

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022074Orig1s004

Trade Name: SOMATULINE DEPOT

Generic or Proper Name: Lanreotide Acetate

Sponsor: Ipsen Pharma

Approval Date: 10/28/2014

Indication: Somatuline Depot (lanreotide) Injection is a somatostatin analog indicated for:

- the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy

CENTER FOR DRUG EVALUATION AND RESEARCH

022074Orig1s004

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022074Orig1s004

APPROVAL LETTER



NDA 022074/S-004

SUPPLEMENT APPROVAL

Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma
Attention: Steven R. Scott
Vice President, U.S. Global Regulatory Affairs
106 Allen Road, 3rd Floor
Basking Ridge, NJ 07920

Dear Mr. Scott:

Please refer to your Supplemental New Drug Application (sNDA) dated April 29, 2010, received May 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Somatuline Depot (lanreotide) injection, 60 mg, 90 mg, 120 mg.

We acknowledge receipt of your amendments dated October 3, 2011, July 2, August 23, and December 21, 2012, January 24 and May 1, 2013, and January 16, and April 4, 2014. We also acknowledge your agreement with our revisions to the package insert via email to Jennifer Johnson of this Division on October 15, 2014.

The January 16, 2014, submission constituted a complete response to our May 25, 2013, action letter.

This “Prior Approval” supplemental new drug application proposes changes to the drug substance and drug product manufacturing processes, and to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. In addition, the syringe dimensions for the three dosage strengths have been harmonized in order to have the three dosage strengths packaged with the same syringe and needle. Your January 16, 2014, submission included a repeat Human Factor Study report, revised labeling, healthcare provider Instructions for Use (IFU) and labels in accordance with our recommendations in the complete response letter dated May 25, 2013.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. We note that the enclosed labels attached to the original sNDA approval letter dated October 28, 2014, included two duplicates of the 120 mg strength pouch label instead of the intended 60 mg and 90 mg pouch labels due to an electronic conversion error in our database. Therefore, this revised approval letter is being issued, with the correct labeling and labels attached, and the original approval date will be retained.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.”

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels (plunger protector label submitted on January 16, 2014; syringe labels submitted via email on May 15, 2014; and pouch and carton labels submitted via email on June 18, 2014), as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022074/S-004.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES: Somatuline Depot (lanreotide) injection, 60 mg, 90 mg, 120 mg:

1. Package Insert
2. Patient Package Insert
3. Healthcare Provider Instructions for Use
4. Plunger protector label
5. Syringe labels
6. Pouch (sachet) labels
7. Carton labels

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/s/

JEAN-MARC P GUETTIER
10/28/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022074Orig1s004

OTHER ACTION LETTERS



NDA 022074/S-004

COMPLETE RESPONSE –CMC

Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma
Attention: Steven R. Scott
Vice President, U.S. Global Regulatory Affairs
106 Allen Road, Third Floor
Basking Ridge, NJ 07920

Dear Mr. Scott:

Please refer to your Supplemental New Drug Application (sNDA) dated April 29, 2010, received May 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Somatuline Depot (lanreotide) injection, 60 mg, 90 mg, 120 mg.

We also refer to your January 16, 2014, resubmission, received January 17, 2014, to your supplemental new drug application.

This resubmission constitutes a complete response to our May 25, 2013, action letter. The user fee goal date is **May 17, 2014**.

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

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Health 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 L JOHNSON
02/26/2014



NDA 022074/S-004

COMPLETE RESPONSE

Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma
Attention: Steven R. Scott
Vice President, U.S. Global Regulatory Affairs
106 Allen Road, Third Floor
Basking Ridge, NJ 07920

Dear Mr. Scott:

Please refer to your Supplemental New Drug Application (sNDA) dated April 29, 2010, received May 5, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Somatuline Depot (lanreotide) injection, 60 mg, 90 mg, 120 mg.

We acknowledge receipt of your amendments dated October 3, 2011, July 2, August 23, and December 21, 2012, and January 24 and May 1, 2013.

The January 24, 2013, submission constituted a complete response to our February 3, 2012, action letter.

This supplemental new drug application proposes changes to the drug substance and drug product manufacturing processes, and to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. In addition, the syringe dimensions for the three dosage strengths have been harmonized in order to have the three dosage strengths packaged with the same syringe and needle. Your December 21, 2012, submission included a Human Factor Study report, and your January 24, 2013, submission included revised labeling, Instructions for Use (IFU) and labels in accordance with our recommendations in the complete response letter dated February 3, 2012.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT DESIGN/HUMAN FACTOR STUDY

1. Our review of your Human Factor study report identified several patterns of use errors associated with the following tasks: verification of dose/expiration date, inserting at a 90 degree angle, and compressing the plunger to the button for the full dose. While there was not a pattern of use error seen in identifying the correct injection site, the clinical

impact of incorrectly injecting into the upper/middle buttock can be significant (i.e., paralysis).

2. We note that the proposed plunger protector appears to be part of the syringe, and the plunger can be depressed with the plunger protector in place. As such it may be difficult for the user to identify that the plunger protector needs to be removed prior to administration of the injection. We recommend adding a statement or a marking on the plunger protector that prompts the user to remove it prior to use. Alternately the plunger protector can be redesigned such that the plunger cannot be reached without the removal of the plunger protector (as seen in the current design of the marketed product).
3. Repeat the Human Factor Study incorporating our recommendations above with 15 representative users (untrained participants), health-care providers and non-professional caregivers combined. These participants should be provided the IFU and proceed with performing the tasks without assistance. This will help determine if the revision to the plunger protector design and the revised IFU (see IFU comments below) mitigated the risks identified in your study.

LABELING/INSTRUCTIONS FOR USE

4. We reserve comment on the proposed labeling and carton and container labels until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

5. Our review of your Instructions for Use indicated that additional information and emphasis should be considered for more adequately communicating to the users. For example, the proposed IFU does not specify that the user has to check the dose/expiration date on the primary container closure. Also, the proposed IFU states to (b) (4) (b) (4) rather than inserting the needle at a 90 degree angle. In addition, the IFU should include safety information emphasizing the importance of selecting the correct injection site, and inserting the needle at full depth.
6. Please revise your IFU as follows to increase the importance of the following tasks, and use the revised IFU in your Human Factor Study:
 - a. Removal of the plunger and maintaining pressure on the plunger in order to activate needle retraction. We request that you increase the emphasis of this task by bolding this step or by adding a statement similar to C1 of the IFU “ (b) (4)

- important (b) (4) ...”. This will act as a reminder to the end users to make sure that the step was done correctly.
- b. Continue compressing plunger to the bottom. We request that you increase in the emphasis of this task by bolding the statement “The medication is thicker and harder to push than you might expect” and relocate this statement so that it is presented as a new paragraph in C8 of the IFU.
 - c. Allow the needle to contract. We request that you increase the emphasis of this task by bolding the statement “If needle does not retract, push plunger again to engage safety mechanism” located in C10 of the IFU.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA’s “Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants”, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Jennifer Johnson, Regulatory Health 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 H PARKS
05/25/2013



NDA 022074/S-004

COMPLETE RESPONSE –CMC

Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma
Attention: Archana Reddy, MPH, MS
Director, Regulatory Affairs
106 Allen Road
Basking Ridge, NJ 07920

Dear Ms. Reddy:

We acknowledge receipt on January 25, 2013, of your January 24, 2013, resubmission to your supplemental new drug application for Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg.

This amendment constitutes a complete response to our February 3, 2012, action letter. The user fee goal date is **May 25, 2013**.

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

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Health 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 L JOHNSON
02/01/2013



NDA 022074/S-004

COMPLETE RESPONSE

Biomeasure, Inc., U.S. Agent for Ipsen Pharma
Attention: Steven R. Scott
Vice President, Regulatory Affairs
27 Maple Street
Milford, MA 01757-3650

Dear Mr. Scott:

Please refer to your Supplemental New Drug Application (sNDA) dated April 29, 2010, received May 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg.

We acknowledge receipt of your amendment dated October 3, 2011, which constituted a complete response to our May 4, 2011, action letter.

This supplemental new drug application proposes changes to the drug substance and drug product manufacturing processes, and to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. In addition, the syringe dimensions for the three dosage strengths have been harmonized in order to have the three dosage strengths packaged with the same syringe and needle. Your October 3, 2011, resubmission included a simulated user study report, as well as responses to comments included in our May 4, 2011, Complete Response letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEVICE/USABILITY VALIDATION STUDY

1. Study Objectives

Your simulated study protocol objective was in alignment with device performance rather than demonstrating the safe and effective use of the device. The primary objective of a summative human factor study should be to demonstrate the safe and effective use of the device by representative user under simulated use conditions. Refer to our original Complete Response letter issued on May 4, 2011.

2. Study Population

Your study population only consisted of Health Care Providers (HCPs) experienced in the administration of deep subcutaneous injections to patients. This is not representative of all Somatuline Depot end users.

The study population should represent all end users, including HCPs, and patients/caregivers experienced in the administration of deep subcutaneous injection, as well as naïve subjects (i.e., with no experience in the administration of deep subcutaneous injection). In our Adverse Events Reporting Systems (AERS) search, we identified a case of a patient self-injecting Somatuline Depot which indicates the need to include patients/caregivers as representative end users. Provide a complete analysis of the intended user population for the proposed device and provide a rationale that the participants recruited for the study are representative of the overall population of users for your device. Note that study participants should not be your own employees, or those who have been exposed to the product prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test be representative of the U.S. population and reside in the U.S.

3. Training

The training provided during the study included a training video that you state will not be available in the U.S. In addition, your study required that participants confirm understanding of the instructions for use (IFU) before proceeding with the testing. This is not representative of actual end user training.

