CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-597

CHEMISTRY REVIEW(S)

NDA 21-597

Serostim®[Somatropin(rDNA origin)for injection]

Serono, Inc

Maria E. Ysern, Msc
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-597

2. REVIEW #1.

3. REVIEW DATE: April 14, 2003

4. REVIEWER: Maria E. Ysern

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-597	Nov 25, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Serono, Inc.
Address:	One Technology Place Rockland ,MA 02370
Representative:	Pamela Williamson Joyce
Telephone:	781-982-9000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Serostim®
•Non-Proprietary Name (USAN):	Somatropin(rDNA origin)for injection
b) Code Name/# (ONDC only):	....
c) Chem. Type/Submission Priority (ONDC only):	Type 6 NDA
• Chem. Type:	
• Submission Priority:	None priority

9. LEGAL BASIS FOR SUBMISSION:
NDA 20-604 for Serostim , a growth hormone is approved for the treatment of AIDS wasting or cachexia. On October 31, 2002 the firm submitted an efficacy supplement to the approved NDA to add an indication for the treatment of short bowel syndrome. After internal discussion between HFD-180 and HFD-510, it was decided that the indication, SBS belonged in HFD-180. It will be a type 6 NDA, to be filed Dec, 30, 2002.

10.PHARMACOL. CATEGORY:
Anabolic and anticatabolic agent approved for the treatment of AIDS wasting or cachexia.
Proposed indication to be used for Short Bowel Syndrome.

11. DOSAGE FORM:
Lyophilized

12. STRENGTH/POTENCY:
4 mg, 5 mg, 6 mg, 8.8 mg

13. ROUTE OF ADMINISTRATION:
Subcutaneous

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

___X___SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Serostim® [somatropin (rDNA origin) for injection] is a human growth hormone produced by recombinant DNA technology. Serostim® has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of the human pituitary growth hormone and is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the human growth hormone gene.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-604	Original NDA, different indication

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	N/A		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical exclusion adequate (21CFR 25.31(a)		
Microbiology			

19. ORDER OF REVIEW N/A

The Chemistry Review for NDA 21-597

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Somatropin (rDNA origin) for injection is an approved drug, under NDA 20-604 for treatment of AIDs wasting or cachexia. This NDA 21-597 is provided for a New indication : Short Bowel Syndrome.
From the standpoint of CMC this application can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Description provided in the Draft package insert
Serostim®[somatropin (rDNA origin) for injection] is human growth hormone produced by recombinant technology. Serostim has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone. Serostim is produced by mammalian cell line (mouse C127) that has been modified by the addition of the human growth hormone gene. Serostim is secreted directly through the cell membrane into the cell culture medium for collection and purification.
Biological potency is determined by measuring the increase in body weight induced in hypophysectomized rats.
Drug product composition: i.e. Each 4 mg vial contains 4.0 mg (APPROX. 12 IU) SOMATROPIN, 27.3 MG SUCROSE, 0.9 MG PHOSPHORIC ACID). The pH is adjusted with sodium hydroxide or phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

B. Description of How the Drug Product is Intended to be Used

Serostim is indicated for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support, in conjunction with optimal management of Short Bowel Syndrome (SBS).
Serostim is reconstituted with Bacteriostatic Water for Injection, USP (0.9% Benzyl alcohol.
In patients with SBS, Serostim should be administered at a dose of 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily. Injection sites should be rotated.
Vials of Serostim® and diluent should be stored at room temperature, (15°-30°C/59-86°F).
After reconstitution with Sterile water for Injection, USP, the reconstituted solution should be used immediately and any unused portion should be discarded.
After reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl alcohol), the reconstituted solution should be stored under refrigeration (2-8°36-46°F) for up to 14 days.

Serostim® is supplied in
Vials containing 4 mg (..12Iu) somatropin with Sterile Water for injection, USP. Package of 7 vials.
Vials containing 5 mg (..15 IU) somatropin with sterile Water for Injection, USP. Package of 7 vials.
Vials containing 6 mg (..18 IU)somatropin with sterile Water for injection, USP. Package of 7 vials.
Vial containing 8.8 mg (..26.4 IU) with Bacteriostatic Water for Injection, USP (0.9% Benzyl alcohol). Package of 1 vial.

Manufacturer: Serono , Inc., Randolph, MA 02368.

C. Basis for Approvability or Not-Approval Recommendation

Based on the fact that Serostim ®[somatropin (rDNA origin) for injection] is and approved formulation, from the standpoint of CMC this application may be approved.

The claim for categorical exclusion for the preparation and submission of an Environmental Assessment is adequatr since the approval of this application will not increase the use of the active moiety, somatropin.

III. Administrative

A. Reviewer's Signature

See DFS.

B. Endorsement Block

Maria Ysern, HFD-180/Date: April 14,2003
Liang Zhou, HFD-180 Chemistry Team Leader/DateApril 14, 2003
Alice Kacuba, Project Manager, HFD-180

C. CC Block

NDA 21-597
HFD-180/Bjustice
HFD-180/Div File/NDA 21-597
HFD-180/Lzhou
HFD-180Mysern
HFD/180/Akacuba
R/D Init by Lzhou
MY final cL/word/nda/21597212.2my

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 1

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/s/

Maria Ysern
4/15/03 12:44:03 PM
CHEMIST

Liang Zhou
4/21/03 01:07:11 PM
CHEMIST

MEMORANDUM

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

DATE: October 17, 2003
FROM: Maria Elena Ysern, MSc, Review Chemist.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Liang Zhou, PhD, Chemistry Team Leader, HFD-180

SUBJECT: NDA 21597AZ/ and 51-597/BZ. Serostim®[somatropin (rDNA origin)for injection]

TO: NDA 21-597

This is a major amendment that contains information requested following the advisory committee and also a new proposed trade name. The proposed labels are almost the same as the currently marketed labels except for the new proposed trade name.
The firm is now proposing to use a separate name for the Serostim product for short bowel syndrome. The two proposed names are Zorbtive and ——— A consult for trade name has been sent Sep 8, 2003 to the Division of Medication Errors and Technical support (DMETS).
A revised package insert with the mechanism of action information inserted in the Clinical Pharmacology section is also provided.
The information provided seems adequate from the standpoint of CMC.

CC:
HFD-180/ MYsern
HFD-180/AKacuba
HFD-180/LZhou
HFD-180/Division Files

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/s/

Maria Ysern
10/21/03 02:50:46 PM
CHEMIST

Liang Zhou
10/21/03 02:54:48 PM
CHEMIST