

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-074

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.2 PATENT CERTIFICATION

1.3.5.2 Patent Certification

The original New Drug Application for Lanreotide Autogel is submitted under 505(b) (1) of the Federal Food Drug and Cosmetic Act, as amended.

Patent Certification is not required.

EXCLUSIVITY SUMMARY

NDA # 22-074

SUPPL # N/A

HFD # 510

Trade Name Somatuline Depot Injection

Generic Name lanreotide

Applicant Name Beaufour Ipsen Pharma (U.S. Agent: Biomeasure, Inc.)

Approval Date, If Known August 30, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

5 years (the applicant qualifies for 7 years of exclusivity due to its orphan drug status)

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1

YES NO

Investigation #2

YES NO

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

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

Investigation #1

YES NO

Investigation #2

YES NO

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

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

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

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

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! 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:

Investigation #2

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

If yes, explain:

Name of person completing form: Jennifer Johnson

Title: Regulatory Project Manager

Date: September 4, 2007

Name of Office/Division Director signing form: Mary H. Parks, M.D.

Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Mary Parks

9/6/2007 08:12:40 AM

1.3.3 DEBARMENT CERTIFICATION

1.3.3 Debarment Certification

Beaufour Ipsen Pharma hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act as amended by of the Generic Drug Enforcement Act of 1992 in connection with this application.

APPLICANT:

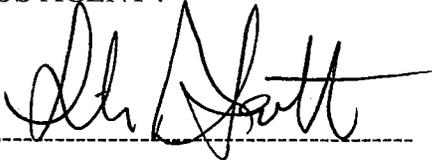


Etienne de Blois
Beaufour Ipsen Pharma
24 rue Erlanger
75781 Paris
Cedex 16, France

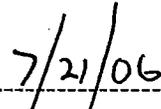


Date

US AGENT :



Steven R. Scott
Biomeasure Inc
27 Maple Street
Milford, MA 01757



Date

1.3.3 DEBARMENT CERTIFICATION

PAGE 2

1.3.3 Debarment Certification (continued)

Ipsen Ltd. who has provided analysis and reporting of the data submitted in the NDA, hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act as amended by of the Generic Drug Enforcement Act of 1992 in connection with this application.

Alistair Stokes

Dr. Alistair Stokes
Ipsen Ltd
190 Bath Road
Slough

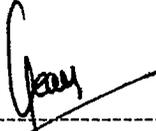
24 July 2006
Date

1.3.3 DEBARMENT CERTIFICATION

PAGE 3

1.3.3 Debarment Certification (continued)

SCRAS Sponsor of IND 53, 993 (07/98 to 12/99) hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act as amended by of the Generic Drug Enforcement Act of 1992 in connection with this application.



Christophe Jean
SCRAS
51-52 rue du Docteur Blanche
75016 Paris
France

July 26, 2006

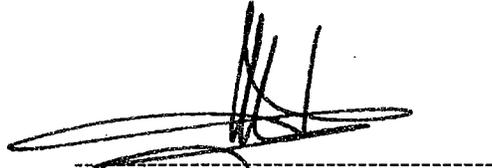
Date

1.3.3 DEBARMENT CERTIFICATION

PAGE 4

1.3.3 Debarment Certification (continued)

Ipsen Pharma Biotech the manufacturer of the drug product hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act as amended by of the Generic Drug Enforcement Act of 1992 in connection with this application.



Bruno Tissier
Ipsen Pharma Biotech
Z.E. de Signes
83970 Signes
France

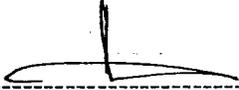
July 20th, 2006
Date

1.3.3 DEBARMENT CERTIFICATION

PAGE 5

1.3.3 Debarment Certification (continued)

Beaufour Ipsen Industrie SAS the manufacturer of the drug product hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act as amended by of the Generic Drug Enforcement Act of 1992 in connection with this application.



Jean-Pierre Dubuc
Beaufour Ipsen Industrie SAS
rue d'Éthe Virton
28100 Dreux
France

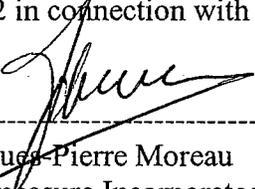
28 July 2006
Date

1.3.3 DEBARMENT CERTIFICATION

PAGE 6

1.3.3 Debarment Certification (continued)

Biomeasure Incorporated the US Agent of the Applicant hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act as amended by of the Generic Drug Enforcement Act of 1992 in connection with this application.



Jacques-Pierre Moreau
Biomeasure Incorporated
27 Maple Street
Milford MA 01757
USA

October 19 2006
Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-074 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: October 30, 2006 PDUFA Goal Date: August 30, 2007

HFD- 510 Trade and generic names/dosage form: Somatuline (lanreotide) Injection, 60 mg, 90 mg, 120 mg

(Note: modifier to be determined; "Autogel" originally chosen, and "SI" has been recently proposed by the Sponsor)

Applicant: Beaufour Ipsen Pharma (U.S. Agent: Biomeasure, Inc.)

Therapeutic Class: somatostatin

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of acromegaly

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

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.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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.

NDA 22-074

Page 3

This page was completed by:

{See appended electronic signature page}

Jennifer Johnson

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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.

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Jennifer Johnson
8/4/2007 03:59:54 PM

ACTION PACKAGE CHECKLIST

Application Information		
NDA # 22-074	NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: Somatuline Depot Established Name: lanreotide Dosage Form: Injection (60 mg, 90 mg, 120 mg)		Applicant: Beaufour Ipsen Pharma (U.S. Agent: Biomeasure, Inc.)
RPM: Jennifer Johnson		Division: DMEP (HFD-510) Phone # 301-796-2194
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A Provide a brief explanation of how this product is different from the listed drug. N/A <input type="checkbox"/> If no listed drug, check here and explain: N/A Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		August 30, 2007
❖ Action Goal Date (if different)		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		X None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input checked="" type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: N/A Other comments: N/A	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	September 6, 2007 (Included)
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> NDA/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<p>X No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____</p>
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<p>X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: N/A Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire _____</p>
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Office Director: August 30, 2007 Division Director: August 28, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	N/A
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	August 30, 2007
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	August 29, 2007
<ul style="list-style-type: none"> Original applicant-proposed labeling 	October 27, 2006
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Patient Package Insert	
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	August 30, 2007
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	August 29, 2007
<ul style="list-style-type: none"> Original applicant-proposed labeling 	October 27, 2006
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Medication Guide	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	October 27, 2006 (applicant instructed to re-submit as a PPI, as a Med Guide is not required)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> Most-recent division-proposed labels (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	August 17, 2007 (Original: October 27, 2006)

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	X DMETS January 12, July 24, and August 29, 2007 X DSRCS August 8, 2007 X DDMAC August 8, 2007 X SEALD August 16, 2007 (entered into DFS by DMEP RPM on August 31, 2007) X Other reviews RPM PLR format review dated July 25, 2007 <input type="checkbox"/> Memos of Mtgs N/A
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Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	August 4, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	September 6, 2007 (Included)
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	X None N/A N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	November 27 and December 8, 2006; January 12, 19, March 8, 29, April 24, May 31, June 8, 15, and 20, July 10, 16, 26, and 27, and August 29 and 30, 2007
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	Meeting: August 1, 2007 DFS Mtg Mins: September 6, 2007 <input type="checkbox"/> No mtg July 26, 2004 X No mtg N/A
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	X No AC meeting N/A N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	December 12, 2006; May 15, July 26, and August 7, 2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X None

❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No N/A
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	May 15, 2007
• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	August 8, 2007
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: July 27, 2007 X Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents	N/A
• Facility review (<i>indicate date(s)</i>)	<input type="checkbox"/> Requested
• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)	<input type="checkbox"/> Accepted
	<input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed
	X Requested
	<input type="checkbox"/> Not yet requested
	<input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	August 21, 2007 and January 4, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	June 19, 2007
❖ ECAC/CAC report/memo of meeting	June 27, 2007
❖ Nonclinical inspection review Summary (DSI)	X None requested

Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	August 2, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Clinical review: August 2, 2007
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	X None
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	X Not needed
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	Clinical review: August 2, 2007
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	X Not needed
❖ DSI Inspection Review Summaries <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested
• Clinical Studies	July 16, 2007
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) <i>(indicate date for each review)</i>	August 27, 2007
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	December 22, 2006 and July 13, 2007

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
9/6/2007 01:04:26 PM

8/30/07

Johnson, Jennifer

From: andrew.slugg@ipsen.com
Sent: Thursday, August 30, 2007 4:14 PM
To: Johnson, Jennifer
Cc: andrew.slugg@ipsen.com; steve.scott@ipsen.com; william.jones@ipsen.com
Subject: RE: NDA 22-074: Packaging Comments from DMETS
Importance: High
Follow Up Flag: Follow up
Flag Status: Purple
Attachments: emfinfo.txt

Dear Jennifer,

Yes, Ipsen will send the letter reflecting the date of commitment: August 29, 2007. Scanned and hard copy to follow this email.

Kind Rgds,

Andrew

Andrew P Slugg
 Regulatory Affairs
 Biomeasure Incorporated
 27 Maple Street
 Milford, MA 01757
 andrew.slugg@ipsen.com
 Tel: 1 508 478-0144 x 144
 Fax: 1 508 473-3531

"Johnson, Jennifer" <jennifer.johnson@fda.hhs.gov>

08/30/2007 03:54 PM

To andrew.slugg@ipsen.com
 cc steve.scott@ipsen.com, william.jones@ipsen.com, "Johnson, Jennifer"
 <jennifer.johnson@fda.hhs.gov>

Subject RE: NDA 22-074: Packaging Comments from DMETS

Dear Andrew,

I forgot to ask you yesterday - for proper documentation purposes, could you please submit a letter (amendment) to the NDA with your commitment to comply with the labeling revision requests below? Also, could you please date the letter with yesterday's date (August 29, 2007) since this is the date that the commitment was agreed-upon?

Thanks for your patience!

8/30/2007

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/s/

Jennifer Johnson
8/30/2007 04:32:25 PM
CSO

8/29/07



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 29, 2007
To: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
Thru: Kellie Taylor, Pharm.D., M.P.H., Acting Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support
From: Laura Pincock, R.Ph., Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support
Subject: Label and Labeling Review for Somatuline Depot
Drug Name(s): Somatuline Depot (Lanreotide) Injection
Application Type/Number: NDA#: 22-074
Submission Number: Amendment 0021
Applicant/sponsor: Ipsen Biomeasure, Incorporated
OSE RCM #: 2007-1825

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1 INTRODUCTION

This memorandum is in response to a request from your Division for a review of the container labels and carton labeling for Somatuline Depot (Lanreotide) Injection. The sponsor submitted draft syringe labels, pouch labels, and carton labeling on August 17, 2007.

1.1 REGULATORY HISTORY

DMETS reviewed the proposed proprietary name, Somatuline Autogel, and the proposed insert labeling in our review (OSE Review # 2006-254, January 12, 2007). In that review, DMETS had no objections to the use of the proprietary name, Somatuline. However, DMETS objected to the use of any modifier with this name. Additionally, DMETS objected to the use of the modifier "Autogel" because it is misleading and may be confusing to healthcare practitioners. On July 11, 2007, the Sponsor submitted a response to DMETS' comments regarding the proposed proprietary name, Somatuline Autogel, and proposed the alternate name, Somatuline. In an email to the Review Division, dated July 27, 2007, DMETS objected to the proposed modifier

_____ DMEP concurred with DMETS recommendations regarding the modifier _____, so the Sponsor was requested to submit additional proposed names. The Sponsor submitted three names in order of preference; Somatuline _____ Somatuline, and Somatuline Depot on August 3, 2007. In an email to the Review Division, dated August 13, 2007, DMETS recommended the use of "Somatuline Depot" due to concerns with the use of the _____ modifier (option 1) and concerns with the global availability of shorter and longer acting Somatuline products in foreign countries that make the name Somatuline (option 2-no modifier) risky. DMEP concurred with DMETS and the Sponsor has now agreed to the name "Somatuline Depot".

1.2 PRODUCT INFORMATION

Somatuline Depot (lanreotide acetate) Injection is a somatostatin analog indicated for: (1) the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy, and/or _____

_____ Somatuline Depot should be injected via deep subcutaneous route in the external quadrant of the buttock _____. It is administered at 90 mg every 4 weeks for 3 months, and then the dose is adapted based on GH, IGF-1 levels, and/or symptoms of acromegaly (see Table 1 below).

Table 1: Somatuline Depot dosing regimen after 3 months of treatment.

GH	Symptoms	Dose
>1 to ≤ 2.5 ng/mL	IGF-1 normal and clinical symptoms controlled	Maintain dosage at 90 mg every 4 weeks
> 2.5 ng/mL	IGF-1 elevated and/or clinical symptoms uncontrolled	Increase dosage to 120 mg every 4 weeks
≤ 1	IGF-1 normal, and clinical symptoms controlled	Decrease dosage to 60 mg every 4 weeks

Somatuline Depot Injection is supplied in a single, sterile, pre-filled, ready-to-use polypropylene syringe fitted with a needle covered by a dry natural rubber sheath. It is available in three strengths; 60 mg/syringe, 90 mg/syringe, and 120 mg/syringe. Each pre-filled syringe is packed

in a _____ laminated pouch and packed in a carton. Somatuline Depot must be stored in a refrigerator at 2° C to 8° C (36° F to 46° F) in the original package.

2 MATERIAL REVIEWED

DMETS reviewed the Sponsor's draft syringe labels (60 mg, 90 mg, and 120 mg), pouch labels (60 mg, 90 mg, and 120 mg), and carton container labeling (60 mg, 90 mg, and 120 mg), which were submitted on August 17, 2007.

3 DISCUSSION

In the review of the container labels and carton labeling for Somatuline Depot Injection, DMETS has identified areas where improvements can be made in the interest of minimizing user error and maximizing patient safety.

The Sponsor uses the same layout for all three strengths of Somatuline Depot. The differentiating feature is the colored, "swoosh" graphic that highlights the strength. The proposed background color for the 60 mg syringe _____, is identical to the color for the 90 mg syringe. The 120 mg syringe has a _____ color. DMETS believes that the use of the same color increases the potential for selection errors with this product. DMETS believes this risk of selection error could be minimized if each syringe strength has a different color.