- a. In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.
- b. We recommend that you include at least two arms in the study: participants in one arm are required to read the IFU prior to simulating the injection, and participants in the second arm are provided the product and the IFU without being asked or required to read the IFU prior to simulating the injection. Ensure that these two arms include representative end users (i.e., HCPs, caregivers/patients, experienced and naïve).

4. Retesting after dimensional modification

We acknowledge that retesting after device modification is necessary to demonstrate that the failures have been addressed adequately and that new failure modes have not been introduced. However, we noted the following deficiencies in your retesting: users were employees of Ipsen Pharmaceuticals Development Department; all users were trained to a

point where they could demonstrate comprehension, technique, and confidence in their ability to attempt the testing of the devices; and the devices used in retesting were unfilled prefilled syringes which are not representative of the performance of filled devices. We believe that your retesting participants and testing environments/conditions did not provide a valid representation of actual use. We expect that retesting could be conducted in the same manner as how you would conduct a Human Factors/usability validation study (i.e., this testing should involve representative users performing tasks during simulated use/user scenarios that emphasize highest priority user tasks, and include a summary of user subjective assessment and findings with respect to the safety of the use of your device, and assessment of the effectiveness of device modifications in terms of how the final product has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users).

Retesting after device modification should follow all the requirements for human factor testing.

5. Your study data focused on device performance rather than the necessary performance and subjective data that we require in a Human Factors/usability validation study. It appears that there are a number of device robustness/performance issues that should be addressed. In addition, as a result of this study, you identified some potential areas where the device user interface could be further optimized (section 7.2. page 14). We recommend that you complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.
6. On page 11 of the study report, we note that in 8 instances, the moderator encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Note that instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures.
7. Your study conclusions indicated improvement in device performance. We expect that for a Human Factors/usability validation study, the conclusions should be based on how your evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

Based on the deficiencies stated above, we do not deem this study adequate to demonstrate that the proposed Somatuline Depot prefilled syringe can be used safely and effectively.

Therefore, we request you perform and provide results of a Human Factors/usability validation study following these recommendations as well as those from the original Complete Response letter dated May 4, 2011. We strongly recommend that you submit your protocol, draft carton and container labeling, and proposed package insert labeling **prior to initiation of your study** to ensure that your methods and the resulting data will be acceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is entitled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

LABELING

8. Submit draft labeling revised as follows.
 - a. Highlights of Prescribing Information
 - i. Section 3 Dosage Forms and Strengths - add the unit “mg” to the strength to read: Single use syringe: 60 mg, 90 mg, and 120 mg.
 - b. Full Prescribing Information
 - i. Section 2 Dosage and Administration
 1. Replace the symbols “>” and “<” with the words “greater than” and “less than”, respectively. These symbols (< and >) are considered dangerous abbreviations. They are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations¹. As part of a national campaign to avoid the use of dangerous abbreviations, symbols, and dose designations, FDA agreed not to approve such error-prone abbreviations in the approved labeling of products.
 2. Create a subsection for Dosing for Renal and Hepatic Impairment so that this dosing adjustment required for this patient population is prominent. Currently, the dosing instructions for renally and hepatically impaired patients appear at the bottom of the Dosage and Administration section and can be easily overlooked. Creating a subsection entitled *Dose for Renal and Hepatic Impairment* will make this information more noticeable. For example:
2 DOSAGE AND ADMINISTRATION
2.1 Dose for Renal and Hepatic Impairment
2.2 Instructions for Use
 - ii. Section 2.1 Instructions for Use
 1. Revise the statement (b) (4) to read (b) (4)
(b) (4) or (b) (4) (90 degree angle)”.

¹ Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations (2011). Available at <http://ismpp.org/Tools/errorproneabbreviations.pdf>

2. Revise the statement (b) (4)

[Redacted]

c. (b) (4) Instructions for Use

- i. We acknowledge receipt via email on January 31, 2012, of your revisions to the 1 labeling following receipt of our revisions and comments sent via email on January 23, 2012. Your revisions included addition of a (b) (4) IFU. Please include a (b) (4) IFU in your response to this letter. The IFU should include sequentially labeled (b) (4) instructions with corresponding figures. The sequential (b) (4) instructions should be labeled as “Step 1”, “Step 2”, etc. The figures should be labeled as “Figure A”, “Figure B”, etc, and placed immediately adjacent to the related step.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

9. Submit draft carton and container labeling revised as follows:

a. Pouch labeling

- i. Revise the statement “ (b) (4) ” to read:

[Redacted]

- ii. Ensure that the expiration date and lot number are included.

b. Carton Labeling

- i. Relocate the “Rx only” statement on the principal display panel toward the upper left portion of the carton.
- ii. For the 90 mg/0.3 mL carton labeling, revise the statement (b) (4) (b) (4) to read “For single use only - Discard unused portion”.
- iii. Revise the statement (b) (4) to read “Usual dosage: See prescribing information”.
- iv. There is no statement on the carton labeling that indicates you must leave the product at room temperature for 30 minutes prior to administration; therefore practitioners may not be aware of this necessary step which can result in delay of care. The container label and carton labeling of the current products and proposed product should prominently display a statement that conveys the duration for the product to be at room temperature prior to administration.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA’s “Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants”, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, 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 H PARKS
02/03/2012



NDA 022074/S-004

COMPLETE RESPONSE – CMC

Biomeasure, Inc., U.S. Agent for Ipsen Pharma
Attention: Shawn McLaughlin
Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757-3650

Dear Mr. McLaughlin:

We acknowledge receipt on October 4, 2011, of your October 3, 2011, resubmission to your supplemental new drug application for Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg.

This amendment constitutes a complete response to our May 4, 2011, action letter. The user fee goal date is **February 4, 2012**.

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 L JOHNSON
10/20/2011



NDA 022074/S-004

COMPLETE RESPONSE

Biomeasure, Inc., U.S. Agent for Ipsen Pharma
Attention: Steven R. Scott
Vice President, Regulatory Affairs
27 Maple Street
Milford, MA 01757-3650

Dear Mr. Scott:

Please refer to your Supplemental New Drug Application (sNDA) dated April 29, 2010, received May 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg.

This supplemental new drug application proposes changes to the drug substance and drug product manufacturing processes, and to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. In addition, the syringe dimensions for the three dosage strengths have been harmonized in order to have the three dosage strengths packaged with the same syringe and needle.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEVICE

1. We have concerns relating to the requirement to maintain pressure on the syringe plunger after administering the drug to avoid retraction of the needle. We are concerned with the risk of the needle retracting while it is in the patient's deep subcutaneous tissue.

Postmarketing medication error cases involving needle retraction have been reported with similarly designed pre-filled syringes. These cases describe the needle retracting while the user injected the drug and repositioned the needle during the slow injection, resulting in the patient not receiving the complete dose. Since Somatuline Depot instructions for use state to slowly inject the drug, and typically 20 seconds are needed to inject the full dose, we are concerned with the risk of the needle retracting prior to the patient receiving the full dose.

Please see item 3 regarding performance of tests to demonstrate that the device is safe and effective for its intended use. Such tests can also be designed to assess the risk of needle retraction associated with device use. Additionally, please see the recommendations within the FDA Guidance *Medical Devices with Sharps Injury Prevention Features, August 9, 2005*. The Guidance provides additional points to consider regarding performance testing for the anti needle stick mechanism. The Guidance also recommends that the Sponsor should provide data to support a 99% confidence interval that the anti-needle stick mechanism will successfully work when activated. To achieve this confidence interval, the Guidance recommends performing 500 actuations of the mechanism and demonstrating zero failures over those 500 activations.

2. You have not performed any testing to demonstrate that the hazards associated with use of this sharps injury prevention device have been successfully mitigated. For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. We recommend that you review the Center for Devices and Radiological Health (CDRH) Guidance Document, “Medical Devices with Sharps Injury Prevention Features” when evaluating device performance. This document is located at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>

3. You have not performed any testing to demonstrate that the auto-injector utilized as part of this combination product is safe and effective for its intended use. Please provide performance data to demonstrate through bench testing that your device is safe and effective for its intended use. We recommend that you review FDA’s Guidance Document “Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products”, when developing the necessary bench testing to demonstrate the performance for your device. This document is located at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

4. You have not performed any human factors/simulated use testing to demonstrate that you have mitigated the hazards associated with the use of your device.

Please conduct a design validation (human factors) study. We recommend that you review CDRH’s Guidance “Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management”. This document is located at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>

We also encourage you to submit a draft of the test protocol before you implement it for

our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions, including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

a. Devices and Labeling Used

- i. For design validation, the devices used in your testing should represent the final design, including the labeling.
- ii. Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

b. User Tasks and Training

- i. FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.
- ii. Please describe and provide a rationale for the tasks you include in your testing and their relative priority. Also describe all activities in which your test participants will engage during the test.

- iii. The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you provide and how it corresponded to realistic training levels.

c. Use Environment and Conditions

- i. You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.
- ii. Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.
- iii. Describe the testing environment and realism of the simulated use in sufficient detail for us to determine if they were appropriate for validation testing.

d. Study Participants

- i. FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels) will use your device, you should include 15 from each group.
- ii. Regardless of the number of groups you test, please provide a rationale that these groups adequately represent the overall population of users for your device. Note that study participants should not be your own employees.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

- i. Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured

directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

- ii. Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, “Did you have any difficulty using this device? [If so] can you tell me about that?” The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Please describe and provide a rationale for including each type of data you collect.

