CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-597

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 21-597 SUPPL #___N/A____

Trade Name: Serostim® for Injection
Generic Name: [somatotropin (rDNA origin)]

Applicant Name Serono, Inc. HFD # 180

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /X/ (Type 6 NDA) NO /___/

b) Is it an effectiveness supplement?
YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

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cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

e) Has pediatric exclusivity been granted for this Active Moiety?

__No_____

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 /_X__/

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 /_X__/

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 /_X__/ NO /___/

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

#(s).

NDA# 20-604 Serostim
NDA# 19-764 Saizen
NDA # 19-640 Humatrope
NDA# 20-280 Genotropin
NDA# 21-148 Noritropin
NDA# 20-168 Nutropin

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 /___/ N/A

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

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 /_X__/ 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 /_X__/ 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:

_____

(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 /_X__/

(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 /_X__/

If yes, explain:

(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 /_X__/

If yes, explain:

(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:

Investigation #1, Study # IMP20317

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 /_X__/

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 /___/ NO /_X__/

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"):

IMP20317

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 # 48,750 YES / X / NO / / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ NO / / Explain _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____
Alice Kacuba
Title: Regulatory Health Project Manager

_____
Robert L. Justice, M.D.
Title: Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

/s/

Alice Kacuba
11/26/03 02:28:07 PM

Robert Justice
11/26/03 02:36:05 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-597 (Type 6 NDA)

Stamp Date: November 1, 2002 Action Date: August 19, 2003

HFD-180 Trade and generic names/dosage form: Zorbtive™ [somatotropin (rDNA origin) for injection]

Applicant: Serono, Inc. Therapeutic Class: Misc. GI

Indication(s) previously approved: Serostim is currently approved under NDA 20-604 for AIDS wasting

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of short bowel syndrome

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

****No waiver, deferral request, no pediatric data submitted.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval

- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960

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

/s/

Alice Kacuba
12/1/03 06:56:30 PM

4. DEBARMENT CERTIFICATION

In accordance with Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned hereby certifies that Serono, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Rosann J. Reinhart

Executive Director, Regulatory Affairs

10-23-02

Date

Division Director Summary Review of a New Drug Application

Application: 21-597
Drug: Zorbtive® [somatropin (rDNA origin) for injection]
Applicant: Serono, Inc.
Date: November 28, 2003

This type 6 new drug application seeks approval of Zorbtive® [somatropin (rDNA origin) for injection] for the indication of "treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Zorbtive® should be used in conjunction with optimal management of Short Bowel Syndrome." Serono's somatropin for injection (rhGH) was previously approved under the tradename Serostim® for the treatment of AIDS wasting and cachexia.

The application is primarily supported by a single, randomized, double-blind, placebo-controlled, parallel group, two-center study (IMP20317). The study design and results are discussed in detail in the medical review by Dr. Hugo Gallo-Torres and in the statistical review by Dr. Dionne Price. Briefly, patients with short bowel syndrome who were dependent on intravenous parenteral nutrition (IPN) were entered into a two week baseline period. During this period their IPN requirements were stabilized and they were started on a specialized oral diet (SOD). At the end of the baseline period 41 patients were randomized in a 2:2:1 ratio to four weeks of treatment with rhGH 0.1 mg/kg/day s.c. plus glutamine 30 g/day p.o. (N=16), rhGH 0.1 mg/kg/day s.c. plus a placebo for glutamine (N=16), or to rhGH placebo plus glutamine 30 g/day p.o. (N=9). All three groups continued their specialized oral diet. The primary endpoint was the change from week 2 to week 6 in weekly total IPN volume defined as the sum of the volumes of IPN, supplemental lipid emulsion, and intravenous hydration fluid. Secondary endpoints included change in weekly IPN caloric content and change in the frequency of IPN administration per week.

Patients randomized to rhGH plus glutamine or to rhGH without glutamine significantly reduced their IPN volume requirements, IPN calorie content, and weekly frequency of IPN relative to subjects randomized to glutamine. For the primary endpoint there was a mean decrease in IPN volume of 7.7, 5.9, and 3.8 Liters/week in patients receiving rhGH with glutamine, rhGH without glutamine, and glutamine alone, respectively. Compared to glutamine alone, the treatment differences in IPN volume were -3.9 L/week for patients receiving rhGH with glutamine and -2.1 L/week for patients receiving rhGH without glutamine. The mean IPN calories per week decreased by 5751, 4338, and 2633 kilocalories/week in patients receiving rhGH with glutamine, rhGH without glutamine, and glutamine alone, respectively. The mean frequency of IPN administration decreased over the treatment period by 4.2, 3.0, and 2.0 days per week. in patients receiving rhGH with glutamine, rhGH without glutamine, and glutamine alone, respectively. The results are summarized in Table 1.

Table 1: Summary of Change in Efficacy Endpoints from Week 2 to Week 6

Endpoint	rhGH+glutamine	rhGH	glutamine
Mean Change in Total IPN Volume (L/wk)	-7.7*	-5.9**	-3.8
Mean Change in Total IPN Calories (kcal/wk)	-5751*	-4338**	-2633
Mean Change in IPN or SLE Frequency (d/wk)	-4.2*	-3.0**	-2.0

*p<0.001; **p<0.05 (compared to glutamine)

The adverse events occurring in >10% of patients and at an incidence higher than glutamine in one of the rhGH arms are shown in Table 2.