Additionally, as currently presented on all labels and labeling, the strength and net quantity of the syringe are combined and stated only in milligrams on the principal display panels. DMETS generally recommends that _____

DMETS notes that the back panel provides clarification with the statement "CONTENTS: This box contains one (1) pre-filled syringe. Each pre-filled syringe contains a super-saturated solution of lanreotide acetate corresponding to XX mg of lanreotide base per XX mg solution, which ensures the injection of XX mg lanreotide." However this statement is confusing and DMETS believes it can be more clearly stated.

The prominence of the storage requirements should be increased. DMETS recommends using a larger font to increase readability.

4 CONCLUSIONS AND RECOMMENDATIONS

DMETS recommends the label changes outlined below. 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. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, project manager, at 301-796-0723.

4.1 GENERAL COMMENTS

4.1.1 Please ensure that the three strengths (60 mg, 90 mg, and 120 mg) of Somatuline Depot each use a different color to differentiate among the strengths on all labels and labeling.

4.1.2 Revise the product strength of each to read _____

4.1.3 Revise the statement on the back panel of the carton labeling to read _____



4.1.4 DMETS recommends using a larger font to increase the prominence of the storage requirements for Somatuline Depot.

1. DRAFT PRODUCT PACKAGING

Somatuline® Depot is available in three dose strengths 60mg, 90mg and 120 mg and provided as a sterile, pre-filled, ready to use polypropylene syringe which is sealed in a laminate pouch contained in a cardboard carton. As described in 3.2.P.7 of the Application, the drug product's immediate container is the syringe, which, _____ is labeled and sealed in a _____ laminate pouch.

_____ the laminate pouch is then labeled and placed in the cardboard carton, the primary display packaging. The syringe draft labels and other packaging elements are provided below and attached.

a) Draft Syringe Labels

Samples of the draft Somatuline Depot syringe label are provided in full color below (Note, not to scale). When fully assembled the label's dimensions are: Length = 68mm, Width = 12 mm

Figure 1. 60 mg Draft Syringe Label

b) Draft Pouch Labels

Samples of the draft Somatuline Depot pouch label are provided in full color and scale on the pages which follow.

The dimensions are: Length = 310 mm, Width = 75 mm.

c) Draft Carton

Samples of the draft Somatuline Depot carton are provided in full color and scale on the pages which follow.

When fully assembled the carton's dimensions are: Length = 285 mm, Width = 80 mm, Height = 20 mm.

A

4 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

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this page is the manifestation of the electronic signature.**

/s/

Laura Pincock
8/29/2007 07:56:28 AM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
8/29/2007 12:57:44 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/29/2007 01:37:33 PM
DRUG SAFETY OFFICE REVIEWER

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, August 29, 2007 2:17 PM
To: 'andrew.slugg@ipsen.com'
Cc: 'steve.scott@ipsen.com'; 'william.jones@ipsen.com'; Johnson, Jennifer
Subject: NDA 22-074: Packaging Comments from DMETS

Dear Andrew,

Here are the comments that I just received from the DMETS team for your draft syringe/pouch/carton labels submitted on August 17, 2007. I am still working on the PI/PPI, but wanted to get these comments to your team while I finish the other labeling. Please let me know if you have any questions about any of these recommendations.

Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

-
1. Please ensure that the three strengths (60 mg, 90 mg and 120 mg) of Somatuline Depot each use a different color to differentiate among the strengths on all labels and labeling.
 2. Revise the product strength of each to read _____
 3. Revise the statement on the back panel of the carton labeling to read " _____"
/ / / / /
 4. DMETS recommends using a larger font to increase the prominence of the storage requirements for Somatuline Depot.

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

/s/

Jennifer Johnson
8/29/2007 02:20:14 PM
CSO

ADRA Rev #1 of Action Package for NDA 22-074, Somatuline Depot (lanreotide acetate injection)

Reviewer: Lee Ripper, HFD-102

Date received: 8/10/07

Date of review: 8/16/07; 8/30/07

Date original NDA received: 10/30/06

UF goal date: 8/30/07

Proposed Indication: (1) long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy _____
_____ By amendment dated August 15, 2007, the applicant
withdrew _____ s indication.

Action type: AP

RPM: Jennifer Johnson

Drug Classification: 1SV

505(b)(1) application

Debarment Certification: AC

Financial Disclosure: AC

Safety Update: Recd 3/12/07. Rev'd in 8/2/07 MOR.

Risk Management Plan: Routine monitoring

Clinical Inspection Summary: Data AC in support of the NDA 7/16/07.

ODS/DMETS Review of Proprietary Name: Tradename "Somatuline" AC per rev dtd 1/12/07; however, object to modifier "Autogel." *DMETS proposed the modifier "Depot" in an email dated 8/13/07; applicant's amendment dated August 17 accepts this suggestion.* Rev of PI in rev dtd 1/12/07. Rev of PPI dtd 7/24/07. Rev of carton and container labels dtd 8/29/07.

DSRCS Review of PPI: 8/8/07

DDMAC Review: Tradename AC per DMETS rev dtd 1/12/07. Labeling rev dtd 8/8/07

SEALD Review of PLR: WPierce concurred with RPM labeling format review; no separate SEALD review

EA: Categorical exclusion, p 62 of 5/15/07 CMC rev

EER: AC 7/27/07

PSC/WU Mtg: 8/1/07. **Minutes not yet final.**

CMC division director review CM, Blair Fraser, 8/7/07
P/T section to Abby Jacobs, 8/17/07; rev dtd 8/20/07

8/8/07



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 8, 2007

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Thru: Toni Piazza-Hepp, Pharm. D., Deputy Director
Division of Surveillance, Research and Communication Support

From: Sharon R. Mills, BSN, RN, CCRP
Division of Surveillance, Research and Communication Support

Subject: DSRCS review of Patient Labeling

Drug Name(s): Somatuline (lanreotide acetate) injection 60 mg., 90 mg., 120 mg.

Application Type/Number: 22-074

Applicant/sponsor: Beaufour Ipsen Pharma

OSE RCM #: 2007-1420

1 INTRODUCTION

The sponsor submitted an NDA for Somatuline (lanreotide acetate) injection 60 mg, 90 mg, and 120 mg, on October 27, 2006, for "the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option", and was granted Orphan status. The sponsor initially submitted patient labeling in the form _____

_____ so
the sponsor was asked to resubmit the patient labeling in the form of a Patient Package Insert (PPI). The sponsor submitted a proposed Package Insert _____
_____ on April 17, 2007.

2 MATERIAL REVIEWED

The r proposed Patient Package Insert (PPI) dated April 17, 2007, and the proposed Professional Labeling (PI) submitted on October 27, 2006 and later revised by the review division on August 3, 2007 were reviewed.

3 DISCUSSION

Formatting issues with the submitted Word copy of the PPI would not allow us check readability scores. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level).

4 CONCLUSIONS AND RECOMMENDATIONS

- See the attached revised PPI (marked up and clean) for our suggested revisions. We have simplified the wording where possible, removed unnecessary information, and made it consistent with the Professional Information (PI). All future relevant changes to the PI should also be reflected in the Patient Package Insert.
- The review division has removed verbage _____
_____ from the PI and PPI. We have therefore deleted the _____ from the PPI.
- Refer to the PI, Section 10. OVERDOSAGE. In order to reference the National Poison Control Center number in the PI, specific language must be included. Refer the sponsor to the website: aapcc.org where they can navigate to "Industry Guidelines for Use of 1-800-222-1222". If the sponsor chooses not to follow these guidelines, delete the 1-800-222-1222 number from the PI.

Comments to the review division are ***bolded, italicized and underlined***. We recommend using the clean copy of the revised PPI as the working document. Please let us know if you have any questions.

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/s/

Sharon Mills
8/8/2007 11:22:23 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
8/8/2007 04:41:23 PM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-074 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Somatuline Autogel Injection
Established Name: lanreotide acetate
Strengths: 60 mg, 90 mg, 120 mg

Applicant: Beaufour Ipsen Pharma
Agent for Applicant (if applicable): Biomeasure, Inc.

Date of Application: October 27, 2006

Date of Receipt: October 30, 2006

Date clock started after UN: N/A

Date of Filing Meeting: December 21, 2006

Filing Date: December 29, 2006

Action Goal Date (optional): August 23, 2007

User Fee Goal Date: August 30, 2007

Indication(s) requested: treatment of acromegaly

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) orphan

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application?
If yes, explain: YES NO X

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES X NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO X

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain: YES NO X
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index?
If no, explain: YES X NO
- Was form 356h included with an authorized signature?
If foreign applicant, both the applicant and the U.S. agent must sign. YES X NO
- Submission complete as required under 21 CFR 314.50?
If no, explain: YES X NO
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES X NO
2. This application is an eNDA or combined paper + eNDA YES NO X
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format X
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) N/A YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? N/A

Additional comments: N/A

3. This application is an eCTD NDA. YES NO X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. (Note: the applicant as also requested 7 years orphan exclusivity due to orphan drug status already granted.)
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 53,993
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) July 26, 2004 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: N/A
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES X NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical (N/A)

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? YES X NO

Microbiology, sterility: Robert Mello
 Microbiology, clinical (for antimicrobial products only): N/A
 DSI: Andrea Slavin
 OPS: N/A
 Regulatory Project Management: Jennifer Johnson
 Other Consults: DMETS/DSRCS/DDMAC/SEALD

Per reviewers, are all parts in English or English translation? YES X NO
 If no, explain:

CLINICAL FILE X REFUSE TO FILE
 • Clinical site audit(s) needed? YES X NO
 If no, explain:
 • Advisory Committee Meeting needed? YES, date if known _____ NO X
 • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES NO X

PHARMACOLOGY/TOX N/A FILE X REFUSE TO FILE

• GLP audit needed? YES NO X

CHEMISTRY FILE X REFUSE TO FILE

• Establishment(s) ready for inspection? YES X NO

• Sterile product? YES X NO

If yes, was microbiology consulted for validation of sterilization? YES X NO

ELECTRONIC SUBMISSION:

Any comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES:
 (Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional):
Letter issued to applicant on January 12, 2007

ACTION ITEMS:

1. X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. X Convey document filing issues/no filing issues to applicant by Day 74.

Jennifer Johnson
Regulatory Project Manager

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/s/

Jennifer Johnson
8/4/2007 06:58:20 PM
CSO

**MEMORANDUM OF MEETING MINUTES
WRAP-UP & PRE-APPROVAL SAFETY CONFERENCE**

MEETING DATE: August 1, 2007
TIME: 1:00 – 2:00 pm
LOCATION: White Oak Building 22, Conference Room 3201
APPLICATION: NDA 22-074
DRUG NAME: Somatuline Depot (lanreotide) Injection
TYPE OF MEETING: Wrap-Up & Pre-Approval Safety Conference (WU/PASC)

MEETING CHAIR: Robert J. Meyer, M.D.

MEETING RECORDER: Jennifer Johnson

FDA ATTENDEES: (Title and Office/Division)

Office of Drug Evaluation (ODE) II

Robert J. Meyer, M.D.	Director
Leah Ripper	Associate Director of Regulatory Affairs

Division of Metabolism and Endocrinology Products (DMEP)

Mary H. Parks, M.D.	Division Director
Theresa Kehoe, M.D.	Clinical Team Leader
Eileen Craig, M.D.	Clinical Reviewer
Dylan Yao, Ph.D.	Pharmacology/Toxicology Reviewer
Lina AlJuburi, Pharm.D., M.S.	Chief, Project Management Staff
Rachel Hartford	Regulatory Project Manager
Jennifer Johnson	Regulatory Project Manager

Office of Clinical Pharmacology

Sally Choe, Ph.D.	Acting Team Leader, Division of Clinical Pharmacology II
Hao Zhu, Ph.D.	Pharmacometrics Reviewer

Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I

Chien-Hua Niu, Ph.D.	Chemistry, Manufacturing and Controls Reviewer
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Office of New Drug Microbiology

Robert Mello, Ph.D.	Microbiology Reviewer
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Office of Safety and Epidemiology (OSE)

Division of Drug Risk Evaluation (DDRE)

Lanh Green, Pharm.D.	Team Leader/Safety Evaluator
Jo Wyeth, Pharm.D.	Safety Evaluator

Division of Medication Errors and Technical Support (DMETS)

Kellie Taylor, Pharm.D.	Acting Team Leader/Safety Evaluator
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Division of Surveillance, Research and Communication Support (DSRCS)

Sammie Beam

Cheryl Campbell, M.S.

Sharon Mills, BSN, RN

Project Manager Team Leader

Project Manager

Patient Product Information Specialist

BACKGROUND:

On October 27, 2006, Beaufour Ipsen Pharma (U.S. Agent: Biomeasure, Inc.) submitted NDA 22-074, Somatuline Autogel (lanreotide acetate) Injection, to be commercially available in single use pre-filled syringes of 60 mg, 90 mg and 120 mg strengths. It is a new molecular entity seeking approval for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. The sponsor has been granted orphan drug status for this product. There have been concerns from DMEP and DMETS regarding the trade name; the sponsor submitted Somatuline Autogel as the trade name in the original application and withdrew the "Autogel" modifier per the DMEP/DMETS request. The sponsor subsequently submitted Somatuline — as the new trade name. However, DMEP and DMETS have agreed that the — modifier poses potential medication error concerns.

MEETING OBJECTIVES:

- To discuss current status and intended regulatory action of each review discipline
- To inform ODE II Director and OSE of any potential safety concerns, including any required postmarketing safety requirements for the sponsor

DISCUSSION POINTS:

1. CLINICAL: Summary of most common adverse reactions related to this drug class (bradycardia, flatulence, gallstones, diarrhea, etc, to be listed in Warnings and Precautions and Adverse Reactions sections). The gastrointestinal (GI) events were stated to be dose-related, but bradycardia was not. There was no concern about an increased safety risk compared to octreotide (another somatostatin analog already approved to treat acromegaly).
2. CLINICAL PHARMACOLOGY: Expressed concern in dosing of patients with renal and hepatic impairment; dose adjusted from 90 mg to 60 mg in these patients.
3. PHARMACOLOGY/TOXICOLOGY: Discussed possible change to Pregnancy Category / from Pregnancy Category / in Section 8 (Use in Specific Populations).
4. CHEMISTRY: Manufacturing site inspected and found acceptable.
5. MICROBIOLOGY: No safety concerns presented.
6. TRADE NAME: DMETS reviewer discussed likelihood of approving the sponsor's recently proposed trade name, Somatuline — A preliminary review and discussion among the DMETS team yielded a likely decision to not approve this trade name due to possible medication errors and confusion with already approved products (lanreotide and octreotide). The other reviewers present at the meeting were in agreement.

