

21322 — ORIG — APPROVAL — PKG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-322

Trade Name: Luveris, 75 I.U.

Generic Name(s): (lutropin alfa for injection)

Sponsor: Serona, Inc.

Agent:

Approval Date: October 8, 2004

Indication: Provides for use concomitantly administered with Gonal-f for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L)

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RESEARCH**

APPLICATION NUMBER:

21-322

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Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your new drug application (NDA) dated April 30, 2001, received May 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris[®] 75 IU (lutropin alfa for injection).

We acknowledge receipt of your submissions dated May 25, June 11, July 16, July 19, July 23(3), September 7 (2), September 24, September 29, and October 5 (4), 2004. The May 25, 2004, submission constituted a complete response to our March 1, 2002, action letter.

This new drug application provides for the use of Luveris[®] 75IU (lutropin alfa for injection), concomitantly administered with Gonal-f[®] (follitropin alfa for injection) for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L). A definitive effect on pregnancy in this population has not been demonstrated. The safety and effectiveness of concomitant administration of Luveris[®] with any other preparation of recombinant human FSH or urinary FSH is unknown.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and immediate container and carton labels submitted June 11 and September 29, 2004, respectively. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-322." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.50, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing study commitment specified in your submission dated October 5, 2004. This commitment, along with the completion dates agreed upon, is listed below.

1. The sponsor commits to conduct a Phase IV confirmatory clinical study to determine the effect of Luveris[®] on time to clinical pregnancy.

The following is the timeline for this commitment:

Protocol submission: Accomplished in the October 5, 2004 submission

Study start: Within one year of the date of receipt of this action letter

Final Report Submission: Within 6 months of the study completion

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated "**Subpart H Postmarketing Study Commitments.**"

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this division and two copies of the promotional materials and package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days for the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and package insert to the address above.

If you have any questions, call Archana Reddy, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

(See appended electronic signature page.)

Daniel Shames, M.D.
Division Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert

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/s/

Daniel A. Shames
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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-322

Approvable Letter (S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your new drug application (NDA) dated April 30, 2001, received May 1, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Luveris™ (lutropin alfa for injection).

We acknowledge receipt of your submissions dated June 12, 26, 29, July 11, 17, August 30, September 4, October 22, November 7, 20, 26, December 14, 17, 20, 21, 2001, January 3, 10, 24, 25, 29, 30, February 7, 11, 13, and 25, 2002.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505 (d) of the Act and 21 CFR 314.125 (b). The deficiency is summarized as follows:

The NDA does not provide sufficient evidence to support the efficacy of the 75 IU day dose of Luveris™ in follicular development and ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2) []

The following is needed to address this deficiency:

Conduct a new Phase 3 clinical trial that is appropriately powered to demonstrate efficacy vs. placebo for ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency, as defined by a baseline LH level <1.2 IU/L. This new Phase 3 trial, should be a dose ranging study that evaluates the 75 IU/day dose of Luveris™ and a lower dose (50 or 25 IU/day) than the 75 IU/ day dose.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

Present tabulations of the new safety data combined with the original NDA data.

Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR

NDA 21-322

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If you have any question, call Archana Reddy, M.P.H., Regulatory Project Manager, at
301-827-4260

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Daniel A. Shames
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