LABELING

5. We reserve comment on the proposed labeling (package insert and patient package insert) until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.
6. Please submit draft carton and container labeling revised as follows:
 - a. Pouch Carton Labeling
 - i. Revise to include the proprietary and established names. Currently, the pouch container label displays only the strength of Somatuline Depot (b) (4). The pouch container label must contain the name of the product for identification purposes should the pouch be removed from the carton.
 - ii. Delete the (b) (4) and add instructions for the user to read the package insert instructions. Placing (b) (4) on the pouch label may lead the user to conclude that (b) (4) the only step necessary to correctly administer the medication. However, there are other important instructions the user must follow to ensure correct use of the product.
 - iii. Add a statement such as “Tear here” to provide guidance on how to open the pouch and remove the syringe.

b. Carton Labeling

- i. Revise the appearance of *ml* to read *mL*. For example, *90 mg/0.3 ml* should read *90 mg/0.3 mL*.
- ii. Relocate the statement *Rx Only* toward the lower left portion of the carton labeling.
- iii. Revise the statement [REDACTED] (b) (4) to read: For single use only – Discard unused portion. (Note deletion of [REDACTED] (b) (4))

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, 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

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

/s/

MARY H PARKS
05/04/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022074Orig1s004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Somatuline Depot safely and effectively. See full prescribing information for Somatuline Depot.

SOMATULINE® DEPOT (lanreotide) INJECTION

Initial U.S. Approval: 2007

INDICATIONS AND USAGE

Somatuline Depot (lanreotide) Injection is a somatostatin analog indicated for:

- the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy (1)

DOSAGE AND ADMINISTRATION

- Dose range of 60 mg to 120 mg every 4 weeks (2)
- Recommended dose is 90 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels (2)
- Renal and Hepatic Impairment: Initial dose is 60 mg every 4 weeks for 3 months in moderate and severe renal or hepatic impairment. Adjust thereafter based on GH and/or IGF-1 levels. (2, 12.3)
- Injected in the superior external quadrant of the buttock. Injection site should be alternated (2)
- Store at 2-8 C (36-46 F) in the original package (16)

DOSAGE FORMS AND STRENGTHS

Single use syringe: 60 mg, 90 mg, and 120 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Gallbladder: Gallstones may occur; consider periodic monitoring (5.1)
- Glucose Metabolism: Hypo- and/or hyperglycemia may occur. Glucose monitoring is recommended and anti-diabetic treatment adjusted accordingly (5.2)
- Cardiac Function: Decrease in heart rate may occur. Use with caution in at-risk patients (5.4)

ADVERSE REACTIONS

Most common adverse reactions are diarrhea, cholelithiasis, abdominal pain, nausea, and injection site reactions (6)

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-866-837-2422 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Hypoglycemia agents: Hypo- and/or hyperglycemia may occur. Glucose monitoring is recommended and anti-diabetic treatment adjusted accordingly (7.1)
- Cyclosporine: Somatuline may decrease the bioavailability of cyclosporine. Cyclosporine dose may need to be adjusted (7.2)
- Drugs affecting heart rate: Somatuline may decrease heart rate. Dose adjustment of coadministered drugs that decrease heart rate may be necessary (7.3)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Start dose is 60 mg in moderate and severe renal impairment (2, 8.6, 12.3)
- Hepatic Impairment: Start dose is 60 mg in moderate and severe hepatic impairment (2, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 10/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Somatuline Depot (lanreotide) Injection 60 mg, 90 mg, and 120 mg is indicated 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.

The goal of treatment in acromegaly is to reduce growth hormone (GH) and insulin growth factor-1 (IGF-1) levels to normal.

2 DOSAGE AND ADMINISTRATION

Somatuline Depot should be administered by healthcare professionals. Please see enclosed Instructions for Use leaflet for administration of Somatuline Depot.

Patients should begin treatment with Somatuline Depot 90 mg given via the deep subcutaneous route, at 4-week intervals for 3 months.

After 3 months, dosage may be adjusted as follows:

- GH greater than 1 to less than or equal to 2.5 ng/mL, IGF-1 normal and clinical symptoms controlled: maintain Somatuline Depot dose at 90 mg every 4 weeks.
- GH greater than 2.5 ng/mL, IGF-1 elevated and/or clinical symptoms uncontrolled, increase Somatuline Depot dose to 120 mg every 4 weeks.
- GH less than or equal to 1 ng/mL, IGF-1 normal and clinical symptoms controlled: reduce Somatuline Depot dose to 60 mg every 4 weeks.

Thereafter, the dose should be adjusted according to the response of the patient as judged by a reduction in serum GH and /or IGF-1 levels; and/or changes in symptoms of acromegaly.

Patients who are controlled on Somatuline Depot 60 mg or 90 mg may be considered for an extended dosing interval of Somatuline Depot 120 mg every 6 or 8 weeks. GH and IGF-1 levels should be obtained 6 weeks after this change in dosing regimen to evaluate persistence of patient response.

Continued monitoring of patient response with dose adjustments for biochemical and clinical symptom control, as necessary, is recommended.

2.1 Dose for Renal and Hepatic Impairment

The starting dose in patients with moderate or severe renal impairment, or moderate or severe hepatic impairment should be 60 mg via the deep subcutaneous route, at 4-week intervals for 3 months followed by dose adjustment as described above [*see Clinical Pharmacology (12.3)*].

2.2 Instructions for Use

Somatuline Depot is provided in a single-dose, pre-filled syringe affixed with an automatic needle protection system. Somatuline Depot should be injected via the deep subcutaneous route in the superior external quadrant of the buttock. The injection site should alternate between right and left sides from one injection to the next. Remove Somatuline Depot from

the refrigerator 30 minutes prior to administration. Keep pouch sealed until just prior to injection.

3 DOSAGE FORMS AND STRENGTHS

60 mg, 90 mg, and 120 mg sterile, single-use, pre-filled syringes fitted with an automatic needle guard. The pre-filled syringes contain a white to pale yellow, semi-solid formulation.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Lanreotide may reduce gallbladder motility and lead to gallstone formation; therefore, patients may need to be monitored periodically [*see Adverse Reactions (6.1), Clinical Pharmacology (12.2)*].

5.2 Hyperglycemia and Hypoglycemia

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Hence, patients treated with Somatuline Depot may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly [*see Adverse Reactions (6.1)*].

5.3 Thyroid Function Abnormalities

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, though clinical hypothyroidism is rare (<1%). Thyroid function tests are recommended where clinically indicated.

5.4 Cardiovascular Abnormalities

The most common overall cardiac adverse reactions observed in three pooled Somatuline Depot Cardiac Studies in patients with acromegaly were sinus bradycardia (12/217, 5.5%), bradycardia (6/217, 2.8%) and hypertension (12/217, 5.5%) [*see Adverse Reactions (6.1)*].

In patients without underlying cardiac disease, lanreotide may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to lanreotide treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with lanreotide in patients with bradycardia.

5.5 Drug Interactions

The pharmacological gastrointestinal effects of Somatuline Depot may reduce the intestinal absorption of concomitant drugs.

Lanreotide may decrease the relative bioavailability of cyclosporine. Concomitant administration of Somatuline Depot and cyclosporine may necessitate the adjustment of cyclosporine dose to maintain therapeutic levels [*see Drug Interactions (7.2)*].

5.6 Monitoring: Laboratory Tests

Serum GH and IGF-1 levels are useful markers of the disease and the effectiveness of treatment [*see Dosage and Administration (2)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience

The data described below reflect exposure to Somatuline Depot in 416 acromegalic patients in seven studies. One study was a fixed-dose pharmacokinetic study. The other six studies were open-label or extension studies, one had a placebo controlled run-in period, and another had an active control. The population was mainly Caucasian (329/353, 93%) with a median age of 53.0 years of age (range 19-84 years). Fifty-four subjects (13%) were age 66-74 and eighteen subjects (4.3%) were ≥ 75 years of age. Patients were evenly matched for gender (205 males and 211 females). The median average monthly dose was 91.2 mg (e.g., 90 mg injected via the deep subcutaneous route every 4 weeks) over 385 days with a median cumulative dose of 1290 mg. Of the patients reporting acromegaly severity at baseline (N=265), serum GH levels were < 10 ng/mL for 69% (183/265) of the patients and ≥ 10 ng/mL for 31% (82/265) of the patients.

The most commonly reported adverse reactions, reported by $> 5\%$ of patients who received Somatuline Depot (N=416) in the overall pooled safety studies in acromegaly patients, were gastrointestinal disorders (diarrhea, abdominal pain, nausea, constipation, flatulence, vomiting, loose stools), cholelithiasis and injection site reactions.

Tables 1 and 2 present adverse reaction data from clinical studies with Somatuline Depot in acromegalic patients. The tables include data from a single clinical study and pooled data from seven clinical studies.

Adverse Reactions in Parallel Fixed-Dose Phase of Study 1:

The incidence of treatment-emergent adverse reactions for Somatuline Depot 60 mg, 90 mg, and 120 mg by dose as reported during the first 4 months (fixed-dose phase) of Study 1 [*see Clinical Studies (14)*], are provided in Table 1.