ACTION ITEMS:

1. CLINICAL: Finalize review in DFS. Begin labeling discussions with sponsor.
2. CLINICAL PHARMACOLOGY: Review in DFS and labeling comments complete to send to the sponsor.
3. PHARMACOLOGY/TOXICOLOGY: Decision to be made regarding Pregnancy Category and review to be finalized in DFS pending P/T supervisor return. Send labeling comments to RPM to send to sponsor.
4. CHEMISTRY: Review completed and will finalize in DFS pending a favorable microbiology review. Labeling comments for sponsor complete.
5. MICROBIOLOGY: Sponsor response to information requests has recently arrived; anticipating review to be finalized in DFS within the next week.
6. TRADE NAME: The DMETS reviewer will send an email to the RPM to send to the sponsor, stipulating which trade names would be looked upon favorably.

NDA 22-074 Somatuline Depot (lanreotide) Injection was approved on August 30, 2007.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Jennifer Johnson
9/6/2007 12:50:58 PM

7/27/07

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Friday, July 27, 2007 4:38 PM
To: 'andrew.slugg@ipsen.com'
Cc: steve.scott@ipsen.com; Johnson, Jennifer
Subject: NDA 22-074: DMETS Preliminary Comments on Proposed Trade Name (Somatuline —

Dear Andrew,

The Division has discussed with the DMETS review team your proposed new trade name, Somatuline — submitted to FDA on July 11, 2007.

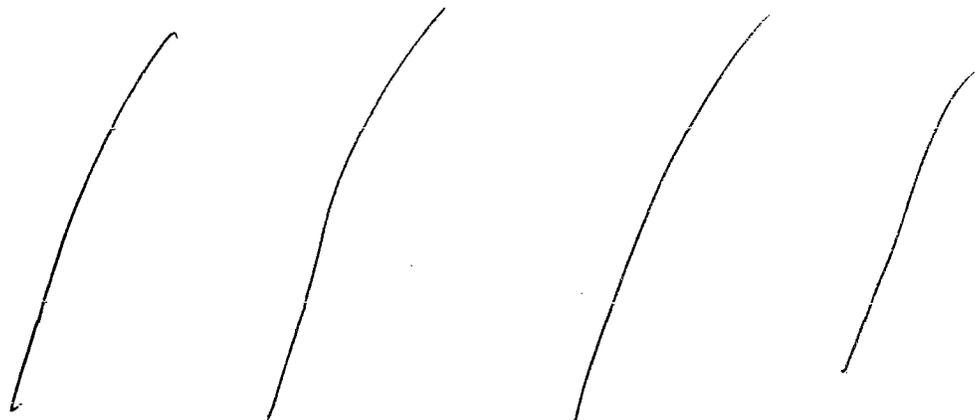
While both the Division and DMETS appreciate your need for a modifier, we are asking that you consider an alternate modifier.

Comments from DMETS are detailed below. When submitting (an) alternate trade name(s), feel free to list more than one for consideration; however, please list them in descending order of preference. If DMETS believes that the first trade name is acceptable, they often do not move on to review the next name in the list due to time and workload constraints.

Please let me know when you anticipate making this submission to FDA, and let me know if you have any questions.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov



7/27/2007

DMETS would like to evaluate the choice of modifier for this product. Please submit the revised name at earliest convenience.

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/s/

Jennifer Johnson
7/27/2007 04:42:15 PM
CSO

7/26/07

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, July 26, 2007 11:27 AM
To: 'andrew.slugg@ipsen.com'
Cc: steve.scott@ipsen.com; Johnson, Jennifer
Subject: NDA 22-074: Label Format Review
Attachments: PLR Format Review to Sponsor.doc

Dear Andrew,

We have completed the format review of your proposed package insert for NDA 22-074. Please see the attached document listing our comments.

Since we have just begun internal labeling discussions, please work on revising the label according to these recommendations for now.

Soon we will have more content-related suggested changes to send to you - I will keep you posted on our progress.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

7/26/2007

Adverse Reactions

- An adverse reaction is an undesirable effect reasonably associated with the use of a drug. This definition does not include all adverse events observed during use of a drug, only those that there is some basis to believe a causal relationship exists. We recommend that you revise your adverse reactions to meet this criteria. See the Adverse Reactions Section of Labeling – Content and Format Guidance for more information.

FDA-Approved Patient Labeling

- This section must reference any FDA-approved patient labeling. The reference [See FDA-Approved Patient Labeling _____] should appear at the beginning of the Patient Counseling Information section.
- Any FDA-approved patient labeling must be appended to or accompany the labeling as a separate document. This requirement went into effect on June 30, 2007. Please insert the FDA-approved patient labeling under section 17.

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/s/

Jennifer Johnson
7/26/2007 11:31:05 AM
CSO

DFS 8/31/07

Johnson, Jennifer

From: Furness, Melissa
Sent: Thursday, August 16, 2007 10:53 AM
To: Johnson, Jennifer
Cc: Burke, Laurie B; CDER SEALD Labeling
Subject: Somatuline - NDA 22-074

Follow Up Flag: Follow up
Flag Status: Yellow

Attachments: NDA 22074_ Somatuline_Content Review 08-15-07_Final.doc

Hi Jennifer,

Please find attached our PLR content review for the Somatuline label. Please let me know if you have any questions or concerns regarding our recommendations/edits.



NDA 22074_
omatuline_Content .

Best regards,

Melissa

Melissa Hancock Furness
FDA/CDER/OND IO
Study Endpoints and Labeling Development Team

B

 1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

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/s/

Jennifer Johnson
7/25/2007 07:02:17 PM
CSO

7/25/07

Division of Metabolism and Endocrinology Products (DMEP)
REGULATORY PROJECT MANAGER LABELING FORMAT REVIEW
(PHYSICIAN LABELING RULE)

Application Number: NDA 22-074

Name of Drug: Somatuline Autogel (lanreotide) Injection, 60 mg, 90 mg, 120 mg

Applicant: Beaufour Ipsen Pharma (U.S. Agent: Biomeasure, Inc.)

Submission Date: October 27, 2006

Receipt Date: October 30, 2006

DMEP Review Date: July 17, 2007

Project Manager: Jennifer Johnson

SEALD Concurrence: William Pierce

Executive Summary

This review provides a list of format revisions for the proposed labeling (Word) that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

DMEP Comments

Highlights

General

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]. Please revise font size and reduce white space in order to accommodate this requirement. There should be white space between each major heading in Highlights.
- Revise the "Initial U.S. Approval" date to 2007.

Drug Name

- Revise established name; it should now read "lanreotide" instead of "lanreotide acetate".

Labeling Format Review – NDA 22-074
Somatuline (lanreotide) Injection, 60 mg, 90 mg, 120 mg

Highlights

General

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]. Please revise font size and reduce white space in order to accommodate this requirement. There should be white space between each major heading in Highlights.
- Revise the “Initial U.S. Approval” date to 2007.

Drug Name

- Revise established name; it should now read “lanreotide” instead of “lanreotide acetate”.

Recent Major Changes

- Remove from Highlights, as this is the initial New Drug Application and thus no Recent Major Changes to list.

Indications and Usage

- Remove (lanreotide acetate) from under this heading. It is not necessary to repeat the established name here.

Contraindications

- List only known hazards and not theoretical possibilities (i.e. _____)

_____ If this is theoretical and there are no other Contraindications, then state “None (4)” in both the Highlights and the FPI.

Adverse Reactions

- In Adverse Reactions statement, replace (_____) with specific manufacturer name. Also, replace _____ with specific contact telephone number. Do not list a v _____

Drug Interactions

- The first bullet under this heading is not a drug interaction. This statement should be removed and placed under the Warnings and Precautions heading or should be reworded to identify the drugs that Somatuline interacts with to produce this effect.

Recent Major Changes

- Remove from Highlights, as this is the initial New Drug Application and thus no Recent Major Changes to list.

Indications and Usage

- Remove (lanreotide acetate) from under this heading. It is not necessary to repeat the established name here.

Contraindications

- List only known hazards and not theoretical possibilities: _____
_____ If this is theoretical and there are no other
Contraindications, then state "None (4)" in both the Highlights and the FPI.

Adverse Reactions

- In Adverse Reactions statement, replace _____ with specific manufacturer name.
Also, replace _____ with specific contact telephone number. Do not list a

Drug Interactions

- The first bullet under this heading is not a drug interaction. This statement should be removed and placed under the Warnings and Precautions heading or should be reworded to identify the drugs that Somatuline interacts with to produce this effect.

Patient Counseling Information Statement

- Revise _____ to read "FDA-approved patient labeling".

Revision Date

- Change revision date from "10/2006" to "XX/200X". The correct date should be updated when approved labeling is finalized.

Full Prescribing Information (FPI): Contents

- Limit to ½ page if possible.
- Remove periods after the numbers for the section headings.
- For Section 16 (How Supplied/Storage and Handling), decrease the indentation.

Full Prescribing Information (FPI)

General

- Remove periods after the numbers for the section headings.

Dosage and Administration

- The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. For example, in this section, the cross reference has been denoted as:

(see 8.5 GERIATRIC USE AND 12.3 PHARMACOKINETICS)

It is preferred to denote the cross-reference in this way (and repeat this format throughout the remainder of the labeling text):

[see Geriatric Use (8.5) and Pharmacokinetics (12.3)]

For all of the following sections, this same recommendation applies:

Contraindications

Warnings and Precautions

Adverse Reactions

Use in Specific Populations

Description

Clinical Pharmacology

Nonclinical Toxicology

Adverse Reactions

- An adverse reaction is an undesirable effect reasonably associated with the use of a drug. This definition does not include all adverse events observed during use of a drug, only those that there is some basis to believe a causal relationship exists. We recommend that you revise your adverse reactions to meet this criteria. See the Adverse Reactions Section of Labeling – Content and Format Guidance for more information.

FDA-Approved Patient Labeling

- This section must reference any FDA-approved patient labeling. The reference [See FDA-Approved Patient Labeling _____] should appear at the beginning of the Patient Counseling Information section.
- Any FDA-approved patient labeling must be appended to or accompany the labeling as a separate document. This requirement went into effect on June 30, 2007. Please insert the FDA-approved patient labeling under section 17.

NDA 22-074
RPM PLR Label Review #1
Page 4

Recommendations

After the comments are conveyed to the applicant and revised labeling is submitted, comments will be checked to ensure that all have been addressed and incorporated into the labeling. At the subsequent labeling meeting(s) the applicant's updated (revised) draft labeling will be used.

Appendix A: Applicant's Proposed Labeling

Attached product labeling.

Drafted: J.Johnson/07.17.07

Revised/Initialed: W.Pierce/07.19.07

Finalized: J.Johnson/07.25.07

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

7/24/07

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)**

DATE RECEIVED: June 25, 2007	DESIRED COMPLETION DATE: July 23, 2007	OSE CONSULT #: 2007-1420
DATE OF DOCUMENT: April 17, 2007		

TO: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

THROUGH: Kellie Taylor, Pharm.D., M.P.H., Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Somatuline Autogel (Lanreotide Acetate) Injection 60 mg, 90 mg, and 120 mg	NDA SPONSOR: Beaufor Ipsen Pharma
NDA #: 22-074	

RECOMMENDATIONS:

DMETS recommends implementation of the labeling revisions outlined in Section II of this review to minimize potential errors with the use of this product.

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. Please copy DMETS on any communications forwarded to the Sponsor regarding this review. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-796-0080.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO 22; Mail Stop 4447
Center for Drug Evaluation and Research**

LABELING REVIEW

DATE OF REVIEW: July 6, 2007

NDA #: 22-074

NAME OF DRUG: **Somatuline Autogel**
(Lanreotide Acetate) Injection
60 mg, 90 mg, and 120 mg

NDA HOLDER: Beaufor Ipsen Pharma

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products, for review and comment on the proposed Patient Prescribing Information labeling for Somatuline Autogel Injection. DMETS reviewed the proposed proprietary name, Somatuline Autogel, and the proposed insert labeling in our January 12, 2007 review (OSE Review # 2006-254). In that review, DMETS had no objections to the use of the proprietary name, Somatuline. However, DMETS objected to the use of any modifier with this name. Additionally, DMETS objected to the use of the modifier "Autogel" because it is misleading and may be confusing to healthcare practitioners. On July 11, 2007, the Sponsor submitted a response to DMETS' comments regarding the proposed proprietary name, Somatuline Autogel, and proposed the alternate name, Somatuline — DMETS is currently reviewing the Sponsor's comments and alternate proposed name and will respond to these issues in a separate review (OSE Review #2007-1556). Thus, this review will focus only on the proposed Patient Prescribing Information labeling.

PRODUCT INFORMATION

Somatuline Autogel (lanreotide acetate) Injection is a somatostatin analog indicated for: (1) the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy, and/or ~~_____~~ Somatuline Autogel should be injected via deep subcutaneous route in the external quadrant of the buttock ~~_____~~. It is administered at 90 mg every 4 weeks for 3 months, and then the dose is adapted based on GH, IGF-1 levels, and/or symptoms of acromegaly (see Table 1 below).

Table 1: Somatuline dosing regimen after 3 months of treatment.

GH	Symptoms	Dose
>1 to ≤ 2.5 ng/mL	IGF-1 normal and clinical symptoms controlled	Maintain dosage at 90 mg every 4 weeks
> 2.5 ng/mL	IGF-1 elevated and/or clinical symptoms uncontrolled	Increase dosage to 120 mg every 4 weeks
≤ 1	IGF-1 normal, and clinical symptoms controlled	Decrease dosage to 60 mg every 4 weeks

Somatuline Autogel Injection is supplied in a single, sterile, pre-filled, ready-to-use polypropylene syringe fitted with a needle covered by a dry natural rubber sheath. Each pre-filled syringe is packed in a laminated pouch and packed in a carton. Somatuline Autogel must be stored in a refrigerator at 2° C to 8° C (36° F to 46° F) in the original package.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS has reviewed the Patient Prescribing Information (PPI) labeling from a medication error perspective and have identified the following areas of improvement, which might minimize potential user error and maximize patient safety.

