FSH and LH, are extracted and purified from the urine of postmenopausal women. Repronex® administered intramuscularly was originally approved for the treatment of female infertility in 1997 under ANDA 73-598/599 as an equivalent of Pergonal®. Repronex® administered subcutaneously was later approved under NDA 21-047 in August 1999 for induction of ovulation and pregnancy in anovulatory infertile patients, and to stimulate development of multiple follicles in ovulatory patients undergoing assisted reproductive therapy. Bioequivalency and clinical efficacy studies with Menopur® were performed under IND 53,954.

Nonclinical data was cross-referenced to NDA 21-289 for Bravelle® which contains qualitatively and quantitatively similar ingredients: 75 IU FSH activity and ~1-2% LH activity. Three nonclinical studies were submitted to NDA 21-289: single subcutaneous injection studies in female Sprague-Dawley rats and female Beagle dogs at doses of 4, 40 and 100 IU FSH/kg., and a cardiovascular study in conscious female Beagle dogs at doses of 4, 40 and 400 IU FSH/kg. In the single dose acute toxicology studies, the only effect was an increase in number and size of ovarian vesicular follicles. Bravelle® was without effect in the cardiovascular study.

No additional nonclinical studies were requested or submitted under IND 53,954 or NDAs 21-047 and 21-663. Safety for FSH and LH is based primarily on prior experience in humans.

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** FSH and LH have a long history of human use. From a toxicological standpoint, there are no new safety issues associated with the described use of the gonadotropins in Menopur® described in this submission.

**Unresolved toxicology issues (if any):** none

**Recommendations:** From a Pharmacology/Toxicology perspective, we recommend approval of this NDA based on the established safety of FSH and LH.

**Suggested labeling:** Sections of the label relative to nonclinical findings are acceptable as submitted by the Sponsor.

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Lynnda Reid  
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PHARMACOLOGIST