Table 1 Adverse Reactions at an Incidence > 5% With Lanreotide Overall and Occurring at Higher Rate in Drug Than Placebo: Placebo-Controlled and Fixed-Dose Phase of Study 1 by Dose

Body System Preferred Term	Placebo-Controlled Double-Blind Phase Weeks 0 to 4		Fixed-Dose Phase Double-Blind + Single-Blind Weeks 0 to 20			
	Placebo (N=25) N (%)	Lanreotide Overall (N=83) N (%)	Lanreotide 60 mg (N=34) N (%)	Lanreotide 90 mg (N=36) N (%)	Lanreotide 120 mg (N=37) N (%)	Lanreotide Overall (N=107) N (%)
Gastrointestinal System Disorders	1 (4%)	30 (36%)	12 (35%)	21 (58%)	27 (73%)	60 (56%)
Diarrhea	0	26 (31%)	9 (26%)	15 (42%)	24 (65%)	48 (45%)
Abdominal pain	1 (4%)	6 (7%)	3 (9%)	6 (17%)	7 (19%)	16 (15%)
Flatulence	0	5 (6%)	0 (0%)	3 (8%)	5 (14%)	8 (7%)
Application Site Disorders (Injection site mass/ pain/ reaction/ inflammation)	0 (0%)	5 (6%)	3 (9%)	4 (11%)	8 (22%)	15 (14%)
Liver and Biliary System Disorders	1 (4%)	3 (4%)	9 (26%)	7 (19%)	4 (11%)	20 (19%)
Cholelithiasis	0	2 (2%)	5 (15%)	6 (17%)	3 (8%)	14 (13%)
Heart Rate & Rhythm Disorders	0	8 (10%)	7 (21%)	2 (6%)	5 (14%)	14 (13%)
Bradycardia	0	7 (8%)	6 (18%)	2 (6%)	2 (5%)	10 (9%)
Red Blood Cell Disorders	0	6 (7%)	2 (6%)	5 (14%)	2 (5%)	9 (8%)
Anemia	0	6 (7%)	2 (6%)	5 (14%)	2 (5%)	9 (8%)
Metabolic & Nutritional Disorders	3 (12%)	13 (16%)	8 (24%)	9 (25%)	4 (11%)	21 (20%)
Weight decrease	0	7 (8%)	3 (9%)	4 (11%)	2 (5%)	9 (8%)

A patient is counted only once for each body system and preferred term.
Dictionary = WHOART.

In Study 1, the adverse reactions of diarrhea, abdominal pain, and flatulence increased in incidence with increasing dose of Somatuline Depot.

Adverse Reactions in Long-Term Clinical Trials:

Table 2 provides the most common adverse reactions that occurred in 416 acromegalic patients treated with Somatuline Depot in seven studies. The analysis of safety compares adverse reaction rates of patients at baseline from the two efficacy studies, to the overall pooled data from seven studies. Patients with elevated GH and IGF-1 levels were either naive to somatostatin analog therapy or had undergone a 3-month washout [see *Clinical Studies (14)*].

**Table 2 Adverse Reactions at an Incidence > 5.0% in Overall Group
Reported in Clinical Studies**

System Organ Class	Number and Percentage of Patients			
	Studies 1 & 2 (N = 170)		Overall Pooled Data (N = 416)	
	N	%	N	%
Patients with any Adverse Reactions	157	92	356	86
Gastrointestinal disorders	121	71	235	57
Diarrhea	81	48	155	37
Abdominal pain	34	20	79	19
Nausea	15	9	46	11
Constipation	9	5	33	8
Flatulence	12	7	30	7
Vomiting	8	5	28	7
Loose stools	16	9	23	6
Hepatobiliary disorders	53	31	99	24
Cholelithiasis	45	27	85	20
General disorders and administration site conditions	51	30	91	22
(Injection site pain /mass /induration /nodule /pruritus)	28	17	37	9
Musculoskeletal and connective tissue disorders	44	26	70	17
Arthralgia	17	10	30	7
Nervous system disorders	34	20	80	19
Headache	9	5	30	7

Dictionary - MedDRA 7.1

In addition to the adverse reactions listed in Table 2, the following reactions were also seen:

- Sinus bradycardia occurred in 7% (12) of patients in the pooled Study 1 and 2 and in 3% (13) of patients in the overall pooled studies.
- Hypertension occurred in 7% (11) of patients in the pooled Study 1 and 2 and in 5% (20) of patients in the overall pooled studies.
- Anemia occurred in 7% (12) of patients in the pooled Study 1 and 2 and in 3% (14) of patients in the overall pooled studies.

Gastrointestinal Adverse Reactions

In the pooled clinical studies of Somatuline Depot therapy, a variety of gastrointestinal reactions occurred, the majority of which were mild to moderate in severity. One percent of acromegalic patients treated with Somatuline Depot in the pooled clinical studies discontinued treatment because of gastrointestinal reactions.

Pancreatitis was reported in < 1% of patients.

Gallbladder Adverse Reactions

In clinical studies involving 416 acromegalic patients treated with Somatuline Depot, cholelithiasis and gallbladder sludge were reported in 20% of the patients. Among 167 acromegalic patients treated with Somatuline Depot who underwent routine evaluation with gallbladder ultrasound, 17.4% had gallstones at baseline. New cholelithiasis was reported in 12.0% of patients. Cholelithiasis may be related to dose or duration of exposure [*see Cholelithiasis and Gallbladder Sludge (5.1)*].

Injection Site Reactions

In the pooled clinical studies, injection site pain (4.1%) and injection site mass (1.7%) were the most frequently reported local adverse drug reactions that occurred with the administration of Somatuline Depot. In a specific analysis, 20 of 413 patients (4.8%) presented indurations at the injection site. Injection site adverse reactions were more commonly reported soon after the start of treatment and were less commonly reported as treatment continued. Such adverse reactions were usually mild or moderate but did lead to withdrawal from clinical studies in two subjects.

Glucose Metabolism Adverse Reactions

In the clinical studies in acromegalic patients treated with Somatuline Depot, adverse reactions of dysglycemia (hypoglycemia, hyperglycemia, diabetes) were reported by 14% (47/332) of patients and were considered related to study drug in 7% (24/332) of patients [*see Hyperglycemia and Hypoglycemia (5.2)*].

Cardiac Adverse Reactions

In the pooled clinical studies, sinus bradycardia (3.1%) was the most frequently observed heart rate and rhythm disorder. All other cardiac adverse drug reactions were observed in < 1% of patients. The relationship of these events to Somatuline Depot could not be established because many of these patients had underlying cardiac disease [*see Cardiovascular Abnormalities (5.4)*].

A comparative echocardiography study of lanreotide and another somatostatin analog demonstrated no difference in the development of new or worsening valvular regurgitation between the two treatments over one year. The occurrence of clinically significant mitral regurgitation (i.e., moderate or severe in intensity) or of clinically significant aortic regurgitation (i.e., at least mild in intensity) was low in both groups of patients throughout the study.

Other Adverse Reactions

For the most commonly occurring adverse reactions in the pooled analysis, diarrhea, abdominal pain, and cholelithiasis, there was no apparent trend for increasing incidence with age. GI disorders and renal and urinary disorders were more common in patients with

documented hepatic impairment; however, the incidence of cholelithiasis was similar between groups.

Laboratory investigations of acromegalic patients treated with Somatuline Depot in clinical studies show that the percentage of patients with putative antibodies at any time point after treatment is low (<1% to 4% of patients in specific studies whose antibodies were tested). The antibodies did not appear to affect the efficacy or safety of Somatuline Depot.

6.2 Postmarketing Experience

As adverse reactions experienced post-approval use are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The profile of reported adverse reactions for Somatuline Depot was consistent with that observed for treatment-related adverse reactions in the clinical studies. Those reported most frequently being gastrointestinal disorders (abdominal pain, diarrhea, and steatorrhea), hepatobiliary disorders (cholecystitis), and general disorders and administration site conditions (injection site reactions). Occasional cases of pancreatitis have also been observed.

7 DRUG INTERACTIONS

7.1 Insulin and Oral Hypoglycemic Drugs

Lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when lanreotide treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

7.2 Cyclosporine

Concomitant administration of cyclosporine with lanreotide may decrease the relative bioavailability of cyclosporine and, therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic levels.

7.3 Other Concomitant Drug Therapy

The pharmacological gastrointestinal effects of Somatuline Depot may reduce the intestinal absorption of concomitant drugs. Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the availability of bromocriptine.

Concomitant administration of bradycardia inducing drugs (e.g. beta-blockers) may have an additive effect on the reduction of heart rate associated with lanreotide. Dose adjustments of concomitant medication may be necessary.

Vitamin K absorption was not affected when concomitantly administered with lanreotide.

7.4 Drug Metabolism Interactions

The limited published data available indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that lanreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution. Drugs metabolized by the liver may be metabolized more slowly during lanreotide treatment and dose reductions of the concomitantly administered medications should be considered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Lanreotide has been shown to have an embryocidal effect in rats and rabbits. There are no adequate and well controlled studies in pregnant women. Somatuline Depot should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Reproductive studies in pregnant rats given 30 mg/kg by subcutaneous injection every 2 weeks (5-times the human dose based on body surface area comparisons) resulted in decreased embryo/fetal survival. Studies in pregnant rabbits given subcutaneous injections of 0.45 mg/kg/day, 2-times the human therapeutic exposures at the maximum recommended dose of 120 mg based on comparisons of relative body surface area shows decreased fetal survival and increased fetal skeletal/soft tissue abnormalities.

8.3 Nursing Mothers

It is not known whether lanreotide is excreted in human milk. Many drugs are excreted in human milk. As a result of serious adverse reactions in animals and potential in nursing infants from Somatuline, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness were observed between elderly patients compared with younger patients, and the other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. It is not necessary to alter the starting dose in elderly patients as expected lanreotide serum concentrations in the elderly are well within the range of serum concentrations safely tolerated in healthy young subjects. Similarly, it is not necessary to alter the titration or maintenance doses of Somatuline Depot as dose selection is based on therapeutic response [*see Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Lanreotide has been studied in patients with end-stage renal function on dialysis, but has not been studied in patients with mild, moderate, and severe renal impairment. It is recommended that patients with moderate and severe renal impairment receive a starting dose of lanreotide of 60 mg. Caution should be exercised when considering patients with moderate

or severe renal impairment for an extended dosing interval of Somatuline Depot 120 mg every 6 or 8 weeks [see *Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

It is recommended that patients with moderate and severe hepatic impairment receive a starting dose of lanreotide of 60 mg. Caution should be exercised when considering patients with moderate or severe hepatic impairment for an extended dosing interval of Somatuline Depot 120 mg every 6 or 8 weeks [see *Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

If overdose occurs, symptomatic management is indicated.