A.



C

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 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

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/s/

Laura Pincock
7/24/2007 12:00:07 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
7/24/2007 04:54:17 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/24/2007 05:01:05 PM
DRUG SAFETY OFFICE REVIEWER

7/16/07

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 27, 2007

TO: Jennifer Johnson, Regulatory Project Manager
Theresa Kehoe, M.D., Clinical Reviewer
Division of Metabolism and Endocrinology Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Andrea Slavin, RN
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-074

APPLICANT: Ipsen Biotech

DRUG: Somatuline® Autogel® (lanreotide acetate) Injection

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of acromegaly

CONSULTATION REQUEST DATE: February 9, 2007

DIVISION ACTION GOAL DATE: August 30, 2007

PDUFA DATE: August 30, 2007

I. BACKGROUND:

Somatuline Autogel (lanreotide acetate) injection is a new somatostatin analogue developed for the treatment of acromegaly. It binds to pituitary somatostatin receptors to inhibit growth hormone secretion.

The goals of the inspections were to assess adherence to FDA regulatory requirements, specifically, investigator oversight, protocol compliance, verification of primary efficacy endpoint data, adequacy of study records and protection of subjects' rights, safety, and welfare. Site selection was based on subject enrollment, and, _____

The following protocols were audited:

#E-28-52030-717, "Phase II, Multi-Centre, Randomized, Double-Blind Study, in Acromegalic Patients Evaluating the Efficacy and Safety of a Single Deep Subcutaneous Administration of Lanreotide Autogel (60, 90, or 120 mg) versus Placebo, Followed by a Single-Blind Fixed Dose Phase Evaluating the Pharmacokinetic, Pharmacodynamic, Efficacy and Safety Profile of Multiple Deep Subcutaneous Administrations of Lanreotide Autogel (60, 90 & 120 mg) Ending in Open Label Dose Titration Phase"

#E-54-52030-081, "Phase III, Multicentre, Open Study to Assess the Efficacy and Safety of Lanreotide Autogel (60, 90 or 120 mg) in Acromegalic Patients Previously Treated or not by Somatostatin Analogues"

#2-47-52030-721, "A Multicentre Prospective Controlled Observer Blinded Cohort Study in Patients with Acromegaly to Evaluate the Risk of Cardiac Valvular Regurgitation in Patients Treated with Lanreotide Relative to Patients Treated with Octreotide"

In addition, a sponsor inspection was completed to assess the sponsor's compliance with FDA regulations.

Summary Report of U.S. and Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	Country	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Shlomo Melmed, MD/701	USA	Los Angeles, CA	E-28-52030-717	4/16/07-4/20/07	6/6/07	NAI
David Cook, MD/703	USA	Portland, OR	E-28-52030-717	3/19/07-3/23/07	4/26/07	VAI
Philippe Caron, MD/6	France	Toulouse	E-54-52030-081	4/23/07-4/27/07	5/22/07	NAI
Josef Marek, MD/301	Czech Republic	Prague	2-47-52030-721	5/14/07-5/18/07	6/21/07	NAI

Sponsor Inspection

Name	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Biomeasure, Inc.	Milford, MA	E-28-52030-717	3/19/07-3/27/07	4/10/07	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviation(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #E-28-52030-717

1. Shlomo Melmed, M.D. (site 701)
Cedars-Sinai Medical Center
8631 W. 3rd Street, Suite 121E
Los Angeles, CA 90048-6121

- a. What was inspected: At this site, 17 subjects were randomized into the study and all subjects' records were audited.
- b. Limitations of inspection: None.
- c. General observations/commentary: No significant deviations from FDA regulations were observed.
- d. Data from this site appear acceptable.

2. David M. Cook, M.D. (Site 703)
Oregon Health & Science University
3181 S.W. Sam Jackson Park Road
Portland, OR 97239-3098

- a. What was inspected: At this site, 19 subjects were screened, 9 subjects were randomized, and 8 subjects completed the study. An audit of all randomized subjects' records was performed.
- b. Limitations of inspection: None.
- c. General observations/commentary: For 4 subjects (0003, 0009, 0011, and 0014), the nurse who was the unblinded administrator of study drug performed study assessments at several subsequent visits during the single-blind phase of the study; subject 0011 received the first injection of study drug before all safety assessments were completed; echocardiogram tapes were not maintained for subjects 0016 and 0017; subject 0016 did not sign an IRB-approved Spanish language version of the consent form.
- d. Data from this site appear acceptable.

B. Protocol #E-54-52030-081

Prof. Philippe Caron (site 6)
CHU de Rangueil
Service d'Endocrinologie
1, Avenue J. Poulhes
31054 Toulouse, Cedex
France

- a. What was inspected: At this site, 14 subjects were screened, 13 subjects were dosed with the study drug and 12 subjects completed the study. An audit of 13 subjects' records was conducted.
- b. Limitations of inspection: Study records were in the French language. The inspection was completed with the assistance of a translator.
- c. General observations/commentary: Subjects 04, 08, 10, and 11 did not have a gallbladder ultrasound at visit 1.
- d. Data from this site appear acceptable.

C. Protocol #2-47-52030-721

Prof. Josef Marek (site 301)
1st School of Medicine, Charles University
U Nemocnice 2
Praha 2
Czech Republic

- a. What was inspected: At this site, 24 subjects were screened; 11 subjects were in the index cohort (lanreotide) and 11 subjects were in the reference cohort (octreotide).
- b. Limitations of inspection: Study records were in the Czech language. The inspection was completed with the assistance of a translator.
- c. General observations/commentary: No significant deviations from FDA regulations were observed.

Page 4 of 4-NDA 22-074 Somatuline Autogel (lanreotide acetate)

d. Data from this site appear acceptable.

D. Biomeasure, Inc.
27 Maple Street
Milford, MA 01757-3650

- a. What was inspected: The inspection audited the trial master file for protocol #E-28-52030-717 and focused on documents for site 701 (Dr. Melmed) and site 703 (Dr. Cook).
- b. Limitations of the inspection: Trial master files for the other studies are not maintained in the United States.
- c. General observations/commentary: No significant deviations from FDA regulations were observed.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, none of the inspectional observations appear to have a significant impact on data integrity or subject safety. Data from all sites appear acceptable in support of the NDA.

{See appended electronic signature page}

Andrea Slavin, RN
Consumer Safety Officer

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Andrea Slavin
7/16/2007 09:45:31 AM
CSO

Constance Lewin
7/16/2007 04:29:28 PM
MEDICAL OFFICER

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Tuesday, July 10, 2007 3:55 PM
To: 'andrew.slugg@ipsen.com'
Cc: steve.scott@ipsen.com; Johnson, Jennifer
Subject: NDA 22-074: Micro Reviewer Request for Information

Dear Andrew,

Our microbiology reviewer is requesting the following information as soon as possible. Please submit officially to the NDA (you may also forward me the responses via email). Please let me know if you have any questions or concerns.

Thanks!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

7/10/2007

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/s/

Jennifer Johnson
7/10/2007 04:00:12 PM
CSO

Executive CAC

Date of Meeting: June 26, 2007

Committee: Barry Rosloff, Ph.D., OPS, Acting Chair
Sushanta Chakder, Ph.D., DGP, Alternate Member
William Taylor, Ph.D., DSPTP, Alternate Member
Karen Davis Bruno, Ph.D., DMEP, Team Leader
Dylan Yao, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Dylan Yao

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-074

Drug Name: Somatuline® Autogel®

Sponsor: Beaufour Ipsen Pharma

Background:

Somatuline Autogel (lanreotide acetate) is a synthetic analogue of somatostatin developed for the treatment of patients with acromegaly with subcutaneous administration once every 4 weeks.

Rat Carcinogenicity Study:

Sprague Dawley rats were administered subcutaneous doses of vehicle (2 control groups) or lanreotide acetate at 0.1, 0.2, and 0.5 mg/kg once daily for 104 weeks. The rationale for the dose selection and daily dose regimen was not specified, and the protocol was not previously assessed by the Executive CAC. The high dose achieved only a fraction (1/10) of the maximum human exposure based on AUC values. The major neoplastic finding was a drug-related, statistically significant increase in the incidence of cutaneous/subcutaneous fibrous connective tissue tumors at the injection sites, including fibrosarcoma and malignant fibrous histiocytoma, in both male and female animals treated at the high dose of 0.5 mg/kg/day. The incidence of both tumors also exceeds the historical range. A statistically significant increase in the incidence of malignant lymphoma was observed in the high dose treated males (4.28%); however, the incidence of this tumor fell within the range of historical data (0.91 to 6%), hence it is not considered a drug-related finding. No drug effect on malignant lymphoma was seen in female rats. The local tumorigenesis may be attributed to the frequency of injection of the drug thereby leading to subcutaneous inflammation and local tissue hyperplasia.

Mouse Carcinogenicity Study:

CD-1 mice were administered daily subcutaneous doses of vehicle (2 control groups) or lanreotide acetate at 0.5, 1.5, 5, 10, and 30 mg/kg for 104 weeks. The protocol was not previously assessed by the Executive CAC. The high dose of 30 mg/kg/day induced higher mortality and premature termination of the animals in Weeks 87 (males) and 97 (females) due to dermal lesions at injection sites. This indicates that the 30 mg/kg/day dose level exceeded the maximum tolerated dose (MTD). The AUC at the high dose was

3X that at the maximum human dose. Subcutaneous fibrosarcoma (both genders) and malignant fibrous histiocytoma (males) at injection sites were observed in animals treated at 30mg/kg/day with statistical significance; the incidence of these tumors exceeds the testing lab's historical values.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee felt that the dosing regimen was suboptimal in that the high frequency of injections in animals (daily) compared to the clinical regimen (once every 4 weeks) resulted in local toxicity which likely precluded attainment of adequate systemic exposure. The Committee noted that the dosing frequency likely contributed to the injection site tumors.
- The Committee agreed that the study showed increased cutaneous and subcutaneous tumors of fibrous connective tissues at injection sites at the high dose, but felt that they might not be relevant to humans undergoing monthly injections.

Mouse:

- The Committee agreed that the study was adequate although, as above, the daily dosing regimen likely limited systemic exposure.
- The Committee agreed that the study was positive for cutaneous and subcutaneous tumors of fibrous connective tissues at the injection sites at the high dose. Fibrosarcomas in both genders and malignant fibrous histiocytoma in males were increased at the high dose which produces 3 times the maximum clinical exposure. Based on the frequency of dosing in mice relative to therapeutic use, the tumors observed may not be clinically relevant.

Barry Rosloff, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DM EP
/KDavisBruno, DM EP
/DYao, DM EP
/JJohnson, DM EP
/ASeifried, OND IO

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/s/

Barry Rosloff
6/27/2007 05:24:36 PM

6/8/07

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Friday, June 08, 2007 5:16 PM
To: 'andrew.slugg@ipsen.com'
Cc: steve.scott@ipsen.com; Johnson, Jennifer
Subject: RE: NDA 22-074: CMC and Clinical Information Requests

Dear Andrew,

Thank you for the update regarding the trade name. I will be getting the DMETS comments to you soon.

Regarding the CMC and clinical inquiries, my clinical reviewer has another question. I don't know if it is too late to include the response in your forthcoming amendment.

1. Two cardiac adverse events observed in the three pooled Somatuline Autogel Cardiac Studies (Studies 721, 717 and 076) were sinus bradycardia (12/217, 5.5%) and bradycardia (6/217, 2.8%). What heart rate range defined sinus bradycardia and bradycardia, <50 bpm?, <60 bpm? Was this the same definition used for all 7 Somatuline Autogel studies?

2. Also, our pharmacometrics (clinical pharmacology) reviewer has a request for a PK analysis dataset:

PK Analysis:

Please submit the following dataset in order for us to perform PK analysis. Please submit it as soon as possible.

Please note:

- All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. Please provide the appropriate unit in the description file.

PK analysis dataset: (Please include information from Study 717, 709/710)

USUBJID = Patient unique ID number, CMIN= C min for a patient at the given visit and the given dose level. CMINSS= C min at steady state for the patient at the given dose level. DOSE = dose given to the patient at the period / visit. GENDER = gender of the patient. AGE = age of the patient, WT = body weight of the patient, RACE = race of the patient. STUDY = study no. VISIT = visit no.

Sample of data set structure

USUBJID	CMIN	CMINSS	DOSE	RACE	STUDY	VISIT	GENDER	AGE	WT
1234	6.8	8.9	60	1	717	1	0	29	75
1234	7.4	8.9	60	1	717	2	0	29	75
1234	8.7	10.5	90	1	717	5	0	29	75

Please let me know if you have any questions or concerns.

6/8/2007

Thanks!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

From: andrew.slugg@ipsen.com [mailto:andrew.slugg@ipsen.com]
Sent: Wednesday, June 06, 2007 2:27 PM
To: Johnson, Jennifer
Cc: andrew.slugg@ipsen.com; steve.scott@ipsen.com
Subject: Re: NDA 22-074: CMC and Clinical Information Requests

Dear Jennifer,

I hope all is well. Thanks for your continued pursuit of DMETS' comments on the Trade Name "Somatuline Autogel". In parallel to DMETS' review, Ipsen has conducted a Trade Name Safety Analysis and will be preparing a report in the coming weeks. In this report we plan to address Dr. Niu's and DMETS' comments regarding the Trade Name.

Additionally, we are working on responses to the CMC and Clinical Inquiries. These will be submitted in paper format as official amendments to the NDA as you requested below.

Kind regards,

Andrew

Andrew P Slugg
Regulatory Affairs
Biomeasure Incorporated
27 Maple Street
Milford, MA 01757
andrew.slugg@ipsen.com
Tel: 1 508 478-0144 x 144
Fax: 1 508 473-3531

6/8/2007

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/s/

Jennifer Johnson
6/8/2007 05:22:23 PM
CSO

5/31/07

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, May 31, 2007 5:03 PM
To: 'andrew.slugg@ipsen.com'
Cc: steve.scott@ipsen.com; Johnson, Jennifer
Subject: NDA 22-074: CMC and Clinical Information Requests

Dear Andrew,

My clinical and CMC reviewers have some more questions for your team. Please respond in an official NDA amendment submission. It is also fine to send electronically as well.