Table 2: Adverse Events During the 4 Week Treatment Period

Adverse Event	rhGH+glutamine %	rhGh %	glutamine %
Total	100	100	89
edema, peripheral	81	69	11
edema, facial	44	50	0
pain	6	19	11
chest pain	0	19	0
edema, generalized	0	13	0
malaise	0	13	0
abdominal pain	13	25	11
nausea	31	13	0
vomiting	19	19	11
arthralgia	31	44	0
myalgia	0	13	11
bacterial infection	0	19	11
viral infection	6	13	0
moniliasis	0	13	0
injection site reaction	25	19	11
injection site pain	0	31	0
dizziness	13	6	0
rash	13	6	0
ear or hearing symptoms	13	0	0
dehydration	0	19	11
increased sweating	0	13	0

These percentages are based on a small number of patients. However, peripheral and facial edema and arthralgias were clearly more common in the rhGH arms. It should be noted that baseline signs and symptoms (BSS) were reported in 88% in each of the rhGH

arms and in 78% of the glutamine arm. Many of the adverse events may be related to the patients' short bowel syndrome or parenteral nutrition.

Medical Officer Reviews

The original Medical Officer Review by Dr. Hugo Gallo-Torres was completed on May 22, 2003. Dr. Gallo-Torres recommended that the application was approvable. However, based on the advice of the GI Drugs Advisory Committee (see below), he recommended that four deficiencies must be addressed before approval: (1) educational plan, (2) additional data in support of replicability/generalizability, (3) initial data in support of durability of effect, and (4) additional work in progress. These deficiencies were discussed at a meeting with Serono on July 23, 2003.

A major amendment addressing these deficiencies was submitted on August 27, 2003. Dr. Gallo-Torres review of the amendment was completed on October 17, 2003. The draft educational plan for patients and health care providers was felt to be adequate. However, there were some editorial suggestions for improving the proposed Patient Handbook.

The issue of replicability and generalizability was addressed by data from a study by Drs. J. Li, N. Li and W. Zhu in Nanjing, China and by a review of the literature on the use of growth hormone in SBS. A summary of updated results of the Chinese study was submitted in the amendment. Thirty-seven patients with SBS received bowel rehabilitation therapy consisting of enteral nutrition for 4 weeks. Treatment included enteral nutrition (500-1500 kcal/day), oral glutamine 0.6 g/kg/day, and a high carbohydrate, low fat diet. Once patients were in positive nitrogen balance, rhGH from Serono was administered at a dose of 0.05 mg/kg/day for 3 weeks. Plasma levels of proteins and intestinal absorptive capacity were significantly improved after treatment ($p<0.05$). Twenty-one patients (57%) were able to wean off parenteral nutrition and lived on enteral nutrition and a special diet. Eighteen patients were living on a high carbohydrate and low fat diet supplemented with enteral nutrition. Three patients were weaned off parenteral or enteral nutrition completely. Concerning this study, Dr. Gallo-Torres wrote that

> "... the results of this trial appear to lend some support to the concept of generalizability of the treatment. But a number of constraints, arising from the design and execution of the trial, preclude the formulation of definitive conclusions on efficacy. Among these constraints are lack of randomization and double-blinding [two powerful tools to minimize bias], lack of a suitable and relevant control, and the fact that --although the treatment duration was 3 weeks-- the product was tested at less than half the daily dose used in pivotal study IMP20317."

The applicant's review of the literature identified 13 studies of growth hormone in SBS. However, only the Li and Zhu study mentioned above utilized the Serono rhGH. Dr. Gallo-Torres concluded that "although they may, somehow, add to the concept that the

GH treatment is generalizable, in the final analysis, results of these studies were not very helpful."

The applicant attempted to provide additional information on the durability of the effect of rhGH by conducting a follow-up survey (study 24236) on the 41 patients treated in study IMP20317. However survey data were obtained from only 22 of the 41 patients. Dr. Gallo-Torres concluded that

> "The MTL and the statistician reviewer, Dr. D. Price, agree with the sponsor that data from the follow-up survey 24236 must be interpreted with caution because of the low number of responses available. Indeed, the MTL concludes that no firm or meaningful conclusions can be drawn from these incomplete data. In the final analysis, the survey data derived from these post-hoc observations are of limited value and do not support durability of effect."

The review concluded with a recommendation that the application should be approved with a Phase 4 commitment to finalize and start the proposed educational plan for patients and health care professionals within four months of approval.

Statistical Review

The statistical review by Dr. Dionne Price was completed on July 25, 2003. Dr. Price concluded that

> "A primary claim of the sponsor is that rhGH, administered singly and as cotherapy with glutamine, reduces the total intravenous parenteral nutrition (IPN) volume requirements of SAS patients. The evidence taken from the reviewed study indicates statistical support favoring Serostim® for the treatment of short bowel syndrome. Additional claims are made regarding IPN calorie content and frequency of IPN administration. Evidence further suggests that Serostim® significantly reduces both IPN calorie content and frequency of administration among SBS patients..."

Chemistry Review

The chemistry review by Maria Ysern was completed on April 15, 2003. The recommendation was that "from the standpoint of CMC this application can be approved." The claim for categorical exclusion of an environmental assessment was adequate.

Pharmacology/Toxicology

The pharmacology/toxicology review was completed by Dr. Jasti Choudary on October 24, 2003. The review recommended that the following statement be deleted from the Mechanism of Action subsection of the package insert: "Animal studies have shown

growth hormone-induced increases in the size, cellularity and mass of the intestinal villi but it is not clear whether similar effects may also occur in man."

Clinical Inspection Summary

The clinical inspection summary by Ele Ibarra-Pratt, R.N., M.P.H. was completed on June 26, 2003. The Division of Scientific Investigations concluded that "the data submitted in support of this NDA appear to be acceptable."