There are no confirmed postmarketing cases of overdose with lanreotide that were serious or led to an adverse reaction.

Up-to-date information about the treatment of overdose can often be obtained from the National Poison Control Center at phone number 1-800-222-1222.

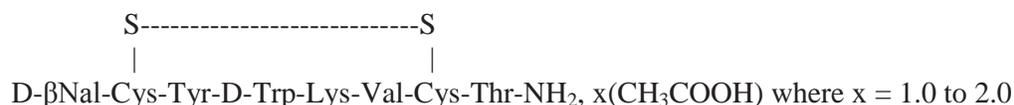
11 DESCRIPTION

Somatuline Depot (lanreotide) Injection 60 mg, 90 mg, and 120 mg is a prolonged-release formulation for deep subcutaneous injection containing the drug substance lanreotide acetate, a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin, water for injection, and acetic acid (for pH adjustment).

Somatuline Depot is available as sterile, ready-to-use, pre-filled syringes containing lanreotide supersaturated bulk solution of 24.6% w/w lanreotide base.

Each syringe contains:	Somatuline Depot 60 mg	Somatuline Depot 90 mg	Somatuline Depot 120 mg
Lanreotide acetate	77.9 mg	113.6 mg	149.4 mg
Acetic Acid	q.s.	q.s.	q.s.
Water for injection	186.6 mg	272.3 mg	357.8 mg
Total Weight	266 mg	388 mg	510 mg

Lanreotide acetate is a synthetic cyclical octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Its molecular weight is 1096.34 (base) and its amino acid sequence is:



For appearance of the formulation, see *Dosage Forms and Strengths (3)*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lanreotide, the active component of Somatuline Depot, is an octapeptide analog of natural somatostatin. The mechanism of action of lanreotide is believed to be similar to that of natural somatostatin.

12.2 Pharmacodynamics

Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR1, 3, and 4. Activity at human SSTR 2 and 5 is the primary mechanism believed responsible for GH inhibition. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine, and paracrine functions.

The primary pharmacodynamic effect of lanreotide is a reduction of GH and/or IGF-1 levels enabling normalization of levels in acromegalic patients [*see Clinical Studies (14)*]. In acromegalic patients, lanreotide reduces GH levels in a dose-dependent way. After a single injection of Somatuline Depot, plasma GH levels fall rapidly and are maintained for at least 28 days.

Lanreotide inhibits the basal secretion of motilin, gastric inhibitory peptide, and pancreatic polypeptide, but has no significant effect on the secretion of secretin. Lanreotide inhibits post-prandial secretion of pancreatic polypeptide, gastrin, and cholecystokinin (CCK). In healthy subjects, lanreotide produces a reduction and a delay in post-prandial insulin secretion, resulting in transient, mild glucose intolerance.

Lanreotide inhibits meal-stimulated pancreatic secretions, and reduces duodenal bicarbonate and amylase concentrations, and produces a transient reduction in gastric acidity.

Lanreotide has been shown to inhibit gallbladder contractility and bile secretion in healthy subjects [*see Warnings and Precautions (5)*].

In healthy subjects, lanreotide inhibits meal-induced increases in superior mesenteric artery and portal venous blood flow, but has no effect on basal or meal-stimulated renal blood flow. Lanreotide has no effect on renal plasma flow or renal vascular resistance. However, a transient decrease in glomerular filtration rate (GFR) and filtration fraction has been observed after a single injection of lanreotide.

In healthy subjects, non-significant reductions in glucagon levels were seen after lanreotide administration. In diabetic non-acromegalic subjects receiving a continuous infusion (21 day) of lanreotide, serum glucose concentrations were temporarily decreased by 20-30% after the start and end of the infusion. Serum glucose concentrations returned to normal levels within 24 hours. A significant decrease in insulin concentrations was recorded between baseline and Day 1 only [*see Warnings and Precautions (5)*].

Lanreotide inhibits the nocturnal increase in thyroid-stimulating hormone (TSH) seen in healthy subjects. Lanreotide reduces prolactin levels in acromegalic patients treated on a long-term basis.

12.3 Pharmacokinetics

Somatuline Depot is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids. The most likely mechanism of drug release is a passive diffusion of the precipitated drug from the depot towards the surrounding tissues, followed by the absorption into the blood stream.

After a single deep, subcutaneous administration, the mean absolute bioavailability of Somatuline Depot in healthy subjects was 73.4, 69.0, and 78.4%, for the 60 mg, 90 mg, and 120 mg doses, respectively. Mean C_{max} values ranged from 4.3 to 8.4 ng/mL during the first day. Single-dose linearity was demonstrated with respect to AUC and C_{max} , and showed high inter-subject variability. Somatuline Depot showed sustained release of lanreotide with a half-life of 23 to 30 days. Mean serum concentrations were > 1 ng/mL throughout 28 days at 90 mg and 120 mg and > 0.9 ng/mL with 60 mg.

In a repeat-dose administration pharmacokinetics (PK) study in acromegalic patients, rapid initial release was seen giving peak levels during the first day after administration. At doses of Somatuline Depot between 60 and 120 mg, linear pharmacokinetics were observed in acromegalic patients. At steady state, mean C_{max} values were 3.8 ± 0.5 , 5.7 ± 1.7 , and 7.7 ± 2.5 ng/mL, increasing linearly with dose. The mean accumulation ratio index was 2.7 which is in line with the range of values for the half-life of Somatuline Depot. The steady-state trough serum lanreotide concentrations in patients receiving Somatuline Depot every 28 days were 1.8 ± 0.3 ; 2.5 ± 0.9 , and 3.8 ± 1.0 ng/mL at 60 mg, 90 mg, and 120 mg doses, respectively. A limited initial burst effect and a low peak-to-trough fluctuation (81% to 108%) of the serum concentration at the plateau were observed.

For the same doses, similar values were obtained in clinical studies after at least four administrations (2.3 ± 0.9 , 3.2 ± 1.1 , and 4.0 ± 1.4 ng/mL, respectively).

Pharmacokinetic data from studies evaluating extended dosing use of Somatuline Depot 120 mg demonstrated mean steady state, C_{min} values between 1.6 and 2.3 ng/mL for the 8- and 6-week treatment interval, respectively.

Specific Populations

Somatuline Depot has not been studied in specific populations. The pharmacokinetics of lanreotide in renal impaired, hepatic impaired, and geriatric subjects were evaluated after IV administration of lanreotide immediate release formulation (IRF) at 7 mcg/kg dose.

Renal Impairment

An approximate 2-fold decrease in total serum clearance of lanreotide, with a consequent 2-fold increase in half-life and AUC was observed. Patients with moderate to severe renal impairment should begin treatment with Somatuline Depot 60 mg. Caution should be exercised when considering patients with moderate or severe renal impairment for an extended dosing interval of Somatuline Depot 120 mg every 6 or 8 weeks.

Geriatric

Studies in healthy elderly subjects showed an 85% increase in half-life and a 65% increase in mean residence time (MRT) of lanreotide compared to those seen in healthy young subjects; however, there was no change in either AUC or C_{max} of lanreotide in elderly as compared to healthy young subjects.

Hepatic Impairment

In subjects with moderate to severe hepatic impairment, a 30% reduction in clearance of lanreotide was observed. Patients with moderate to severe hepatic impairment should begin treatment with Somatuline Depot 60 mg. Caution should be exercised when considering patients with moderate or severe hepatic impairment for an extended dosing interval of Somatuline Depot 120 mg every 6 or 8 weeks.

In studies evaluating excretion, < 5% of lanreotide was excreted in urine and less than 0.5% was recovered unchanged in feces, indicative of some biliary excretion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given daily subcutaneous doses of lanreotide acetate at 0.5, 1.5, 5, 10, and 30 mg/kg for 104 weeks. Cutaneous and subcutaneous tumors of fibrous connective tissues at the injection sites were observed at the high dose of 30 mg/kg/day. Fibrosarcomas in both genders and malignant fibrous histiocytomas were observed in males at 30mg/kg/day resulting in exposures 3 times higher than the clinical therapeutic exposure at the maximum therapeutic dose of 120 mg given by monthly subcutaneous injection based on the AUC values. Rats were given daily subcutaneous doses of lanreotide acetate at 0.1, 0.2, and 0.5 mg/kg for 104 weeks. Increased cutaneous and subcutaneous tumors of fibrous connective tissues at the injection sites were observed at the dose of 0.5mg/kg/day resulting in exposures less than the clinical therapeutic exposure at 120 mg given by monthly subcutaneous injection. The increased incidence of injection site tumors in rodents is likely related to the increased dosing frequency (daily) in animals compared to monthly dosing in humans and therefore may not be clinically relevant.

Lanreotide was not genotoxic in tests for gene mutations in a bacterial mutagenicity (Ames) assay, or mouse lymphoma cell assay with or without metabolic activation. Lanreotide was not genotoxic in tests for the detection of chromosomal aberrations in a human lymphocyte and *in vivo* mouse micronucleus assay.