I have not yet forgotten your inquiries regarding the trade name and syringe label. (CMC has addressed a few labeling issues below; I will follow up with an email that includes trade name recommendations from the Division of Medication Errors and Technical Support.) I will be out of the office tomorrow and Monday, and look forward to addressing these outstanding issues when I return to the office on Tuesday, June 5th.

Please let me know if you have any questions or concerns. The information requests follow below:

CMC

Drug Product:

A. Dissolution:

1. Please explain

~~_____~~

2. A typographic error is found in Figure 26 (page 37 in Section 3.2.P.2 "Pharmaceutical Development"). The label legend of "M001-2100513 T24 25°C" should be replaced with "M001-2100513 T24 5°C".

~~_____~~

C. Specifications:

5/31/2007

1. As _____ is formed (Section 3.2.P.2.3.6.2). Please include the limit for the _____ in release as well as in shelf-life specifications according to long term stability data as well as accelerated stability data.

2. There are a number of the known manufacturing impurities in the drug substance, including _____ (see page 1 in Section 3.2.S.4.1 "Specification" and page 2 in Section 3.2.P.5.5.1 "List of Expected Impurities"). If the levels of these impurities are more than _____, then they should be listed in the release specifications.

D. Characterization of Impurities:

1. Please provide a narrative explanation for figures shown on the following pages (see Appendixes 3.2.P.5.5-2 and 3.2.P.5.5-4 in Section 3.2.P.5.5 "Characterization of Impurities": Pages 14, 15, 16, 17, 30 (Figure 9) and 31 (Figure 10).

2. Regarding the identification of _____ impurity (Appendix 3.2.P.5.5-6), please explain why there is so great of a difference between Sample 48857UK and Sample 48856UK in terms of the _____ compound (see Figure 4 and Figure 5 on page 38 in Section 3.2.P.5.5).

3. Regarding the unspecified impurities described in Table 11 (page 7 in Section 3.2.P.5.6.3.3 "Unspecified Impurities"), are these impurities the known manufacturing impurities of the drug substance, including _____ impurity samples. Please identify these impurities with authentic _____ impurity samples.

E. Extractables:

1. There are two different values for minimum quantitative limits (MQL) listed in Table 25 (page 21 in Section 3.2.P.5.6.9), one from development batches and other from primary stability batches. Please clarify whether MQL stated in Table 26 (page 21 in the same Section) is below the MQL values from either development batches or the MQL values from the primary stability batches.

F. Stability:

1. In the stability commitment, you should commit (a) to withdraw from market any batch found to fall outside the approved specifications for the drug product and to report the incident to the Agency and (2) the stability results from primary stability batches as well as post-approval batches will be reported to the Agency in an annual report.

E. Labeling:

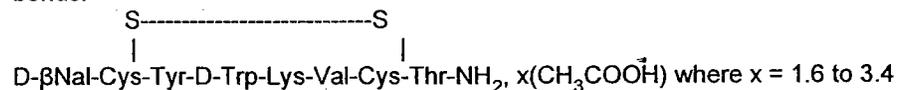
1. Established Name and Trade Name:

(a). For all labeling components, including syringe, carton, and pouch labels as well as packaging insert, the trade name should be changed from "Somatuline Autogel Injection" to "Somatuline Injection" and the established name changed from "lanreotide acetate" to "lanreotide". The reason for removal of the modifier "Autogel" from the trade name is to eliminate a term that is considered confusing and misleading to healthcare practitioners. The reason for removal of the term "acetate" from the established name is so that the established name and the labeled strengths will be in agreement with one another.

2. Package Insert:

(a). Description Section:

The amino acid sequence of lanreotide acetate should be revised as follows to show the positions of the disulfide bonds:



(b). How Supplied Section:

(1). The first sentence should be revised to read "Somatuline is supplied _____"

(2). The National Drug Code (NDC) numbers for each dose strength should be included.

(3). The drug product is known to be light sensitive. Also, an injectable drug that is stored in a refrigerator is typically allowed to equilibrate to room temperature prior to injection. Therefore, the sentence describing storage should be revised to read " _____, Somatuline must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package. F _____

(4). Names and addresses for manufacturer and distributor should be included _____ [see 21 CFR 201.1(h)(5)]

Clinical

1) There were 23 patients with impaired hepatic function in the pooled Lanreotide Autogel studies. Please tell me how many patients were CHILD PUGH classification A, B, or C. Please separate the adverse events seen in this group by their CHILD-PUGH classification.

2) Throughout the studies, the symptoms of acromegaly such as headache, perspiration, fatigue, swelling of extremities, joint pain, impotence and oligomenorrhea were assessed as absent, mild, moderate or severe by the investigator both before and after treatment with lanreotide. Please tell me where in the submission I can find the following:

- A copy of the instrument(s) used to assess this symptoms and how the determination of mild, moderate or severe were made.
- Documentation that shows the instrument is reliable, valid, and able to detect a minimal level of change in this acromegalic population

Many thanks for all of your help!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
5/31/2007 05:06:06 PM
CSO

3/29/07

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, March 29, 2007 5:42 PM
To: 'andrew.slugg@ipsen.com'
Cc: 'steve.scott@ipsen.com'; Johnson, Jennifer
Subject: NDA 22-074/Somatuline Autogel/Questions from Clinical and Clinical Pharmacology Reviewers

Dear Andrew,

Our clinical and clinical pharmacology reviewers have some more follow-up questions for you. Could you please send responses to these questions in an official submission to the Agency? Please let me know if you have any questions.

Thanks so much!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

Clinical Pharmacology

There is no information on how the concentrations of growth hormone and IGF-1 in serum were analyzed and validated. Please submit this information or indicate its location in the NDA if already submitted.

Clinical

Study Number: 2-47-52030-721

Questions for Study 721:

1. Please provide an explanation as to why there were such a high number of patients with non-evaluable valvular regurgitation data.
2. You state in Volume 75, page 91, that there were a total of 21 cases of newly occurring clinically significant valvular regurgitation among patients treated with lanreotide and 11 cases among those receiving octreotide. These included 18 cases of newly occurring aortic regurgitation (seven lanreotide and 11 octreotide), two cases of tricuspid and two cases of pulmonic regurgitation in each cohort, four cases of mitral regurgitation (all in the lanreotide cohort) and four cases of newly occurring, clinically significant regurgitation involving more than one valve (three cases lanreotide and one case octreotide). Please provide the patient numbers for these 32 cases as well as treatment group and whether they were *de novo* or pre-treated subjects. Additionally, in these 32 cases of newly occurring significant valvular regurgitation, please identify which subjects also experienced an increase in cardiac chamber size.
3. Please provide narrative summaries with particular detail to cardiac history on the following patients:
 - a. Subject #8050002 in the ITT matched octreotide group who experienced an increase from physiologic to

3/29/2007

severe pulmonic regurgitation

b. Subject #8050004 in the ITT Matched lanreotide group who experienced an increase from physiologic to moderate mitral regurgitation

c. Subject #7010020 (not in the ITT Matched group) who experienced an increase from moderate to severe aortic regurgitation while on lanreotide

4. Were all readers experienced echocardiographers and board-certified cardiologists? How many echocardiograms had each reader interpreted over what period of time as an assessment of their baseline experience as echocardiographers?

5. Were the echo evaluations based on guidelines from the American Society of Echocardiography? If not, what guidelines were used?

6. Please provide an assessment of concordance between the primary and secondary readers for the ITT matched population echoes at Month 12 with respect to valvular insufficiency (for each valve) in tables similar to the ones below:

Primary Reader	Secondary Readers				
	Degree of aortic-valve insufficiency				
Degree of aortic-valve insufficiency	None	Trace	Mild	Moderate	Severe
None					
Trace					
Mild					
Moderate					
Severe					

*Concordant results should be indicated by boldface or highlighted type.

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/s/

Jennifer Johnson
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CSO

3/8/07



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-074

Biomeasure, Inc.
U.S. Agent for Beaufour Ipsen Pharma
Attention: Steven R. Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

Dear Mr. Scott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Somatuline Autogel (lanreotide acetate) Injection, 60 mg, 90 mg, 120 mg.

We also refer to your February 2, 2007, correspondence, received February 5, 2007, requesting a teleconference to discuss your proposed revised structure for the longitudinal PK, efficacy and safety datasets requested by our Clinical Pharmacology reviewers. We have considered your request and concluded that the teleconference is unnecessary. Clinical Pharmacology has reviewed your proposed dataset structures and they are acceptable.

If you have any questions, please call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks

3/8/2007 07:32:43 PM



Food and Drug Administration
Division of Metabolism and
Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2007

To: Steven Scott / Andrew Slugg	From: Jennifer Johnson
Company: Ipsen Biomedicine	Division of Metabolism and Endocrinology Products
Fax number: 508-473-3531	Fax number: (301) 796-9712
Phone number: 508-478-0144	Phone number: 301-796-2194

Subject: 74 Day Filing Letter (Issued 1/12/07)

Total no. of pages including cover: 6

Comments: Please contact me with any questions or concerns.
Thanks, Jennifer

Document to be mailed: YES NO

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1/12/07



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-074

Biomeasure, Inc.
U.S. Agent for Beaufour Ipsen Pharma
Attention: Steven R. Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

Dear Mr. Scott:

Please refer to your October 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Somatuline Autogel (lanreotide acetate) Injection, 60mg, 90 mg, and 120 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 29, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues, and request that you submit the following information:

Clinical

1. Please provide the risk management plan or notify us exactly where it is located in the application.

Clinical Pharmacology

2. Please submit the pivotal PK and PD study reports electronically.

3. Population PK/PD Analysis: please submit data sets as follows.

4. Please submit the following datasets to support the population PK/PD analysis of studies A 47 52030 705, E88 52030 044, and 52030 ST8065.

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets, i.e. PK/PD data from the non-responders should also be included in the datasets.

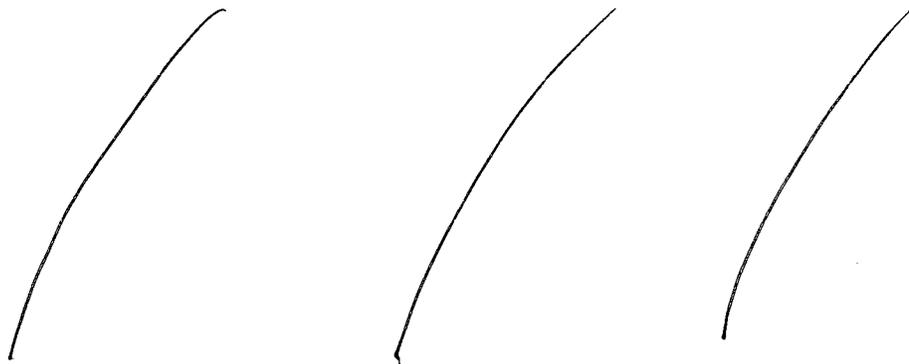
9. Adverse event data format

Study number (integer), Patient number (integer), dose group (dose received in mg or mg/kg), Treatment group, Visit number (including dropout visit) (integer), elapsed time since first dose (hr), AUC_{ss}, C_{ss}, Adverse events (0=no, 1=yes), diarrhea, abdominal pain, and covariates.

Sample of adverse event data structure

PATNO	STUDY	DOSE	GROUP	AUC _{ss}	C _{ss}	AE	Diarrhea	Abdominal pain			
1	1	X	1	45	4.5	0	0	0			
2	1	X	1	76	4	1	0	1			
3	2	Y	2	23	5	1	1	1			
4	2	Y	2	33	4	0	0	0			
5	3	Z	1	42	7	1	1	0			
6	4	X	2	11	8	1	0	1			
...											

Microbiology/ _____



We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 22-074

Page 4

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at
(301) 796-2194.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ON ORIGINAL**

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/s/

Enid Galliers
1/12/2007 01:30:11 PM

1/12/07

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, STOP: 4447)**

DATE RECEIVED: September 13, 2006	DESIRED COMPLETION DATE: November 15, 2006	OSE REVIEW #: 2006-254
DATE OF DOCUMENT: August 28, 2006 (IND# 53,993) & August 29, 2006 (NDA# 22-074)	PDUFA DATE: August 30, 2007	

TO: Mary Parks, MD
Director, Division of Metabolism and Endocrine Products
HFD-510

THROUGH: Nora Roselle, PharmD., Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Somatuline Autogel
(Lanreotide Acetate) Injection
60 mg, 90 mg, and 120 mg

DA#: 22-074 (IND#: 53,993)

NDA SPONSOR: Beaufour Ipsen

RECOMMENDATIONS:

- DMETS has no objections to the use of the proprietary name, Somatuline. However, we object to the use of any modifier with this proprietary name. Moreover, we specifically object to the use of the modifier 'Autogel' because it is misleading and may be confusing to healthcare practitioners. If the Division allows the use of a modifier, DMETS recommends use of a more appropriate modifier than Autogel.
- DMETS recommends consulting the Office of New Drug Quality Assessment for the proper designation of the established name.
- DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
- DDMAC finds the proprietary name, Somatuline Autogel, acceptable from a promotional perspective.

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 301-796-0080.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, STOP: 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: October 10, 2006

NDA#: 22-074 (IND#: 53,993)

NAME OF DRUG: Somatuline Autogel
(Lanreotide Acetate) Injection
60 mg, 90 mg, and 120 mg

NDA HOLDER: Beaufour Ipsen

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrine Products (HFD-510), for assessment of the proprietary name, "Somatuline Autogel", regarding potential name confusion with other proprietary or established drug names. Draft insert labeling was provided for review and comment.