Gastrointestinal Drugs Advisory Committee Meeting

The application was discussed at the Gastrointestinal Drugs Advisory Committee meeting on June 25, 2003. The questions and the Committee's vote and discussion are summarized below:

1. The primary endpoint of this study was change in Total IPN volume from week 2 to week 6. Pairwise comparisons of results of the primary endpoint yielded statistically significant differences between the recombinant human growth hormone (rhGH)-containing arms and the control group. Are the findings in the table below clinically meaningful? In your response consider the definition of the primary endpoint and the duration of study treatment.

Changes in Total IPN Volume

Mean Change in Total IPN Vol.			Difference in Total IPN Volume [L/wk] (p-value)	
Group A rhGH (n=16)	Group B rhGH + GLN (n=16)	Group C GLN (n=9)	Group B vs C	Group A vs C
-5.9	-7.7	-3.8	-3.9 (<0.001)	-2.1 (0.043)

Baseline IPN Requirements:
Group A: 10.3 L/wk
Group B: 10.5 L/wk
Group C: 13.5 L/wk

The committee voted 6 to 3 that the reductions in total IPN volume were clinically meaningful.

2. Secondary endpoints were change in Total IPN calories and change in IPN or lipid frequency. Pairwise comparisons of the results of these secondary endpoints yielded statistically significant differences between the rhGH-containing arms and the control group. Are the findings in the table below clinically meaninful?

Secondary Efficacy Analysis

Treatment Groups				
Group A rhGH (n=16)	Group B rhGH + GLN (n=16)	Group C GLN (n=9)	Group B vs C	Group A vs C
Change in Total IPN Calories [kcal/wk] / (p-value)				
-4338.3	-5751.2	-2633.3	-3117.9 (<0.001)	-1705.0 (0.005)
Change in IPN or Lipid frequency [d/wk] (p-value)				
-3.0	-4.2	-2.0	-2.2 (<0.001)	-1.0 (0.025)

The Committee voted 6 to 3 that the changes in total IPN calories and IPN or lipid frequency were clinically meaningful.

3. The primary endpoint was change in Total IPN volume. Only 1 of the 3 components (IPN volume) was recorded between week 6 and 18. Is the measurement of IPN volume adequate to demonstrate durability of effect? If not, what do you recommend as a minimum follow up period?

   The Committee voted 4 yes and 5 no and suggested a minimum follow-up of from 6 months to 2 years.

4. The data were primarily derived from a single, nutritional support tertiary care center. Are these data generalizable to the population of short bowel syndrome patients?

   The Committee voted 2 yes and 7 no. Of the members voting no, one commented that a few more patients in a few more centers would make a difference. Another member commented that a company sponsored educational program would help to ensure that the results of the trial are generalizable to clinical practice.

5. Are there specific safety concerns considering the potential for long term use of rh-GH in the treatment of short bowel syndrome patients?

   Although the Committee voted 6 yes with 3 abstentions that there are safety concerns with long-term use, several members commented that there were no major concerns with the proposed 4-week treatment.

6. Do the data support the safety and effectiveness of rh-GH alone or in co-therapy with glutamine in patients with short bowel syndrome? Are there any additional studies that you would recommend, e.g., dose finding?

The Committee voted 3 yes and 6 no. Members voting no generally recommended additional multicenter, phase 3 studies or more patients in another center in a non-ideal setting.

Meeting with Serono following the Advisory Committee Meeting

A meeting was held with Serono on July 23, 2003 to discuss the outcome of the Advisory Committee meeting and what would be needed to approve the application. The company proposed a follow-up mail survey of patients on study IMP20317, a meta-analysis of the literature, results of studies conducted in China and in France (if conducted with Serono's rhGH), and an educational plan. A major amendment addressing these proposals was submitted on August 27, 2003 and was reviewed by Dr. Gallo-Torres (see above).

Consultation from the Division of Medication Errors and Technical Support, ODS

The applicant proposed to use the proprietary name Zorbtive®. The DMETS consult of November 4, 2003, had no objections to the use of the name from a safety perspective but did have labeling recommendations that were considered during review of the labeling. DMETS noted that DDMAC did not recommend the use of the proprietary name Zorbtive because it suggests that the product will increase absorption of nutrients. Since the labeling does state that "in human clinical studies the administration of growth hormone has been shown to enhance the transmucosal transport of water, electrolyes, and nutrients," in a verbal communication DDMAC withdrew its objections.

Consultation from the Division of Surveillance, Research, and Communication Support, ODS

DSRCS was consulted on the draft outline of a proposed patient handbook. The DSRCS consult of October 6, 2003, commented that "the patient handbook is an excellent idea but it should be used as an adjunct education/risk communication material, not the only patient education/risk communication material provided to patients for this product. Patient Information (PPI) should be the primary risk communication tool provided to patients with each prescription and refill." Editorial and formatting comments to be communicated to the applicant were provided.

Discussion

While this application is primarily supported by the results of a single two-center, randomized, controlled clinical trial, it is the largest randomized study reported in SBS. Although one of the two centers contributed only 3 patients, the results of the study are statistically robust and the outcomes of the primary and secondary endpoints are internally consistent. The Advisory Committee's primary concern was whether the results of a study conducted mainly at a single tertiary care center could be generalized to SBS patients receiving treatment in the community. While the Li and Zhu study utilized patients as their own controls, the results can be considered supportive of generalizability. Methods to help ensure that the results can be generalized include labeling the drug for

use by physicians who are experienced in the diagnosis and treatment of SBS and by educating healthcare professionals in the proper management of SBS. The sponsor has agreed to a phase 4 commitment to conduct a comprehensive educational program for patients and healthcare professionals. The program will start within 4 months of approval. In addition, the sponsor has agreed to submit within 30 days of approval a labeling supplement containing a patient package insert.