Subcutaneous dosing (30mg/kg/2 wks) before mating and continuing into gestation in rats at doses 5 times the human clinical exposure (120 mg every 4 weeks) based on mg/m² had reduced fertility. Gestation length was statistically significantly increased suggesting some delay in parturition at 3 times human exposure. The reduction in fertility in non-acromegalic animals is likely related to the pharmacologic activity (decreased growth hormone secretion) of lanreotide acetate.

14 CLINICAL STUDIES

The effect of Somatuline Depot on reducing GH and IGF-levels and control of symptoms in patients with acromegaly was studied in two long-term, multiple-dose, randomized multicenter studies.

Study 1

This one-year study included a 4-week double-blind, placebo-controlled phase, a 16-week single-blind, fixed-dose phase, and a 32-week open-label dose-titration phase. Patients with active acromegaly based on biochemical tests and medical history entered a 12-week washout period if there was previous treatment with a somatostatin analog or a dopaminergic agonist.

Upon entry, patients were randomly allocated to receive a single deep subcutaneous injection of Somatuline Depot 60 mg, 90 mg, or 120 mg or placebo. Four weeks later, patients entered a fixed-dose phase where they received 4 injections of Somatuline Depot followed by a dose-titration phase of 8 injections for a total of 13 injections over 52 weeks (including the placebo phase). Injections were given at 4-week intervals. During the dose-titration phase of the study, the dose was titrated twice (every fourth injection), as needed, according to individual GH and IGF-1 levels.

A total of 108 patients (51 males, 57 females) were enrolled in the initial placebo-controlled phase of the study. Half (54/108) of the patients had never been treated with a somatostatin analog or dopamine agonist, or had stopped treatment for at least 3 months prior to their participation in the study and were required to have a mean GH level > 5 ng/mL at their first visit. The other half of the patients had received prior treatment with a somatostatin analog or a dopamine agonist before study entry and at study entry were to have a mean GH concentration > 3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication.

One hundred and seven (107) patients completed the placebo-controlled phase, 105 patients completed the fixed-dose phase, and 99 patients completed the dose-titration phase. Patients not completing withdrew due to adverse events (5) or lack of efficacy (4).

In the double-blind phase of study 1, a total of 52 (63%) of the 83 lanreotide-treated patients had a > 50% decrease in mean GH from baseline to Week 4 including 52%, 44%, and 90% of patients in the 60 mg, 90 mg, and 120 mg groups, respectively, compared to placebo (0%, 0/25). In the fixed-dose phase at Week 16, 72% of all 107 lanreotide-treated patients had a decrease from baseline in mean GH of > 50% including 68% (23/34), 64% (23/36), and 84% (31/37) of patients in the 60 mg, 90 mg, and 120 mg lanreotide treatment groups, respectively. Efficacy achieved in the first 16 weeks was maintained for the duration of the study (see Table 3).

Table 3 Overall Efficacy Results Based on GH and IGF-1 Levels by Treatment Phase in Study 1

		Baseline	Before Titration 1 (16 weeks)	Before Titration 2 (32 weeks)	Last Value Available*
		N=107	N=107	N=105	N=107
GH					
≤5.0 ng/mL	Number of Responders (%)	20 (19%)	72 (67%)	76 (72%)	74 (69%)
≤2.5 ng/mL	Number of Responders (%)	0 (0%)	52 (49%)	59 (56%)	55 (51%)
≤1.0 ng/mL	Number of Responders (%)	0 (0%)	15 (14%)	18 (17%)	17 (16%)
Median GH	ng/mL	10.27	2.53	2.20	2.43

GH Reduction	Median % Reduction	--	75.5	78.2	75.5
IGF-1					
Normal [†]	Number of Responders (%)	9 (8%)	58 (54%)	57 (54%)	62 (58%)
Median IGF-1	ng/mL	775.0	332.0 [‡]	316.5 [§]	326.0
IGF-1 Reduction	Median % Reduction	--	52.3 [‡]	54.5 [§]	55.4
IGF-1 Normal + GH ≤2.5 ng/mL [†]	Number of Responders (%)	0 (0%)	41 (38%)	46 (44%)	44 (41%)

* Last Observation Carried Forward

[†] Age-adjusted

[‡] n=105

[§] n=102

Study 2

This was a 48-week, open-label, uncontrolled multicenter study which enrolled patients who had an IGF-1 concentration ≥ 1.3 times the upper limit of the age-adjusted normal range. Patients receiving treatment with a somatostatin analog (other than Somatuline Depot) or a dopaminergic agonist had to attain this IGF-1 concentration after a washout period of up to 3 months.

Patients were initially enrolled in a 4-month fixed-dose phase where they received four deep subcutaneous injections of Somatuline Depot, 90 mg, at 4-week intervals. Patients then entered a dose-titration phase where the dose of Somatuline Depot was adjusted based on GH and IGF-1 levels at the beginning of the dose-titration phase and, if necessary, again after another 4 injections. Patients titrated up to the maximum dose (120 mg) were not allowed to titrate down again.

A total of 63 patients (38 males, 25 females) entered the fixed-dose phase of the trial and 57 patients completed 48 weeks of treatment. Six patients withdrew due to adverse reactions (3), other reasons (2), or lack of efficacy (1).

After 48 weeks of treatment with Somatuline Depot at 4-week intervals, 43% (27/63) of the acromegalic patients in this study achieved normal age-adjusted IGF-1 concentrations. Mean IGF-1 concentrations after treatment completion were 1.3 ± 0.7 times the upper limit of normal compared to 2.5 ± 1.1 times the upper limit of normal at baseline.

The reduction in IGF-1 concentrations over time correlated with a corresponding marked decrease in mean GH concentrations. The proportion of patients with mean GH concentrations < 2.5 ng/mL increased significantly from 35% to 77% after the fixed-dose phase and 85% at the end of the study. At the end of treatment, 24/63 (38%) of patients had both normal IGF-1 concentrations and a GH concentration of ≤ 2.5 ng/mL (see Table 4) and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of < 1 ng/mL.

Table 4 Overall Efficacy Results Based on GH and IGF-1 Levels by Treatment Phase in Study 2

		Baseline	Before Titration 1 (12 wks)	Before Titration 2 (28 wks)	Last Value Available*
		N=63	N=63	N=59	N=63
IGF-1					
Normal[†]	Number of Responders (%)	0 (0%)	17 (27%)	22 (37%)	27 (43%)
Median IGF-1	ng/mL	689.0	382.0	334.0	317.0
IGF-1 Reduction	Median % Reduction	--	41.0	51.0	50.3
GH					
≤5.0 ng/mL	Number of Responders (%)	40 (64%)	59 (94%)	57 (97%)	62 (98%)
≤2.5 ng/mL	Number of Responders (%)	21 (33%)	47 (75%)	47 (80%)	54 (86%)
≤1.0 ng/mL	Number of Responders (%)	8 (13%)	19 (30%)	18 (31%)	28 (44%)
Median GH	ng/mL	3.71	1.65	1.48	1.13
GH Reduction	Median % Reduction	--	63.2	66.7	78.6 [‡]
IGF-1 normal[†] + GH ≤2.5 ng/mL	Number of Responders (%)	0 (0%)	14 (22%)	20 (34%)	24 (38%)

* Last Observation Carried Forward

[†] Age-adjusted

[‡] N= 62

Examination of age and gender subgroups did not identify differences in response to Somatuline Depot among these subgroups. The limited number of patients in the different racial subgroups did not raise any concerns regarding efficacy of Somatuline Depot in these subgroups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Somatuline Depot is supplied in strengths of 60 mg, 90 mg, and 120 mg in a single, sterile, pre-filled, ready-to-use, polypropylene syringe (fitted with an automatic needle guard) fitted with a 20 mm needle covered by a low density polyethylene sheath.

Each pre-filled syringe is sealed in a laminated pouch and packed in a carton.

NDC 15054-0060-3	60-mg, sterile, pre-filled syringe
NDC 15054-0090-3	90-mg, sterile, pre-filled syringe
NDC 15054-0120-3	120-mg, sterile, pre-filled syringe

Storage and Handling

Somatuline Depot 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. Thirty (30) minutes prior to injection, remove sealed pouch of Somatuline Depot from refrigerator and allow it to come to room temperature. Keep pouch sealed until injection.

Each syringe is intended for single use. Do not use beyond the expiration date on the packaging.

17 PATIENT COUNSELING INFORMATION

The physician should provide a copy of the FDA-Approved Patient Labeling and review the contents with the patient. Patients should be advised to inform their doctor or pharmacist if they develop any unusual symptoms, or if any known symptom persists or worsens.

Patients should be advised that response to Somatuline Depot should be monitored by periodic measurements of GH and IGF-1 levels, with a goal of decreasing these levels to the normal range.

Manufactured by:
Ipsen Pharma Biotech
83870 Signes, France

Distributed by:
Ipsen Biopharmaceuticals, Inc.
Basking Ridge, NJ 07920 USA

Patient Information

Somatuline® Depot (So-mah-tu-leen Dee-Poh) (lanreotide) Injection

Read this Patient Information before you receive your first Somatuline® Depot injection and before each injection. There may be new information. This information does not take the place of talking with your healthcare professional about your medical condition or your treatment.

What is Somatuline® Depot?

Somatuline® Depot is a prescription medicine used for the long-term treatment of people with acromegaly when:

- surgery or radiotherapy have not worked well enough or
- they are not able to have surgery or radiotherapy

It is not known if Somatuline® Depot is safe and effective in children.

What should I tell my healthcare professional before receiving Somatuline® Depot?