PRODUCT INFORMATION

Somatuline Autogel is a somatostatin analog indicated for: (1) the long-term treatment of patients with acromegaly who have had inadequate response to or cannot be treated with surgery and/or radiotherapy, ? Somatuline is injected via deep subcutaneous route in the external quadrant of the buttock ——— It is administered at 90 mg every 4 weeks for 3 months, and then the dose is adapted based on GH, IGF-1 levels, and/or symptoms of acromegaly (See Table 1 below). It is supplied in a single, sterile, pre-filled, ready-to-use polypropylene syringe fitted with a needle covered by a dry natural rubber sheath. Each pre-filled syringe is packed in a ——— laminated pouch. Somatuline Autogel must be stored in a refrigerator at 2° C to 8° C (36° F to 46° F) in its original package.

Table 1: Somatuline dosing regimen after 3 months of treatment.

GH	Symptoms	Dose
>1 to ≤2.5 ng/mL	IGF-1 normal and clinical symptoms controlled	Maintain dosage at 90 mg every 4 weeks
> 2.5 ng/mL	IGF-1 elevated and/or clinical symptoms uncontrolled	Increase dosage to 120 mg every 4 weeks
≤ 1	IGF-1 normal, and clinical symptoms controlled	Decrease dosage to 60 mg every 4 weeks

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^{3,4} for existing drug names which sound-alike or look-alike to Somatuline Autogel 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 conducted⁵. The Saegis⁶ 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 consisting of two written studies (requisitions) and one verbal requisition 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 (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Somatuline Autogel. Potential concerns regarding drug marketing and promotion related to the proposed name were 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 finds the proprietary name, Somatuline Autogel, acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Somatuline Autogel. Of the four names identified, DMETS found that three names warranted further evaluation based on look-alike, sound-alike and product characteristics (see Table 2 on page 4). Upon further review, it was determined that the name Somatokine was identified on the orphan drug list. No additional information is available. Thus, the name Somatokine will not be reviewed further.

¹ MICROMEDEX Integrated Index, 2006, 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 AMF Decision Support System [DSS], Drugs@FDA, New Drug Approvals 98-06, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA).

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 2: Potential Sound-alike/Look-alike Names Identified by DMETS Expert Panel

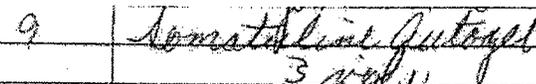
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Somatuline Autogel	Lanreotide Acetate Injection 60 mg, 90 mg, and 120 mg	90 mg deep subcutaneously every 4 weeks for 3 months. After 3 months: GH > 1 ≤ 2.5 ng/mL, IGF-1 normal and clinical symptoms controlled, 90 mg every four weeks. GH > 2.5 ng/mL, IGF-1 elevated and/or clinical symptoms uncontrolled, 120 mg every 4 weeks. GH ≤ 1 ng/mL, IGF-1 normal and clinical symptoms controlled, 60 mg every 4 weeks.	N/A
Somatropin	Somatropin Powder for Injection: 5 mg/mL, 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL Injection: 0.2 mg/vial, 0.4 mg/vial, 0.6 mg/vial, 0.8 mg/vial, 1 mg/vial, 2 mg/vial, 1.2 mg/vial, 1.4 mg/vial, 1.5 mg/vial, 1.6 mg/vial, 1.8 mg/vial, 4 mg/vial, 5 mg/vial, 5.8 mg/vial, 6 mg/vial, 8 mg/vial, 8.8 mg/vial, 10 mg/vial, 12 mg/vial, 13.8 mg/vial, 24 mg/vial	0.006 mg/kg/day to 0.125 mg/kg/day subcutaneous 0.1 mg/kg/week to 0.375 mg/kg divided three times a week 0.004 mg/kg/day to 0.034 mg/kg/day six to seven times a week 0.04 mg/kg/week to 0.7 mg/kg/week	LA
Famotidine	Famotidine Tablets: 10 mg, 20 mg, 40 mg Chewable Tablets: 10 mg Orally Disintegrating Tablets: 20 mg and 40 mg Powder for Oral Suspension: 40 mg/5 mL Injection: 0.4 mg/mL, 10 mg/mL	20 mg to 40 mg once or twice a day 20 mg to 160 mg every six hours 0.5 mg/kg/day to 1 mg/kg/day divided bid 20 mg intravenously every 12 hours	LA
Loratadine	Loratadine Tablets: 10 mg Orally disintegrating tablets: 10 mg Rapidly disintegrating tablets: 10 mg Syrup: 5 mg/5 mL	10 mg once daily Children aged 2-5 years: 5 mg	LA

*Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Somatuline Autogel with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two requisitions were written, each consisting of a combination of marketed and unapproved drug products and a requisition for Somatuline Autogel (see below). These requisitions were optically scanned and one requisition was delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal requisition was 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 requisition orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN REQUISITION	VERBAL REQUISITION
Requisition #1: 	Order code #9: Somatuline Autogel three vials
Requisition #2: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies. However, one participant from the outpatient written study and two from the verbal study omitted the modifier, Autogel. Additionally, one participant from the verbal study omitted the proprietary name, Somatuline, and responded using only the modifier, Autogel.

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Since Somatuline Autogel is available in foreign markets, DMETS conducted an AERS search to determine if there were any reported errors involving this product. The search did not identify any errors relating to nomenclature, dosing, packaging, or administration.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Somatuline Autogel, the primary concerns relating to potential look-alike and sound-alike confusion with Somatropin, Famotidine, and Loratadine. Since there are no additional Somatuline products in the U.S. marketplace from which to differentiate Somatuline Autogel, DMETS expects that the modifier 'Autogel' may be omitted in an order for this product. Additionally, DMETS has concerns about the inclusion of the modifier in an order, in that it may be misinterpreted as a second medication. Therefore, DMETS will evaluate both of these concerns.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. 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 a small sample size. One participant from the outpatient written study and two from the verbal study omitted the modifier, Autogel. Additionally, one participant from the verbal study omitted the proprietary name, Somatuline, and responded using only the modifier, autogel.

1. Look-alike and Sound-alike issues

- a. Somatropin was identified as a name that may have similar appearance to Somatuline Autogel, particularly if the modifier is omitted. Somatropin is indicated in the treatment of long-term growth failure as a result of lack of adequate endogenous growth hormone.

Both names begin with the same five letters (Somat). However, the rest of the letters are orthographically different (uline vs. ropin). Where Somatuline has an upstroke for the letter 'l', Somatropin has a downstroke for the letter 'p'. These orthographic differences may help to distinguish between these two names when written.

Although both Somatuline Autogel and Somatropin are injectable products, they do differ with respect to dose, frequency of administration, and strength.

It is not uncommon to omit the strength when ordering injectable products, because the final dose would have to be included. For the maximum final dose of Somatropin to overlap with the minimum final dose of Somatuline (60 mg) the minimum weight of the patient would have to be 86 kg (188 lbs). This dose would be unlikely as the indication of need for Somatropin is for growth failure. Moreover, this dose would be a total weekly dose, and would need to be divided further in order to determine the final dose. Thus, in addition to the orthographic differences, the dose and frequency of administration will help to differentiate these two products when ordered.

Somatropin
Somatuline

- b. Famotidine was identified as a name that has similar appearance to Somatuline Autogel, particularly if the modifier were omitted in an order. Famotidine is indicated in the treatment of benign gastric ulcer, duodenal ulcer, gastroesophageal reflux disease, as well as hypersecretory conditions.

Both names contain the same number of letters (10) that may look similar when scripted (Somat vs. Famot and uline vs. idine). Although both products have an overlapping dosage form (**injection** vs. tablets, powder for oral suspension, and **injection**), there are some differentiating product characteristics, such as dose (60 mg, 90 mg, and 120 mg vs. 20 mg to 40 mg or one or two tablets), frequency of administration (every 4 weeks vs. once daily, twice daily, or every twelve hours), strength (60 mg, 90 mg, and 120 mg vs. 10 mg, 20 mg, 40 mg, 0.4 mg/mL, 10 mg/mL, and 40 mg/5 mL), and route of administration (subcutaneous vs. oral and intravenous). Neither the dose, frequency of administration, nor the strength of these two products overlap. Thus, even though the two products share similar orthographic characteristics, the differences in the dose, strength, and frequency of administration will help to differentiate these two products.

Famotidine
Somatuline

- c. Loratadine was identified as a name that may look similar to Somatuline Autogel, if the modifier were to be omitted. Loratadine is indicated in the treatment of allergic rhinitis.

Both names contain ten letters that may look similar when scripted (Somat vs. Lorat and uline vs. adine). However, there are some differentiating product characteristics, such as dose (60 mg, 90 mg, or 120 mg vs. 5 mg, 10 mg, 1 tablet or 5 mL), strength (60 mg, 90 mg, or 120 mg vs. 5 mg, 10 mg, or 5 mg/mL), frequency of administration (every four weeks vs. once daily), and route of administration (subcutaneous vs. oral). Although orders for orally administered products, such as Loratadine, may omit the strength or dose and may be written with a general direction of 'Loratadine Tablets, once daily', an order for Somatuline Autogel would need to include a strength, none of which overlap with that of Loratadine. Additionally, Loratadine is an over-the-counter product, and is less likely to be included on an outpatient prescription order. Despite the potential for orthographic similarities, the dose, route of administration, and frequency of administration will help to differentiate these two products when written.

Somatuline
Loratadine

2. Modifier issues

The sponsor has proposed to use the modifier, Autogel, for this product. The use of this modifier can be both misleading and confusing to healthcare practitioners. Therefore, DMETS does not recommend use of the modifier, Autogel, for the following reasons.

- a. Modifiers are generally used to differentiate different dosage forms of the same active ingredient. Since there are no additional Somatuline products available from which to differentiate this product, DMETS questions why the proposed proprietary name for this product contains a modifier or needs a modifier. Additionally, the FDA participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) on drug name suffixes. At this meeting, the FDA heard from practicing health care providers that the FDA should stop approving modifiers that are ambiguous and don't have a standard meaning. Autogel has no standard meaning. Moreover, 'Auto' implies an automatic injection device which this is not. Furthermore, the July 20, 2006, Institute of Medicine report on Medication Error Preventing recommends that drug naming terms be standardized to the extent possible to improve safety and minimize misinterpretation.
- b. The use of the word 'Auto' in the modifier implies that this product is an automatic injector device. However, the product is packaged so that one has to remove a rubber cover to the needle and perform a manual injection. Therefore, the term 'Auto...' is misleading and inaccurate. Additionally, patients or care providers who assume that this is an automatic injector may experience an inadvertent needle stick in the attempt to activate the injection. Moreover, the use of the dosage form 'gel' in the proprietary name implies that this product is a gel formulation, when in fact it is an injection.

III. COMMENTS TO THE SPONSOR:

Although DMETS has not identified any look-alike or sound-alike names that may cause confusion with Somatuline Autogel, we object to the use of any modifier with this proprietary name. Moreover, we specifically object to the use of the modifier 'Autogel'. If the Division allows use of a modifier with the proprietary name of this product, we do not believe this is a safe modifier to use. DMETS objects to use of the modifier, Autogel, for the following reasons:

The sponsor has proposed to use the modifier, Autogel, for this product. The use of this modifier can be both misleading and confusing to healthcare practitioners. DMETS does not recommend use of the modifier, Autogel, for the following reasons.

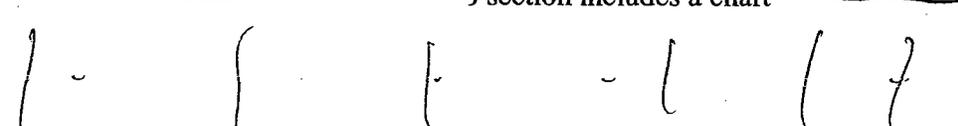
- A. Modifiers are generally used to differentiate different dosage forms of the same active ingredient. Since there are no additional Somatuline products available from which to differentiate this product, DMETS questions why the proposed proprietary name for this product contains a modifier or needs a modifier. Additionally, the FDA participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) on drug name suffixes. At this meeting, the FDA heard from practicing health care providers that the FDA should stop approving modifiers that are ambiguous and don't have a standard meaning. Autogel has no standard meaning.

Moreover, 'Auto' implies an automatic injection device which this is not. Furthermore, the July 20, 2006, Institute of Medicine report on Medication Error Preventing recommends that drug naming terms be standardized to the extent possible to improve safety and minimize misinterpretation.

- B. The use of the word 'Auto' in the modifier implies that this product is an automatic injector device. However, the product is packaged so that one has to remove a rubber cover to the needle and perform a manual injection. Therefore, the term 'Auto...' is misleading and inaccurate. Additionally, patients or care providers who assume that this is an automatic injector may experience an inadvertent needle stick in the attempt to activate the injection. Moreover, the use of the dosage form 'gel' in the proprietary name implies that this product is a gel formulation, when in fact it is an injection.

In the review of the insert labeling of Somatuline Autogel, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement which may minimize user error.

1. According to the DOSAGE FORMS AND STRENGTHS Section of the package insert labeling, the strength of Lanreotide is based on the active moiety and not the acetate salt. However, the manner in which this information is presented throughout the labeling is inconsistent. It appears that the milligram amount pertains to the base and not the amount of salt; however the sponsor includes the salt in the presentation of the established name. We recommend revising the labeling so that it is consistent throughout the labeling. For guidance on this presentation, contact the Office of New Drug Quality Assessment.
2. We note the labeling includes trailing zeroes. The use of trailing zeroes has led to medication errors. Because of these errors, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., trailing zeros such as 1.0 mg/0.5 mg). Thus, we request that the Divisions not approve or use these abbreviations in their labels and labeling. Also, the use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list trailing zeros on their "Do Not Use" list. As evidenced by our post-marketing surveillance, the use of terminal or trailing zeros could potentially result in a ten-fold medication dose error. Thus, DMETS recommends that trailing zeroes be removed from all labels and labeling.

3. The _____, section includes a chart _____
- 

Revise the presentation of this chart to include an introductory statement that states "Each pre-filled syringe contains the following...". Additionally, label the header's of each column with the proper name and strength. See example on page 10.

Each syringe contains:	Somatuline 60 mg	Somatuline 90 mg	Somatuline 120 mg
Lanreotide (INN) acetate	XX	XX	XX
Water for Injection	XX	XX	XX

4. The HOW SUPPLIED section refers to a '...syringe fitted with a needle covered with a natural rubber sheath'. We suggest that you include the gauge of the needle as each person's amount of subcutaneous tissue is different and may require a readjustment in the size of the needle used for the injection.