Regulatory Action

The application should be approved.

{see appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation 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/

Robert Justice
11/28/03 04:51:55 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-597		
Drug: Serostim® [somatotropin (rDNA origin) for injection]	Applicant: Serono, Inc.	
RPM: Alice Kacuba	HFD-180	Phone # 7-7310
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	6
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	December 1, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	X

Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* **February 3, 2003**	X
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling **November 24, 2003**	X
• Original applicant-proposed labeling **August 27, 2003**	X
• Labeling reviews (including DDMAC **November 4, 2003**, Office of Drug Safety trade name review (**November 17, 2003**), nomenclature reviews, DSCRS **October 6, 2003-Education plan outline**) and minutes of labeling meetings	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X (NDA 20-604)
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Will place final version here
• Applicant proposed **November 25, 2003**	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments (**November 17, 2003**)	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only for NMEs)	N/A
• Other: **Pre-IND October 19, 1994, Post AC meeting July 23, 2003**	X
❖ Advisory Committee Meeting	
• Date of Meeting	June 25, 2003
• 48-hour alert- **Flash minutes**	X
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
❖ Clinical review(s) *(indicate date for each review)* **August 26, 2003; November 13, 2003**	X
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MOR dated August 26, 2003
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	Draft
❖ Statistical review(s) *(indicate date for each review)* **July 25, 2003**	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies **July 2, 2003**	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)* **April 21, 2003; October 21, 2003**	X
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See CMC review dated April 21, 2003
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	N/A
❖ Methods validation	N/A
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* **October 24, 2003**	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-597

Name of Drug: Serostim® [somatropin (rDNA orgin) for Injection

Sponsor: Serono, Inc.

Material Reviewed

Type of Submission: Paper

Submission Date: October 31, 2002

Receipt Date: November 1, 2002

Filing Date: December 31, 2002

User-fee Goal Date: 10 month user fee date = September 1, 2003

Proposed Indication: The treatment of Short bowel syndrome (SBS)

Other Background Information: This application was submitted as an efficacy supplement to NDA 20-604,which is approved for AIDS wasting in HFD-510. The application was administratively split to make for a Type 6 NDA in HFD-180 (the Division where the indication for treatment of SBS is managed).

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 1.1, page 001
2. Form FDA 356h (original signature)	X		Volume 1.1, page 002-003
a. Establishment information		X	Using Approved product

b. Reference to DMF(s) & Other Applications		X	Using Approved product
3. User Fee FDA Form 3397	X		Page 009
4. Patent information & certification	X		Cross reference to 20-604 provided
5. Debarment certification (Note: Must have a definitive statement)	X		Volume 1.1, page 007
6. Field Copy Certification		X	
7. Financial Disclosure	X		Volume 1.1, page 010
8. Comprehensive Index	X		Volume 1.1, page 005
9. Pagination	X		Page number located lower right hand corner.
10. Summary Volume	X		Volume 1.1
11. Review Volumes	X		Archival, Clinical, and statistical set
12. Labeling (PI, container, & carton labels)			
a. unannotated PI	X		
b. annotated PI		X	
c. immediate container		X	Using approved product
d. carton		X	Using approved product
e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Volume 1.8
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Volume 1.8

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits		X	Type 6 NDA
2. Foreign Marketing History		X	
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)		X	Cliamed categorical exclusion from EA
b. Nonclinical Pharmacology/Toxicology		X	
c. Human Pharmacokinetic & Bioavailability		X	
d. Microbiology		X	
e. Clinical Data & Results of Statistical Analysis		X	Entire NDA is 1 clinical study report
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies		X	
5. Summary of Safety		X	
6. Summary of Efficacy		X	

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		Volume 1.4, page 211

2. Controlled Clinical Studies			
a. Table of all studies		X	Entire NDA is 1 clinical study
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)		X	
4. Integrated Summary of Safety (ISS)		X	
5. Drug Abuse & Overdosage Information		X	
6. Integrated Summary of Benefits & Risks of the Drug		X	
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		X	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			

a. Proposed unannotated labeling in MS WORD		X	Submitted December 19, 2002 to edr
b. Stability data in SAS data set format (only if paper submission)		X	N/A
c. Efficacy data in SAS data set format (only if paper submission)	X		Submitted to edr
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)		X	

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Additional Comments: None

Conclusions

Application was filed on December 31, 2002

Alice Kacuba
Regulatory Project Manager

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

/s/

Alice Kacuba
2/3/03 04:47:12 PM
CSO

NDA 21-597

Public Communication

This section is not applicable this review cycle.

Alice Kacuba 8-26-03

Alice Kacuba
Regulatory Health Project Manager

1. SUMMARY

This SNDA provides clinical data from one pivotal trial to support the use of Serostim® [somatropin (rDNA origin) for injection] in the treatment of short bowel syndrome. A meeting was held with FDA on September 6, 2002 to discuss the content and format of this SNDA.

A proposed revised package insert in provided in Attachment 1. For ease of reference, copies of FDA meeting minutes are provided in Attachment 2. One pivotal clinical trial was conducted in this orphan population at two clinical sites, Brigham and Women's Hospital, Boston MA and University of Nebraska, Omaha NE. Forty-one patients were enrolled at the two clinical sites. The Serostim® treatment was well tolerated in these patients and IPN requirements were reduced. A full clinical report is provided in Attachment 3.