Before you receive Somatuline® Depot, tell your healthcare professional if you have:

- gallbladder problems
- diabetes
- thyroid problems
- heart problems
- kidney problems
- liver problems
- are pregnant or plan to become pregnant. It is not known if Somatuline® Depot will harm your unborn baby. Talk to your healthcare professional if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if Somatuline® Depot passes into your breast milk. Talk to your healthcare professional about the best way to feed your baby if you receive Somatuline® Depot.

Tell your healthcare professional about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Somatuline® Depot and other medicines may affect each other causing side effects.

Somatuline® Depot may affect the way other medicines work, and other medicines may affect how Somatuline® Depot works. Your dose of Somatuline® Depot or your other medicines may need to be adjusted.

Especially tell your healthcare professional if you take:

- insulin or other diabetes medicines
- a cyclosporine (Gengraf, Neoral, or Sandimmune)
- a medicine called bromocriptine (Parlodel)
- medicines that lower your heart rate such as beta blockers

Know the medicines you take. Keep a list of them to show your healthcare professional when you get a new medicine.

How will I receive Somatuline® Depot?

- You will receive a Somatuline® Depot injection every 4 weeks in your doctor's office. Your prescriber may change your dose of Somatuline® Depot or the length of time between your injections. Your healthcare provider will tell you how long you need to receive Somatuline® Depot.
- Somatuline® Depot is injected deep under the skin of the upper outer area of your buttock.
- Your injection site should change (alternate) between your right and left buttock each time you receive an injection of Somatuline® Depot.
- During your treatment with Somatuline® Depot, your healthcare professional may do certain blood tests to see if Somatuline® Depot is working. Your healthcare professional

may change your dose, or length of time between your Somatuline® Depot injections as needed.

Please see enclosed Instructions for Use leaflet.

What are the possible side effects of Somatuline® Depot?

Somatuline® Depot may cause serious side effects, including:

- **gallstones.** Tell your healthcare professional if you have any of these symptoms:
 - sudden pain in your upper right stomach area (abdomen)
 - sudden pain in your right shoulder or between your shoulder blades
 - yellowing of your skin and whites of your eyes
 - fever with chills
 - nausea
- **changes in your blood sugar** (high blood sugar or low blood sugar). If you have diabetes, test your blood sugar as your healthcare professional tells you to. Your healthcare professional may change your dose of diabetes medicine especially when you first start receiving Somatuline® Depot or if your dose of Somatuline® Depot changes.
- **slow heart rate**
- **high blood pressure**

The most common side effects of Somatuline® Depot include:

- diarrhea
- stomach area (abdominal) pain
- nausea
- pain, itching or a lump at the injection site

Tell your healthcare professional if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Somatuline® Depot. For more information, ask your healthcare professional

Call your healthcare professional for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch.

General information about the safe and effective use of Somatuline® Depot.

Medicines are sometimes prescribed for conditions other than those listed in the patient leaflet. This Patient Information leaflet summarizes the most important information about Somatuline® Depot. If you would like more information about Somatuline® Depot, talk with your healthcare professional. You can ask your healthcare professional for information about Somatuline® Depot that is written for health professionals.

For more information, go to www.somatulinedepot.com or call Ipsen Biopharmaceuticals at 1-866-837-2422.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Somatuline[®] Depot is manufactured by Ipsen Pharma Biotech, Parc d'Activities du Plateau de Signes, 83870 Signes, France for Ipsen Biopharmaceuticals, Inc., 106 Allen Road, Basking Ridge, NJ 07920 USA

Revised 10/2014

Somatuline[®] Depot (lanreotide) Injection

Article No. 1024297

IMPORTANT

If you have any questions about this medication or procedure, call 1-888-880-2888



Ipsen Pharma Biotech
69870 Signes
France

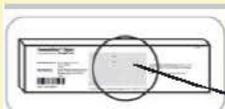
Before You Begin Injection

- Please follow both sides of these Instructions for Use before using the device. Follow this procedure exactly, as it may differ from your past experience.
- Somatuline Depot should be administered by a Healthcare Professional.
- If this device is dropped or damaged in any way, please call 1-888-880-2888.

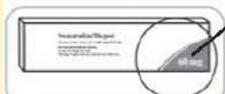
A. Storage of Somatuline Depot

When you receive the medication, follow these steps for storing Somatuline Depot.

Important: Somatuline Depot must be refrigerated. Do not allow it to reach room temperature until ready to use.

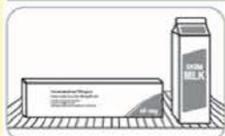


A1. Remove box from cold pack.
Do not open box.

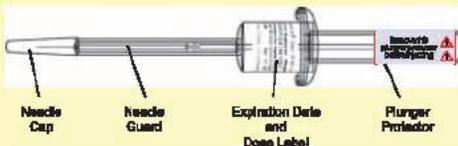


A2. Check the following:
a. Box does not look damaged.
b. Expiration date has not passed.
c. Dose is as prescribed.
• 60 mg, or
• 90 mg, or
• 120 mg

Note: Call 1-888-880-2888 if you have any questions.



A3. Place unopened box in your refrigerator.
• Do not place in freezer.

**B. Prepare to Inject**

B1. Confirm that date of this injection is as prescribed.



B2. Remove box from refrigerator. Open box and remove contents.

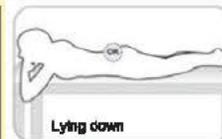


B3. Confirm that pouch is sealed and not damaged.

B4. Check that the dose is as prescribed and the expiration date has not passed.

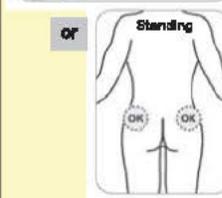


B5. Let pouch sit for 30 minutes to reach room temperature. Do not open the pouch until ready to inject.
• Injection of cold medication may be painful.



Lying down

OR



Standing

B6. Find a clean, comfortable area for the patient to relax during procedure.

• It's important that the patient remains as still as possible during the injection.

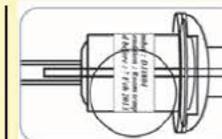


B7. The person administering the injection must wash his/her hands with soap and water.

Follow the doctor or institution's policy on the use of surgical gloves during this procedure.



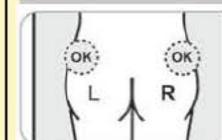
B8. Tear open pouch along dotted line starting at the notch.



B9. Do the following:

- Confirm that expiration date on the device has not passed
- Make sure it is the right dosage:
• 60 mg, or
• 90 mg, or
• 120 mg
- Set device aside on the empty pouch.

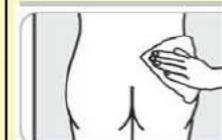
Note: Call 1-888-880-2888 if you have any questions.



B10. Choose which side of the buttocks to inject.

- Switch sides with each injection.
- Avoid areas with moles, scar tissue, reddened skin, or skin that feels lumpy.
- Only inject in the areas marked with OK in the picture.

Important: It is very important that you only inject in one of the areas marked OK in the picture (upper outer quadrants of the right or left buttocks).



B11. Clean area to be injected.

Turn page over for additional instructions.



Instructions for Use - Page 2 **IMPORTANT**

If you have any questions about this medication or procedure, call 1-888-880-2889



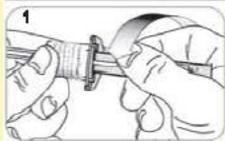
Ipsen Pharma Biotech
69870 Signes
France

C. Inject

Important: This is a 1-time use device with a retractable needle.

- ALL the medication must be injected during this use.
- If you drop or damage this device in any way, please call 1-888-880-2889.

Follow these injection instructions exactly! This procedure may be different from your past experience.



C1. **Important:** Remove the plunger protector before injecting. Do not remove the elastar.

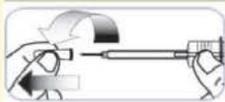
Hold device and twist and pull off plunger protector.

Discard plunger protector.

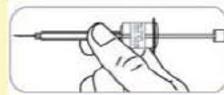


C2. Remove needle cap by twisting and pulling.

Discard needle cap.



C3. Hold device by the needle guard.



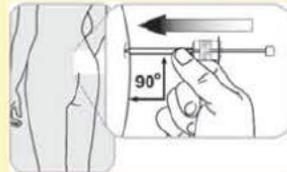
C4. Flatten injection area with your other hand and thumb.



Do NOT pinch skin.

Note: Effort will be required to insert the entire length of the needle through the skin.

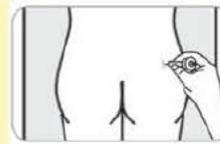
C5. Insert the needle perpendicular to the skin (90 degree angle).



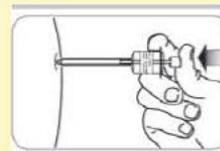
- Use a strong, straight, dart-like motion to quickly insert the needle all the way into the skin.
- It is very important that you insert the needle completely. You should not see any needle once it is fully inserted.
- Do not aspirate (do not draw back).



1. Do not insert needle at an acute angle.
2. Make sure needle is fully inserted.



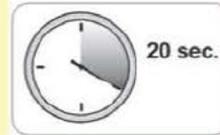
C6. When needle is completely inserted, release injection site that has been flattened by your hand.



C7. Push plunger with steady, very firm pressure.

The medication is thicker and harder to push than you might expect.

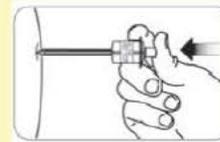
Note: Pushing plunger too fast may cause discomfort to the patient or may break device.



20 sec.

C8. While depressing plunger, slowly count to 20 and continue steady pressure on the plunger. You may find it helpful to say:

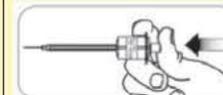
- "1 one-thousand"
- "2 one-thousand"
- "3 one-thousand" up to "20 one-thousand"



Give plunger a final push to engage needle. You may feel a soft click.