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A:

Inpatient Written	Outpatient Written	Verbal
Somatiline Autogel	Somaterline Autogel	? auto gel
Somatuline Autogel	Somatesline Autogel	Semetraline
Somatuline Autogel	Somatiline	Semetrelene autogel
Somatuline autogel	Somatulin autogel	Simatchaline Autogel Neuvacid
Somatuline autogel	Somatuline Autogel	Simetriline Autoge
Somatuline Autogel	Somatuline Autogel	Somageline Autogel
Somatuline Autogel	Somatuline Autogel	Sumatralene
Somatuline Autogel	Somatuline Autogel	Symmatraline autogel3
Somatuline Autogel	Somatuline Autogel	
Somatuline Autogel	Somatuline Autogel	
	Somatuline autogel	

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/s/

Linda Wisniewski
1/11/2007 01:00:31 PM
DRUG SAFETY OFFICE REVIEWER

Nora L. Roselle
1/11/2007 01:04:30 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/12/2007 08:04:08 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her
absence

1/4/07

NDA Filing Meeting Checklist

NDA #: 22-074

DRUG: Somatuline Autogel (lanreotide acetate) Injection 60, 90, 120 mg

Sponsor: Beaufour Ipsen Pharma

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		

<p>4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?</p> <p>(Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA - e.g., safety pharm, genotox, reprotox, chronic tox, carcinogenicity)</p>	X		<p>Have electronic files of the carcinogenicity studies been submitted for statistical review?</p> <p>Not needed</p>
<p>5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?</p>	X		
<p>6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?</p>	X		
<p>7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?</p>	X		

ITEM	YES	NO	COMMENT
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

 Reviewing Pharmacologist

 Supervisory Pharmacologist

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/s/

Karen Davis-Bruno
1/4/2007 10:57:18 AM

12/8/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-074

NDA ACKNOWLEDGMENT

Biomeasure, Inc.
U.S. Agent for Beaufour Ipsen Pharma
Attention: Steven R. Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

Dear Mr. Scott:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Somatuline Autogel© (lanreotide acetate), 60/90/120 mg Injection
Review Priority Classification:	Standard (S)
Date of Application:	October 27, 2006
Date of Receipt:	October 30, 2006
Our Reference Number:	NDA 22-074

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 30, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

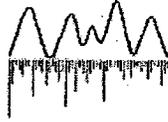
Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jennifer Johnson
12/8/2006 05:34:23 PM

Biomeasure



Fax

To: Dr. Stephen Moore Office of New Drugs - FDA CDER	From: Steven R. Scott Regulatory Affairs Biomeasure Inc Phone: 508-475-9144 ext. 423
Fax: 181-994-9747	Pages: 3 (incl cover)
From:	Date: 11/27/2006
Re: FDA 21-cv-074 Surveillance: Ausupril Request for Right to Privacy Information	CC:
<input type="checkbox"/> Urgent	<input type="checkbox"/> For Review
<input type="checkbox"/> Please Cancel	<input type="checkbox"/> Please Reply
<input type="checkbox"/> Please Reply	<input type="checkbox"/> Please Reply

AS ACS

Pieces are attached.

CONFIDENTIAL

Best Possible Copy

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ON ORIGINAL



Confidential

November 27, 2006

VIA FACSIMILE

Dr. Stephen Moore
Office of New Drug Quality
Center for Drug Evaluation and Research
Food and Drug Administration
3901-B Annandale Road
Bethesda, MD 20705-1206

Re: NDA 22-874
SOMATILINE AUTOGEL (bupivacaine) Injection 0.5, 0.75, 1.00mg
Request for Drug Establishment Information related to NDA 22-874

Dev: Dr. Moore

Disclosure for the authorized US Agent for NDA 22-874 herein provides the Drug Establishment information requested by telephone on November 21, 2006. Please note that the Drug Substance Manufacturer, Ipsen Manufacturing Ireland Limited, and the Drug Product Manufacturer, Ipsen Pharma Biotech have both changed their company names since their initial establishment registrations. In addition, Somatiline recently changed its name from Somatiline Diagnostics Incorporated. Ipsen Manufacturing Ireland Limited and Ipsen Pharma Biotech are all affiliated with one another and are members of the Ipsen Group of companies.

Drug Substance Manufacturer

Company Name: Ipsen Manufacturing Ireland Limited - IMIL
Formerly: Somatiline
Contact Person: Dr. Peter Larkin - Vice President
Address: Blanchardstown Industrial Park
Dublin 15
IRELAND
Phone: +353 1 809 8200
Labeler Code: 14318
Registration Number: 3022801202

Drug Substance Contract Testing Laboratory

Company Name:
Contact Person:
Address:

Phone:
Labeler Code:
Registration Number:

IPSEN, INCORPORATED
27 Maple Street, Weymouth, MA 01978-0001 USA
Telephone: 800-478-9144, Fax: 818-479-8681
www.ipsen.com

Best Possible Copy

APPEARS THIS WAY
ON ORIGINAL

Confidential

Drug Product Manufacturer:

Company Name: Ipsen Pharma Biotech, SAS
 (formerly Pharmax Biotech)
 Contact Person: Bruno Tillet - Directeur Général
 Address: Parc 8' Arctique du Plateau de Sures
 Chemin départemental No. 401
 81870 Sures
 FRANCE
 Phone: +33 4 94 10 50 70
 Labeler Code: 060108
 Registration Number: See entry below

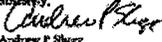
Drug Product Contract

Company Name:
 Contact Person:
 Address:
 Phone:
 Labeler Code:
 Registration Number:

II

Please note that Ipsen Pharma Biotech, originally Pharmax Biotech, did not receive a completed FDA Form 2636 with the labeler code and registration number after initially registering its facility with FDA on December 23, 2000. The subsequent Annual Registration letter from FDA, dated November 14, 2004 indicated only the labeler code 060108. This was communicated to FDA Information Management Team in the most recent Annual Registration for Ipsen Pharma Biotech submitted to FDA November 10, 2006.

Should you require any additional information, please contact me at (508) 478-0144 x 142 or by e-mail at steve.scott@ipson.com

Sincerely,

 Andrew F. Sherr
 for
 Steven E. Scott
 Senior Director, Regulatory Affairs
 Biometrics Inc.

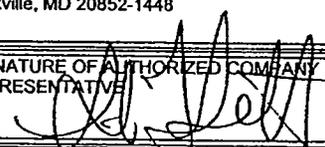
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/s/

Stephen Moore
11/27/2006 02:38:04 PM
CHEMIST

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET
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 BEAUFOR IPSEN PHARMA Steve Scott 27 Maple Street Milford MA 01757 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-074
2. TELEPHONE NUMBER 508-478-0144		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Somatuline Autogel (lanreotide acetate)		6. USER FEE I.D. NUMBER PD3006659
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input checked="" type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
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 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. Food and Drug Administration CDER, HFD-94 1242Q Parklawn Drive, Room 3046 CBER, HFM-99 Rockville, MD 20852 1401 Rockville Pike Rockville, MD 20852-1448		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Sr. Director Regulatory Affairs
		DATE 8/25/06
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$.00		
Form FDA 3397 (12/03)		

(IBE PRMT CLOSE G) (Print Cover sheet)

5/2/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 53,993

Biomeasure Inc., U.S. Agent for Ipsen Biotech
Attention: Stephen R. Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

Dear Mr. Scott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for — (lanreotide acetate injection) Somatuline Autogel, 60 mg, 90 mg, 120 mg.

We also refer to your February 23, 2006, correspondence, received February 24, 2006, requesting a meeting to discuss technical details of a partial electronic NDA submission. We have considered your request and concluded that the meeting is unnecessary. However, in order to assist you in your drug development program, we are providing the following comments in response to questions included in your meeting request. The Office of Business Process Systems (OBPS) provides guidance on the format of electronic submissions, and we are inserting the comments Mr. Kenneth Edmunds of OBPS emailed to your Mr. Andrew Slugg on April 3, 2006, as part of this response.

OBPS General Comments: You appear to be proposing the submission of what is usually called a "hybrid" submission. This is where the basic structure and organization of the CTD is used with navigation provided by PDF table of contents files rather than the newer eCTD XML based navigation. Although a complete eCTD application including XML backbone files for building a comprehensive, dynamic table of contents for navigational purposes is preferred, the older hybrid method is acceptable, especially when the submission will consist of paper and electronic records as proposed in this NDA.

In developing PDF table of contents documents for a partial paper and partially electronic submission, it is recommended that the table of contents indicate not only those items provided in electronic format but also identifies items that are only found in paper form. This can help the reviewer locate both the paper and electronic records more easily.

Specific questions:

1. The company seeks FDA input and agreement with the proposal in terms of the adequacy of the approach proposed to provide electronic CRT datasets and analysis data sets in lieu of paper CRT's listings and patient profiles.

OBPS Comment: You propose using the CDISC SDTM 3.1 standard for tabulation (CRT) data sets. This is acceptable across CDER, but, because the CDISC standard is relatively new, reviewers may require additional data sets beyond those that meet the CDISC standard. These additional data sets can be provided as analysis data sets. The decision to accept the data sets in lieu of traditional patient profiles is determined by the review division. I understand a meeting with the CDER review statisticians is coming up and this would be an excellent time to discuss the data sets required for review.

Biometrics Comment: The SDTM and ADaM standards for CRT datasets and the Analysis datasets, respectively, are acceptable. The CDISC standard is satisfactory.

2. The company seeks FDA input and agreement with the proposal in terms of the adequacy of the structure and organization of data to be provided to electronic format.

OBPS Comment: In general the structure and organization of electronic records proposed is acceptable. Two minor changes to the proposed structure are recommended:

a. The integrated data sets and clinical summary of efficacy (CSE) proposed for Module 2 are recommended to be located in Module 5 (along with the ISS). Module 2 is intended for truly concise summaries and is not accompanied by integrated data. These report documents (PDF files) might be better located under the heading "5.3.5.3 reports of analyses of data from more than one study". The integrated data sets might be better located with the other data sets in the "datasets" directory of Module 5.

b. The case report forms (CRF) proposed for Module 5 section 5.3.7 are acceptable. Reviewers generally prefer that the CRFs be co-located with the appropriate study report files in Module 5.

3. The company seeks FDA input and agreement with the proposal in terms of the adequacy of the ability of the submission to meet the FDA standards for review (file ability of the application).

OBPS Comment: Unfortunately, it is impossible to make a filability determination until the review division receives the actual application. But based on the submission proposed we do not anticipate any technical issues.

DMEP Comment: In order to be able to locate specific items in the paper CTD volumes, include a comprehensive table of contents that reflects a unique volume number for each volume in the entire NDA submission. The Table of Contents (TOC) should correlate the unique volume number with the module number and volume number within the module as well as the page number (or file number/name in electronic folders) as shown in the enclosed examples. The format is a suggestion, not a requirement. Any TOC should allow the reviewer to locate a particular report easily whether it is available only in paper or electronic form.

IND 53,993

Page 3

DMEP General Comment: Please note the requirement to submit **all** labeling pieces in pdf (including scale, color mock-ups of container labels and cartons). In addition, package inserts and patient package inserts or instructions for use and MedGuides should also be submitted in MS Word. Finally, note that the ‘content of labeling’ must be submitted in structured product labeling (SPL) format, and refer to the guidances at the CDER website pertaining to SPL.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology
Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Two sample Tables of Contents for hybrid NDAs

SAMPLE -

Table of Contents

for HYBRID of
eNDA Guidance and CTD format

Item Description	Paper archive Volume number	CTD module #/ volume #/ page #	Electronic archive copy folder name
1. Table of Contents	1	Mod 1/ vol. 1/ pg 1	Main folder or module 1
Cover Letter	1	Mod 1/ vol. 1/ pg 4	Main folder or module 1
FDA Form 356h	1	Mod 1/ vol 1/ pg 7	Main folder or module 1
2. Labeling	1	Mod 1/ vol 1/ pg10	labeling folder or module 1
3. Summary	2	Mod 2/ vol 1/	Summary folder or module 2
4. Chem, Mfg, Control (CMC)	3 - 6	Mod 3/ vol 1 - vol 4	Cmc folder or module 3
5. Nonclinical Pharmacology and Toxicology	7 - 17	Mod 4/ vol 1 - 11	Pharmtox folder or module 4
6. Human Pharmacology and Bioavailability/Bioequivalence	18 - 23	Mod 5/ vol 1 - 6	Hpbio folder or module 5
7.			
8. Clinical	24 - 58	Mod 5/ vol 7 - 41	Clinstat folder or module 5
11. Case Report Tabulations	59 - 60	Mod 5/ vol 42 - 43	Crt folder or module 5
12. Case Report Forms	61 - 66	Mod 5/ vol 44 - 49	crf folder or module 5
13. Patent Information	1	Mod 1/ vol 1/ page x	Other folder or module 1
14. Patent Certifications	1	Mod 1/ vol 1/ page y	Other folder or module 1
16. Debarment Certification	1	Mod 1/ vol 1/ page z	Other folder or module 1

SAMPLE

Table of Contents
for Paper NDA in CTD Format

(If some of the NDA is submitted electronically, add a column for "Electronic Folder Name." The TOC should indicate which items are only electronic, only paper, or both.)

Item Description	Comprehensive Volume No.	Module Number	Volume No. in Module	Page No.
Cover Letter	1	1	1	1
Package insert	1	1	1	54
	1	1	1	76
	2	2	1	1
	3	2	2	
	4	3	1	
	5	3	2	
	6	3	3	
	7	4	1	
	8	4	2	
	9	4	3	
Study Report xyz	10	4	4	
	11	5	1	
	12	5	2	
	13	5	3	

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/s/

Mary Parks
5/2/2006 08:24:57 PM

8/15/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 53,993

Ipsen Biotech
Biomeasure Incorporated, US Agent for Ipsen Biotech
Attention: Steven R. Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

Dear Mr. Scott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lanreotide Autogel (lanreotide — , 60, 90, and 120 mg.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on July 6, 2004. The purpose of the meeting was to discuss the proposed content and format for your proposed NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301)827-6410.