2. LABELING

A revised package insert in provided in Attachment 1 which highlights in red the proposed changes for the new indication of short bowel syndrome.

3. PATENTS

3.1 PATENT INFORMATION

Cross reference is made to NDA 20-604 for information on patents on the Drug Substance (active ingredient), Drug Product (formulation and composition) and Method of Use.

3.2 PATENT CERTIFICATION

Cross reference is made to NDA 20-604 for patent certification.

5. USER FEE DOCUMENTS

Form FDA 3397 is provided on the following page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Serono, Inc.
One Technology Place
Rockland, MA 02370

2. TELEPHONE NUMBER *(Include Area Code)*

(781) 982-9000

3. PRODUCT NAME

Serostim [somatropin (rDNA origin) for injection]

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 20-604

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President US Regulatory Affairs	October 31, 2002

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

6. FINANCIAL DISCLOSURE

Form FDA 3454 is provided on the following pages as well as Financial Disclosure statements for the following investigators and co-investigators.

Investigator Name	Investigator Address	Protocol No.
David Lautz, MD	Brigham and Women's Hospital Boston, Massachusetts	IMP20317
Co-Investigator Name(s)	**Investigator Address**	**Protocol No.**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Investigator Name	Investigator Address	Protocol No.
Kishore Iyer, MB, BS, FRCS	University of Omaha Omaha, Nebraska	IMP20317
Co-Investigator Name	**Investigator Address**	**Protocol No.**
[redacted]	[redacted]	[redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	David Lautz MD, Investigator	Kishore Iyer, MBBS, Investigator

2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Pamela Williamson Joyce	Vice President, US Regulatory Affairs
FIRM/ORGANIZATION: Serono, Inc.	
SIGNATURE	DATE: October 31, 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

6 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 9/23/03	**DESIRED COMPLETION DATE:** 10/23/03 **PDUFA GOAL DATE:** 12/1/03	**ODS CONSULT #:** 03-0264

TO:

Robert Justice, MD
Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

THROUGH:

Alice Kacuba
Regulatory Health Project Manager
(HFD-180)

PRODUCT NAME: **Zorbtive** [Somatropin (rDNA origin) for Injection]; 4 mg, 5 mg, 6 mg, and 8.8 mg NDA#: 21-597	**NDA SPONSOR:** Serono, Inc.

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY:

In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Zorbtive" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Zorbtive, from a safety perspective. The name, Zorbtive and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

2. DMETS recommends implementation of the labeling recommendations outlined in Section III. of this review.

3. DDMAC does not recommend the use of the proposed proprietary name Zorbtive. DDMAC considered the proposed proprietary name, Zorbtive, problematic because it suggests that the product will increase absorption of any nutrients

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 4, 2003

NDA# 21-597

NAME OF DRUG: **Zorbtive** [Somatropin (rDNA origin) for Injection];
4 mg, 5 mg, 6 mg, and 8.8 mg

NDA HOLDER: Serono, Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), for an assessment of the proposed proprietary name, "Zorbtive". The name, "Serobix", was submitted by the sponsor as an alternate name. Draft container labels, carton and package insert labeling was submitted with this consult for review.

PRODUCT INFORMATION

Zorbtive is the proposed proprietary name for somatropin (rDNA origin) for injection, a lyophilized powder for injection. Somatropin is a human growth hormone produced by recombinant DNA technology. It is an anabolic and anticatabolic agent that exerts its influence by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Serono currently markets the somatropin products, Saizen, indicated for childhood and adult growth hormone deficiencies and Serostim, indicated for the treatment of AIDS wasting or cachexia. Zorbtive is indicated for treatment of short bowel syndrome. The usual dose is 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily. Each milligram of somatropin is approximately equivalent to 3 international units. The sponsor proposes to market the product in vials of 4 mg, 5 mg, and 6 mg, strength individually cartoned with a vial of sterile water for injection then further packaged in cartons of seven. The sponsor also proposes vials of 8.8 mg, packaged with bacteriostatic water for injection USP. The outer packaging will bear a unique holograph designed by the sponsor to thwart counterfeiting of the product.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Zorbtive" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for the name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, "Zorbtive". Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC does not recommend the use of the proposed proprietary name Zorbtive. DDMAC considered the proposed proprietary name, Zorbtive, problematic because it suggests that the product will increase absorption of any nutrients.

2. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with Zorbtive. This product is listed in Table 1 (below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel - Zorbtive

Product Name	**Established name, Dosage form(s)**	**Usual Dose***	**Other****
Zorbtive	**Somatropin (rDNA origin) for Injection; 4 mg, 5 mg, 6 mg, and 8.8 mg**	**4 mg to 6 mg subcutaneously daily at bedtime.**	
ZORprin	Aspirin Extended-Release Tablets USP; 800 mg	Take one tablet every 6 hours.	SA
*Frequently used, not all-inclusive. **S/A (sound-alike)			

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-03, the electronic online version of the FDA Orange Book and POCA.

[4] WWW location http://www.uspto.gov/maintrademarks.htm .

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA to determine the degree of confusion of "Zorbtive" with U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. The studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Zorbtive" (below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

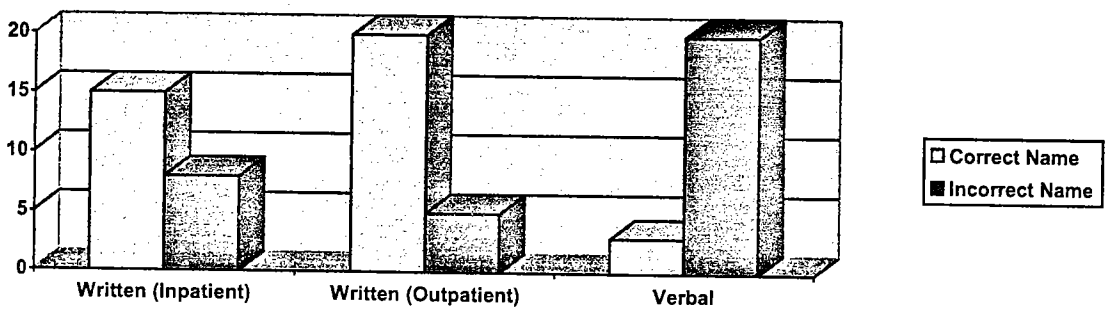
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Zorbtive 5mg 5mg SQ daily as dir. #30	Zorbtive 5 mg 5 mg subcutaneously daily as directed. #30
Inpatient RX: Zorbtive 5mg SC QD qs dis #30	

2. Results:

The results for "Zorbtive" are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) "Zorbtive"	Incorrectly Interpreted (%)
Written Inpatient	43	23 (53%)	15 (65%)	8 (35%)
Written Outpatient	41	25 (61%)	20 (80%)	5 (20%)
Verbal	43	23 (53%)	3 (13%)	20 (87%)
Total	127	71 (56%)	38 (54%)	33 (46%)



Among participants in the written prescription studies, 13 of 48 respondents (27%) interpreted the name incorrectly. The interpretations were misspelled variations of "Zorbtive". Incorrect interpretations of written prescriptions included: *Zorptive, Zorative* (3 occurrences), *Zorotive, Zorstive* (2 occurrences), *Zorbtiv* (2 occurrences), *Zorbative* (3 occurrences), and *Zortive.* None of the interpretations are similar to a currently marketed drug product.

Among participants in the verbal prescription studies, 20 of 23 (87%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Zorbtive". Incorrect interpretations of the verbal prescription included: *Zorbtiv* (4 occurrences), *Zoltive, Sorbtive, Zorptive* (4 occurrences), *Sorbitz, Zortib, Zogtiv, Zorptiv, Zorbitave, Zoritive, Zoptiv, Zorptis, Zortive,* and *Xorptive.* None of the interpretations are similar to a currently marketed drug product.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. SOUND-ALIKE/ LOOK-ALIKE NAMES

In reviewing the proposed proprietary name "Zorbtive", the primary concerns raised related to sound-alike confusion with a name already in the U.S. marketplace. The product considered to have potential for name confusion with **Zorbtive** was ZORprin.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that "Zorbtive" can be confused with "ZORprin". However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. Most of the incorrect interpretations for the prescription studies were misspelled interpretations or phonetic variations of "Zorbtive".

ZORprin and *Zorbtive* may sound similar when spoken. ZORprin is a proprietary name for Aspirin Extended-Release Tablets USP, 800 mg. ZORprin is used to relieve mild to moderate pain, reduce fever, and to reduce inflammation and swelling in conditions such as arthritis. Phonetic similarity between the names ZORprin and Zorbtive may be attributed to the shared letters "Zor", which are identically placed in each two syllable name. The plosive consonants, "p" vs. "b" in ZORprin and Zorbtive and the "i" sound in the last syllable may also contribute to phonetic similarities. The endings of each name, "in" for ZORprin vs. "ive" for Zorbtive may serve to distinguish the names phonetically. Despite some sound-alike properties, ZORprin and Zorbtive have differences which make them distinct from each other. Product differences between ZORprin and Zorbtive include strengths (800 mg vs. 4 mg, 5 mg, 6 mg, and 8.8 mg), dosage form (tablets vs. lyophilized powder for injection), route of administration (oral administration vs. subcutaneous injection), and dosing regimen (every 6 hours vs. once daily), respectively. DMETS believes that the potential for confusion is minimal given these differences.

2. MULTIPLE TRADENAME ISSUES

DMETS is aware that somatropin products are marketed under various proprietary names (see Appendix 1) and that the sponsor, Serono, currently markets somatropin products under two different proprietary names for two different indications of use. As shown in the table below, Serono hopes to gain approval for two additional somatropin products with entirely different indications and has proposed the proprietary name Zorbtive for the product currently under review.

Proprietary Name *Proposed	**Indication**	**Special Delivery System**	**Marketing Status**
Saizen	Treatment of growth hormone deficiencies	Cool.click (needle free) One.click (retractable needle) Click.easy	Currently Marketed
Serostim	Treatment of AIDS wasting	Seroject – a needle free delivery system	Currently Marketed
*Zorbtive	Treatment of Short Bowel Syndrome	-----	Under review and the subject of this consult
DMETS is unaware of proposed proprietary name	Treatment of HIV-associated adipose redistribution syndrome (HARS); Treatment of lipodystrophy	-----	Phase III studies, in "pipeline" per Serono web site

DMETS is particularly concerned that two health care professionals may prescribe the same active ingredient (with different proprietary names) to a single patient for two different indications, thereby exposing the patient to an increased dose of the medication. DMETS envisions a scenario, for example, where an AIDS patient receiving Serostim for treatment of AIDS wasting is ordered and administered another somatropin product with a different proprietary name for HARS. From the information provided for review it is difficult to determine the safety risks of possible concomitant administration. What is the sponsor's rational for proposing multiple proprietary names for the same active ingredient? DMETS requests the sponsor provide the following information to support the safe use of their products under multiple trademarks:

- Risk information about the concomitant use of somatropin products.
- How the sponsor plans to minimize the risk of confusion among these products.
- The rationale for proposing multiple proprietary names.