Sincerely,

{See appended electronic signature page}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 6, 2004
TIME: 10:00 a.m.
LOCATION: Parklawn Conference Center, Potomac Room
APPLICATION: IND 53,993
DRUG NAME: Lanreotide Autogel
TYPE OF MEETING: Pre-NDA Type B meeting
MEETING CHAIR: Mary Parks, MD
MEETING RECORDER: Holly Wieland, RN, MPH

FDA ATTENDEES:

Division of Metabolic and Endocrine Drug Products

Mary Parks, MD	Deputy Director
Karen Davis-Bruno, PhD	Pharmacology/Toxicology, Supervisor
Dylan Yao, PhD	Pharmacology/Toxicology Reviewer
Kati Johnson, CPMS	Chief, Project Management Staff
Holly Wieland, MPH	Regulatory Project Manager

Division of Pharmaceutical Evaluations II

Hae Young Ahn, PhD	Clinical Pharmacology Team Leader
Xiao Xiong Wei, PhD	Clinical Pharmacology Reviewer

Division of New Drug Chemistry II

Blair Fraser, PhD	Supervisory Chemist
Steve Moore, PhD	Chemistry Team Leader I
Chien Hua Niu, PhD	Chemistry Reviewer

Division of Biometrics II

Todd Salhroot, PhD	Biometrics Team Leader
Lee-Ping Pian, PhD	Biostatistics Reviewer

Center for Devices and Radiologic Health

Viola Hibbard, BSN	Assistant Regulator, CDRH, HFZ-480
--------------------	------------------------------------

EXTERNAL CONSTITUENT ATTENDEES:

<u>Participant</u>	<u>Title</u>
Helen Amine-Eddine	Director of Biometrics, Ipsen Limited
Virginie Boulifard	Director of Toxicology, SCRAS IHB
France Catus	Medical Sciences Director, Endocrinology, Beaufour Ipsen Pharma, SAS
Ernest Loumaye	Vice President, Medical Sciences, Endocrinology, SCRAS IHB
Sophie Laboulbenne	Associate Director, CMC Regulatory Submission, SCRAS IHB
Martin Montes	Manager of Analytical Sciences, Ipsen Pharma SA
Rosendo Obach	Vice President, Nonclinical Development, Ipsen Pharma SA
Mireille Peyrac	Regulatory Affairs Manager, Ipsen Pharma Biotech SAS
Phil Weatherill	Director, Global Pharmacovigilance, Ipsen Limited
Steven R. Scott	Sr. Director, Regulatory Affairs, Biomeasure Incorporated
Shaun Stapleton	Director, Regulatory Affairs, Ipsen Limited

BACKGROUND INFORMATION

The firm requested a preNDA meeting to obtain concurrence from the Agency that there is sufficient information to file an NDA for IND 53,993 Lanreotide Autogel (lanreotide which is under investigation for treatment of acromegaly.

There are currently two injectable lanreotide acetate formulations. _____, an immediate release formulation (IRF) administered every 7-14 days, and Autogel (IND 53,993), a prolonged release formulation (PRF) administered every four weeks.



The firm has since changed the manufacturing and drug product to a semi-solid gel, a _____ lanreotide that does not contain _____. Autogel is presented in 3 strengths, 60, 90, and 120 mg, in a ready to use syringe.

The firm has submitted information on the pivotal and supportive studies for this application. A brief discussion of the firm's eight clinical studies follows.

Two Pivotal Studies: E-28-52030-717 and E-54-52030-081

The two pivotal studies were conducted in 171 acromegalic patients. The first pivotal study (E-28-52030717) was a placebo controlled, double-blind study evaluating safety and efficacy of repeated subcutaneous administration of Autogel. The second pivotal study (E-54-52030-081) was a controlled baseline study evaluating the effect of Autogel on GH/IGF-I levels compared to pretreatment values.

Two Supportive Studies:

Two supportive studies, E-28-52030-709 and E-28-52030-710, were also conducted. The first supportive study (E-28-52030-709) is a switch study from the microparticle formulation (MPF) of lanreotide to the Autogel formulation, demonstrating that Autogel is not less effective than the MPF in controlling GH and IGF-I levels. The second supportive study (E-28-52030-710) is a long-term follow up study of patients treated in E-28-52030-709 allowing dose titration.

Four Additional Supportive Studies:

A-47-52030-704/045 and A-47-52030-705/044 are two controlled studies with its respective follow-up studies to support the conclusions of E-28-52030-709 and E-28-52030-710. These studies were part of the NDA submission for Ipstyl NDA 21-296.

The firm estimated they would be ready to submit an NDA for IND 53,993 Lanreotide Autogel in June 2005.

CLINICAL AND BIOPHARMACEUTICS QUESTIONS:

(The Sponsor's questions are **bolded**. FDA responses are in *italics*.)

Question 1

The sponsor believes that the design of the pivotal studies and the biochemical endpoints chosen are adequate to provide substantial evidence of effectiveness of Lanreotide Autogel for the treatment of acromegaly. Does FDA agree?

This firm's proposal is acceptable, with comment. The pivotal studies used the autogel formulations while the supportive trials studied the MPF and the PRF. As a result, the supportive studies will contribute to the evaluation of safety, but because the MPF is not approved, it cannot be referenced for evaluation of efficacy. The resulting package insert will not include

Question 2

Would FDA comment on the adequacy of the pharmacokinetic package to support the Lanreotide Autogel formulation?

It appears acceptable.

Question 3

Does FDA agree with the approach to safety evaluation and reporting for the NDA?

The firm is proposing to limit the report of safety data to studies conducted in acromegalics (irrespective of formulation) and in healthy volunteers with Autogel and IRF. According to the firm, other populations studied are not representative of the acromegalic population. The FDA requests a narrative summary of all serious adverse events (drug-related) from other indications.

Question 4

The sponsor believes that the number of patients exposed to lanreotide and the proposed safety information are adequate to support the safety evaluation. Does the FDA agree with the proposed approach to safety evaluation and reporting to FDA?

It appears acceptable.

Questions 5 and 6

The sponsor believes that the design of the cardiac safety study (study E-47-52030-721) choice of comparators, end-points and number of patients, as described in the briefing document will constitute an adequate package to assess the safety of Lanreotide Autogel regarding the valvular regurgitation. Does FDA agree?

In addition to the study E-47-52030-721, non-clinical studies as well as central analysis of echocardiographies and ECGs of patients included in studies E-47-52030-721 and E-47-52030-076 will complete the package for lanreotide cardiac safety assessment. Does FDA agree that this would provide an adequate package to allow the evaluation of effects related to cardiac function?

During the review of — there was a numerical increase in cardiac valvular regurgitation observed in a study whose hypothesis was that lanreotide would improve it. Although there were no clinical manifestations observed, a cardiac safety study was requested. This firm's proposal is acceptable with comment. FDA requested the company submit the report from this cardiac study in addition to a comprehensive cardiac safety assessment of reported adverse events in countries where the product is approved.

Question 7a

Considering that efficacy data will not be integrated, their presentation will be provided in the clinical overview and clinical summary sections of the CTD, an ISE will not be prepared. Does FDA agree with the proposal?

This firm's proposal is acceptable; however, the firm will have to provide a justification as to why they are reporting safety data on approximately one fourth of the patients in the clinical database (408 of 1691 patients).

Question 7b

Does FDA agree with the sponsor's proposed approach for summarizing individual efficacy data by dose and efficacy parameters as listed in the briefing documents?

It appears acceptable.

Question 8

Does FDA have any additional comments or recommendations regarding the clinical efficacy and safety package?

Because the pivotal study E-28-52030-717 enrolls two patient populations, treatment-naïve and non treatment-naïve, FDA requested, in addition to the overall efficacy results, that results be presented separately for treatment-naïve and non treatment-naïve populations. Also provide a detailed presentation of patient disposition (especially Study E-28-52030-717).

NON-CLINICAL QUESTIONS

(The Sponsor's questions are bolded. FDA responses are in italics.)

Questions 1-4

Would FDA comment on the adequacy of the proposed non-clinical package as summarized in the briefing document to support the filing of an NDA for Lanreotide Autogel in the indication of acromegaly?

As Autogel is a formulation of the active lanreotide acetate in water, the sponsor believes that the above-mentioned studies are sufficient to support the safety of Lanreotide Autogel. Does FDA agree?

Can FDA comment on the adequacy of the overall package of old and new tests to form a complete package allowing the assessment of genotoxic potential of lanreotide supportive of the Lanreotide Autogel formulation?

Would FDA comment on the adequacy of the present reproductive toxicity package to support Lanreotide Autogel application?

In preparation for _____, the firm stated its plans to conduct 6-month chronic toxicity studies in rats and dogs with the autogel formulation. These planned studies may serve as a bridge to the previous toxicology studies provided an assessment of exposure is performed. No additional reproductive toxicology studies will be required if bridging is done between the immediate release and the autogel formulations. The firm has repeated the battery of genetic toxicology tests with the autogel formulation and according to them, was negative. The Agency stated that if our review of the studies yields the same conclusion, then the preclinical package appears to be acceptable.

Question 5.

Does FDA have any additional comments or recommendations with regards to the non-clinical package?

No.

CHEMISTRY (CMC) AND BIOPHARMACEUTICS QUESTIONS

(The Sponsor's questions are **bolded**. FDA responses are in *italics*.)

Question 1

The inherent characteristics (semi-solid nature) of the finished product presents a unique challenge when trying to develop an In Vitro Release test. The sponsor has addressed this by _____ during dissolution. The sponsor would like FDA feedback on the adequacy of the method to assess the in vitro release of the product as a quality control test.

The Agency finds that although the approach is novel, the information provided in the package is acceptable. The Agency requested a full characterization of the gel: how it forms, how it dissolves, what it becomes at the concentrations lower than 24.6% (any transitional status between gel and liquid). The Agency had questions about the _____

_____ p. The Agency requested a videotape demonstrating the dissolution procedure.

Question 2

The sponsor has developed an in vitro release test for the drug product. This test will be used as a quality control test only. _____

Does FDA agree with the sponsor's approach of using the In Vitro Release Test as a quality control test?

Yes, the Agency agrees with the sponsor's approach of using the novel in vitro dissolution test as a quality control test.

Question 3

The proposed limits for the In Vitro Release test will be based on analysis of batches of product used in pivotal clinical studies demonstrating safety and efficacy. Does FDA agree with the sponsor's approach to the setting of limits for the commercial finished product to be included in the NDA?

The firm's proposal is acceptable with comments. The Agency recommended using both clinical and commercial batches to set the specifications for the in vitro release test.

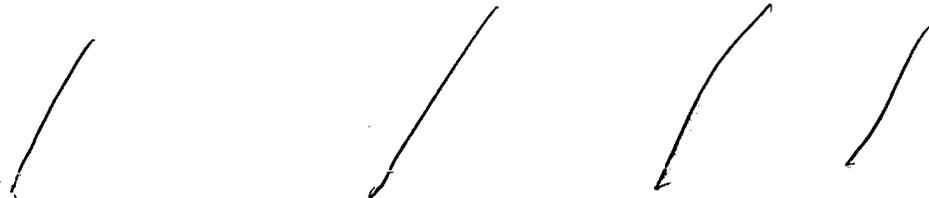
Question 4

Finished product used in clinical trials of Autogel was manufactured at the sponsor's site in Dreux, France. Commercial product will be manufactured at a different site, Ipsen Pharma Biotech, France. Manufacture of the product is identical at the two sites, using the same equipment and manufacturing process. The equipment and manufacturing processes have been validated. Physiochemical characterization and quality control testing of the finished product according to the specifications show the products from the two sites to be comparable.

Considering the mechanism of in vivo release of the drug, the sponsor believes that the physiochemical characterization and quality control testing of the finished product are adequate to demonstrate the comparability of the products from both manufacturing sites supporting the use of Ipsen Pharma Biotech manufactured supplies as commercial product for the USA. Does FDA agree with this approach?

The Agency does not have any experience with a drug product like Autogel as an extended release formulation. However, according to the "Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms," a change in the site of the drug product manufacturing (a level 3 change) requires a single-dose BE study, unless there is an established in vitro/in vivo correlation. Because the firm has not established an in vitro/in vivo correlation, a single dose bioequivalence study is recommended. The Agency stated its willingness to consider a parallel-design study, in lieu of the traditional crossover design since time appears to be an issue with the firm. However, the firm responded that it would only conduct the in vitro comparative tests and present its reasons that a BE study is not necessary. The Agency suggested that prior to the planned NDA submission, the firm submit to the Agency a review package justifying its position not to conduct a BE study. The Agency is willing to further review and discuss this issue internally.

Question 5



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Question 6

Autogel is supplied in a sterile, prefilled, single use, syringe. As such, Autogel is considered a combination product. The sponsor wishes to confirm with FDA that the preliminary review responsibility for the product and its container-closure system remain with CDER. Would FDA confirm this assumption?

CDER will be the lead Center with consults to CDRH and others as needed.

Question 7

The primary container closure system (syringe) is of a proprietary design. All materials and components of the syringe have undergone testing according to the

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as described in the briefing document. For the NDA filing, information supporting the use of the syringe components, syringe assembly and testing will be filed directly in the NDA or by reference to a Master File. Can FDA confirm that the types of studies and test performed on the syringe and syringe components are adequate to support the approval of the primary container closure system?

These are considered review issues that cannot be confirmed until the NDA is submitted. Inclusion of information regarding the syringe in a DMF is acceptable. The firm was requested to assess whether the

_____ . FDA requested sample syringes be sent to CDER and CDRH. FDA discussed the use of unmarked syringes and consequent inability to determine the amount of drug remaining in the syringe in the event that a partial dose was administered.

Question 8

Physiochemical characterization of the finished dosage has involved assessment of the

_____ . The finished product test parameters and specifications are described in the briefing document. Does FDA agree with the adequacy of the characterization and proposed finished product specifications?

It appears acceptable. FDA requested the complete report, referenced in the Briefing Document, page 102, item #6 entitled, Biomimetic organization: octapeptide self assembly into nanotubes of viral capsid like dimension. Proc. Natl. Acad. Science. 2003, 100(18), 10258-10262, authored by Valery, C., Paternoste, M., Robert B., et al. The firm was also requested to determine whether, when dissolved upon injection, aggregates are formed.

Question 9

The sponsor has provided an abbreviated sampling proposal in the briefing document. Does FDA agree with this proposal?

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this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
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Signing for Holly Wieland