III. COMMENTS TO THE SPONSOR:

DMETS has no objections to the use of the proprietary name, Zorbtive, however, DMETS has the following comments regarding the use of multiple tradenames for the same active ingredients.

DMETS is aware that somatropin products are marketed under various proprietary names and that the sponsor, Serono, currently markets somatropin products under two different proprietary names for two different indications of use. As shown in the table below, Serono hopes to gain approval for two additional somatropin products with entirely different indications and has proposed the proprietary name Zorbtive for the product currently under review.

Proprietary Name *Proposed	**Indication**	**Special Delivery System**	**Marketing Status**
Saizen	Treatment of growth hormone deficiencies	Cool.click (needle free) One.click (retractable needle) Click.easy	Currently Marketed
Serostim	Treatment of AIDS wasting	Seroject – a needle free delivery system	Currently Marketed
*Zorbtive	Treatment of Short Bowel Syndrome	-----	Under review and the subject of this consult
DMETS is unaware of any proposed proprietary name	Treatment of HIV-associated adipose redistribution syndrome (HARS); Treatment of lipodystrophy	-----	Phase III studies, in "pipeline" per Serono web site

DMETS is particularly concerned that two health care professionals may prescribe the same active ingredient (with different proprietary names) to a single patient for two different indications, thereby exposing the patient to an increased dose of the medication. DMETS envisions a scenario, for example, where an AIDS patient receiving Serostim for treatment of AIDS wasting is ordered and administered another somatropin product with a different proprietary name for HARS. From the information provided

for review it is difficult to determine the safety risks of possible concomitant administration. What is the sponsor's rational for proposing multiple proprietary names for the same active ingredient? DMETS requests the sponsor provide the following information to support the safe use of their products under multiple trademarks:

- Risk information about the concomitant use of somatropin products.
- How the sponsor plans to minimize the risk of confusion among these products.
- The rationale for proposing multiple proprietary names.

Additionally, in the review of the container labels, carton, and package insert labeling of Zorbtive, DMETS has focused on safety issues relating to possible medication errors, and has identified several areas of possible improvement, which might minimize potential user error.

1. GENERAL

a. DMETS notes that substantial patient education is required for the proper use of the proposed product. The patient should be informed of risks and benefits associated with treatment, with the proper reconstitution of the product, rotation of injection sites, and product disposal. We also note that no patient information has been forwarded for review and comment. What plans does the sponsor have to provide patient information to ensure proper use of this product?

b. DMETS does not recommend the use of "IU" as an expression of dosage strength. This abbreviation is dangerous and has been misinterpreted as IV. Revise "IU" to read "international units" on all labels and labeling.

c. We note two different diluents are proposed for this product line (single use preservative-free and multiple use, with benzyl alcohol). Since both may be in the marketplace at the same time, DMETS is concerned about either inadvertent multiple use of the single use product or inadvertent administration of preserved product by patients allergic to benzyl alcohol. We are also concerned because product labeling proposed is very similar and could result in selection of the wrong product. Please propose safety measures that would prevent the types of confusion described above.

d. Please provide container labels for the diluents used to reconstitute this product when they become available.

e. Adequately differentiate the appearance of this product from other somatropin products in the market place.

2. CONTAINER LABELS (4 mg, 5 mg, 6 mg, 8.8 mg)

Use boxing, contrasting colors, or some other means to differentiate the product strengths.

3. CARTON LABELING

a. See first comment under CONTAINER LABELS above.

b. Since you propose two different diluents for this product line, please state what diluent is provided on the principal display panel rather than, "1 Vial Sterile Diluent".

c. DMETS is aware of post marketing reports of counterfeiting of somatropin products and notes that carton labeling for this product will bear a holograph. The holograph feature may be an important safety tool to thwart counterfeiting of this product and DMETS suggests that a brief explanation of the holograph appear as part of the text appearing on carton labeling.

d. Please provide more detailed directions for the reconstitution of this product which include the expected concentration after reconstitution.

e. Allow the route of administration to appear as a separate and distinct item on the principal display panel (rather than as part of a bulleted list), and increase its prominence.

3. PACKAGE INSERT LABELING

a. DOSAGE AND ADMINISTRATION

i. Include information regarding bringing refrigerated solution to room temperature prior to administration.

ii. Include information about the type of needle to be used for administration of this product.

b. HOW SUPPLIED

i. Include information regarding the volumes of waters for reconstitution.

ii. Relocate the information regarding the storage of this product to appear in this section.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Zorbtive from a safety perspective. The name, Zorbtive and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DMETS recommends implementation of the labeling recommendations outlined in Section III. of this review.

C. DDMAC does not recommend the use of the proposed proprietary name Zorbtive. DDMAC considered the proposed proprietary name, Zorbtive, problematic because it suggests that the product will increase absorption of any nutrients.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix 1. Listing of Somatropin Recombinant Products (From New Drug Approvals 00-03, the electronic online version of the FDA "Orange Book")

019774	5MG/ML	TEV-TROPIN	BIO TECH GEN
020168	10MG/VIAL	NUTROPIN	GENENTECH
021075	13.5MG/VIAL	NUTROPIN DEPOT	GENENTECH
021075	18MG/VIAL	NUTROPIN DEPOT	GENENTECH
021075	22.5MG/VIAL	NUTROPIN DEPOT	GENENTECH
020522	5MG/ML	NUTROPIN AQ	GENENTECH
020522	5MG/ML	NUTROPIN AQ PEN	GENENTECH
020168	5MG/VIAL	NUTROPIN	GENENTECH
019640	12MG/VIAL	HUMATROPE	LILLY
019640	24MG/VIAL	HUMATROPE	LILLY
019640	5MG/VIAL	HUMATROPE	LILLY
019640	6MG/VIAL	HUMATROPE	LILLY
021148	10MG/1.5ML	NORDITROPIN	NOVO NORDISK
021148	15MG/1.5ML	NORDITROPIN	NOVO NORDISK
019721	4MG/VIAL	NORDITROPIN	NOVO NORDISK
021148	5MG/1.5ML	NORDITROPIN	NOVO NORDISK
019721	8MG/VIAL	NORDITROPIN	NOVO NORDISK
020280	0.2MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	0.4MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	0.6MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	0.8MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	1.2MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	1.4MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	1.5MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	1.6MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	1.8MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	13.8MG/VIAL	GENOTROPIN	PHARMACIA AND UPJOHN
020280	1MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	2MG/VIAL	GENOTROPIN PRESERVATIVE FREE	PHARMACIA AND UPJOHN
020280	5.8MG/VIAL	GENOTROPIN	PHARMACIA AND UPJOHN
020604	4MG/VIAL	SEROSTIM	SERONO
019764	5MG/VIAL	SAIZEN	SERONO
020604	5MG/VIAL	SEROSTIM	SERONO
019764	6MG/VIAL	SAIZEN	SERONO
020604	6MG/VIAL	SEROSTIM	SERONO
019764	8.8MG/VIAL	SAIZEN	SERONO
020604	8.8MG/VIAL	SEROSTIM	SERONO

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

/s/

Charles Hoppes
11/17/03 02:03:58 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
11/17/03 02:44:00 PM
DRUG SAFETY OFFICE REVIEWER

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

'Division/Office):	FROM: Alice Kacuba, Regulatory Health Project Manager, HFD-180
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34	

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Sept 8, 2003		21-597	Major amendment	August 27, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Serostim	High	Misc GI	Oct 23, 2003

NAME OF FIRM: Serono, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☒ OTHER *(SPECIFY BELOW)*: Trade name review
☐ MEETING PLANNED BY		

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: NDA 21-597 was submitted as a Type 6 NDA on Oct 31, 2002. The parent NDA 20,604 is approved for AIDS wasting and lives in HFD-510.

Following the Advisory Committee Meeting this summer, HGD-180 requested the firm to submit several items to address the Advisory Committee's concerns. The firm submitted their response on August 27, 2003, a day before the user fee date of August 29, 2003. HFD-180 considered this amendment as a major amendment and extended the user fee date 3 months making the user fee date Dec 1, 2003.

In the major amendment, the firm is now proposing use to use a separate tradename for the Serostim product for short bowel syndrome. They have proposed 2 tradenames. Consider them in the order that they are presented in the submission.

Attached (in the hardcopy version) are copies of the package insert as well as copies of the proposed bottle labels and carton labels. Please note that the "Serostim" labels are how the labels are currently marketed.

The short turn around time can not be helped (the week before the due date is Thanksgiving week).

Please contact me if you need further information

PDUFA DATE: December 1, 2003
ATTACHMENTS: Draft Package Insert, Container and Carton Labels

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Alice Kacuba

9/17/03 04:59:00 PM

MEMORANDUM

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

DATE: October 6, 2003

TO: Robert Justice, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

VIA: Alice Kacuba, Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Draft Serostim [somatotropin (rDNA origin)] for injection/SBS Patient Handbook Outline, NDA 21-597

Background

Serono submitted a draft outline of a proposed patient handbook (August 27, 2003) for the purpose of aiding patients with short bowel syndrome (SBS) understand their syndrome, nutrition and dietary management, and treatment with Serostim [somatotropin (rDNA origin) for injection. Serostim is currently approved for the treatment of AIDS wasting. Serono plans to tradename and label the indications separately.

Comments

The patient handbook is an excellent idea but it should be used as an adjunct education/risk communication material, not the only patient education/risk communication material provided to patients for this product. Patient Information (PPI) should be the primary risk communication tool provided to patients with each prescription and refill. The Serostim PPI should:

- contain comprehensive information based on the prescribing information (PI)
- be written in a Medication Guide question and answer type format (see 21 CFR 208).

This format has research and experience to support its communication effectiveness.

- be written at a 6th to 8th grade reading comprehension level. This is an optimal comprehension level for all patient materials.
- be non-promotional
- have instructions for use appended at the end of the PPI and be clearly written. Refer to *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers* for more information on writing instructions for patients.

The patient handbook appears to provide comprehensive information on the disease, management, and treatment with Serostim. The patient handbook should:

- be written at a 6th to 8th grade reading comprehension level. Keep sentences shorts, words simplified, explain any medical or technical term, and bullet information when possible.
- have a font size of at least 10 point to aid in ease of readability
- have adequate background contrast and white space to aid in ease of readability; not be overwhelmed by background pictures or artwork
- be non-promotional in tone

Ideally, the patient handbook would be tested for comprehension among a cross section (varying educational levels, including those with low literacy) of Serostim treated SBS patients.

Please call us if you have any questions.

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

/s/

Jeanine Best
10/6/03 11:15:14 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/6/03 05:48:04 PM
DRUG SAFETY OFFICE REVIEWER

NDA 21-597

Foreign Labeling

This section is not applicable.

Alice Kacuba 7.18.03

Alice Kacuba
Regulatory Health Project Manager