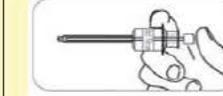
Confirm that plunger is at the bottom and no medication remains.

Remove the syringe from the injection site **WHILE** keeping your finger on the plunger rod.



C9. While continuing to hold down the plunger, remove the needle from the injection site, then allow the needle to retract by removing your thumb from the plunger.

If needle does not retract, push plunger again to engage safety mechanism. The needle will then retract.



C10. If needed, gently apply a gauze pad to injection area.

Important: Never rub or massage the injection site.



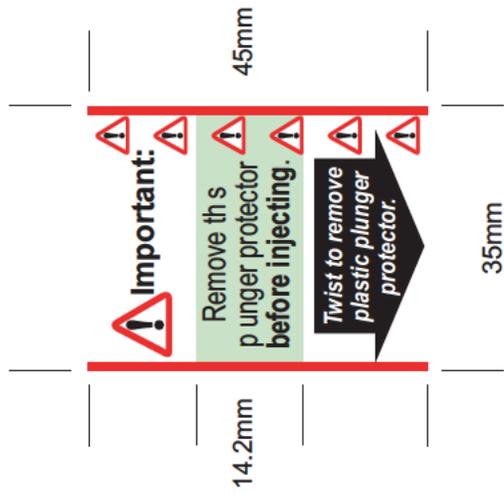
D. Dispose of Device



D1. Discard used device into a hard plastic container with a screw top (such as a detergent bottle) or a sharps container as per your institutional policy.



D2. Wash your hands.



Proposed Language Printed on Actual Syringe Labels for

Somatuline® Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg

NDA 22-074, Supplement-004

Label size: 45 mm x 20 mm

Fonts: Times New Roman – Arial

Font sizes: point 6 – point 7

Color: Black

Syringe Label for 60 mg dose

Somatuline® Depot
(lanreotide) Injection 60 mg/0.2 mL
Manufacturer: Ipsen Pharma Biotech;
Signes France. FOR SINGLE USE ONLY
Exp : 00 /0000 DISCARD UNUSED
Lot : X00000 PORTION

Syringe Label for 90 mg dose

Somatuline® Depot
(lanreotide) Injection 90 mg/0.3 mL
Manufacturer: Ipsen Pharma Biotech;
Signes France. FOR SINGLE USE ONLY
Exp : 00 / 0000 DISCARD UNUSED
Lot : X00000 PORTION

Syringe Label for 120 mg dose

Somatuline® Depot
(lanreotide) Injection 120 mg/0.5 mL
Manufacturer: Ipsen Pharma Biotech;
Signes France. FOR SINGLE USE ONLY
Exp : 00 / 0000 DISCARD UNUSED
Lot : X00000 PORTION

Proposed Language Printed on Actual Pouch Labels for

Somatuline® Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg

NDA 22-074, Supplement-004

Label size: 73 mm x 32 mm

Fonts: Times New Roman – Arial

Font sizes: point 6, point 7 and point 8

Color: Black

***Pouch (or sachet) labels are placed on the back side of the pouches (sachets)**

Pouch Label for 60 mg dose

ES628

Somatuline® Depot (lanreotide) Injection
60 mg/0.2 mL
FOR SINGLE USE ONLY. DISCARD UNUSED PORTION
Manufacturer: Ipsen Pharma Blotech, Signes France

Leave at room temperature for 30 minutes before administration

EXP: 00/0000
Lot: X00000 (Y00000)

Pouch Label for 90 mg dose

ES930

Somatuline® Depot (lanreotide) Injection
90 mg/0.3 mL
FOR SINGLE USE ONLY. DISCARD UNUSED PORTION
Manufacturer: Ipsen Pharma Blotech, Signes France

Leave at room temperature for 30 minutes before administration

EXP: 00/0000
Lot: X00000 (Y00000)

Pouch Label for 120 mg dose

ES1234

Somatuline® Depot (lanreotide) Injection
120 mg/0.5 mL
FOR SINGLE USE ONLY. DISCARD UNUSED PORTION
Manufacturer: Ipsen Pharma Blotech, Signes France

Leave at room temperature for 30 minutes before administration

EXP: 00/0000
Lot: X00000 (Y00000)

FILET TECHNIQUE

35 mm



85 mm

290 mm

FILET TECHNIQUE

35 mm



85 mm

290 mm

FILET TECHNIQUE

35 mm

The diagram shows a rectangular box for Somatuline Depot (lanreotide) Injection. The box is oriented vertically. At the top, there is a green banner with the text "60 mg per 0.2 mL" in white. Below the banner, the product name "Somatuline® Depot (lanreotide) Injection" is printed in black. Underneath the name, there are four lines of text: "For deep subcutaneous injection.", "IMPORTANT Somatuline® Depot should be administered by a healthcare professional. Call 1-888-980-2889 and request training that includes delivering a practice injection.", "REMEMBER Read both sides of the yellow instructions for use and prescribing information for complete instructions.", and "STORAGE Refrigerate at 2°C-8°C (36°F-46°F) in its original package. Protect from light." Below the text is a barcode with the number "1505400603" underneath it. To the left of the barcode is the number "1039707". At the bottom of the box, there is a green horizontal line with a dashed white line in the center, and a red arrow pointing to it with the text "Tear Here".

85 mm

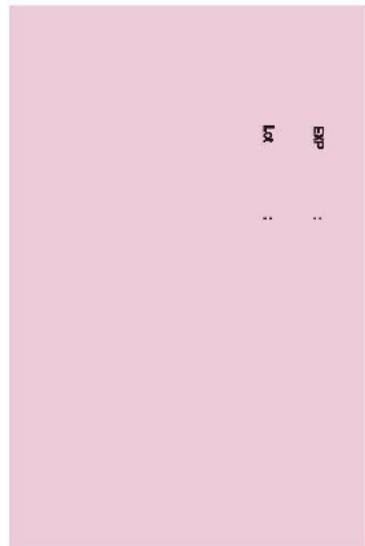
290 mm

		Couleurs	
		(b) (4)	
Date Création	18 DECEMBRE 2012		
Client	IPSEN		
Produit	SOMATULINE DEPOT 60 MG SNS US		
Code Article	1031767		
Dimension	89 x 21 x 296	Points particuliers :	
Mise à Jour	18 NOV 2014		

Somatuline® Depot
(lanreotide) Injection **60 mg/0.2 mL**

Manufactured by: Ipsen Pharma Biotech
83870 Signes
France
Distributed by: Ipsen Biopharmaceuticals Inc.
Basking Ridge, NJ 07920
USA

If you have any questions about Somatuline® Depot, please call 1-888-980-2889



STORAGE: Refrigerate at 2°C - 8°C (36°F - 46°F) in its original package.
Protect from light
USUAL DOSAGE: see prescribing information.
Each syringe contains lanreotide acetate corresponding to 60 mg of lanreotide base per 0.2 mL solution, which is the equivalent of 60 mg lanreotide per syringe.

1031767

Rx only

Somatuline® Depot
(lanreotide) Injection
60 mg/0.2 mL

For deep subcutaneous injection

For single use only. Discard unused portion.
Somatuline® Depot should be administered by a healthcare professional.
Leave at room temperature for 30 minutes before administration.

CONTENTS: This box contains one (1) pre-filled syringe.

IPSEN

Somatuline® Depot
(lanreotide) Injection **60 mg/0.2 mL**

NDC 15054 0060 3



Somatuline® Depot
(lanreotide) Injection **60 mg/0.2 mL**

Distributed by :
Ipsen Biopharmaceuticals, Inc. Basking Ridge, NJ 07920
USA

Somatuline® Depot
(lanreotide) Injection **60 mg/0.2 mL**

IPSEN

Somatuline® Depot
(lanreotide) Injection **60 mg/0.2 mL**

IPSEN

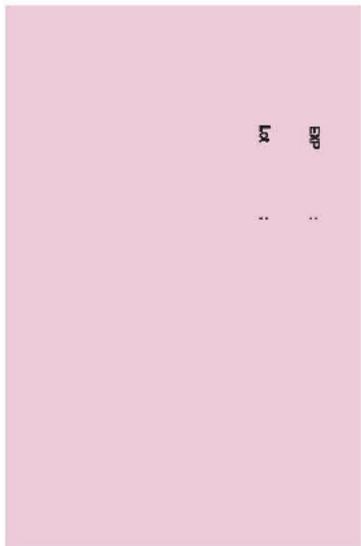
		Couleurs	
		(b) (4)	
Date Création	18 DECEMBRE 2012		
Client	IPSEN		
Produit	SOMATULINE DEPOT 90 MG SNS US		
Code Article	1031768		
Dimension	89 x 21 x 296	Points particuliers :	
Mise à Jour	16 MARS 2014		



Somatuline® Depot
(lanreotide) Injection **90 mg/0.3 mL**

Manufactured by: Ipsen Pharma Biotech
83870 Signes
France
Distributed by: Ipsen Biopharmaceuticals Inc
Basking Ridge, NJ 07920
USA

If you have any questions about Somatuline® Depot, please call 1-888-980-2889



SNP :
Lot :

STORAGE: Refrigerate at 2°C - 8°C (36°F - 46°F) in its original package.
Protect from light
USUAL DOSAGE: see prescribing information.
Each syringe contains lanreotide acetate corresponding to 90 mg of lanreotide base per 0.3 mL solution, which is the equivalent of 90 mg lanreotide per syringe.

1031768

90 mg/0.3 mL

Rx only

Somatuline® Depot
(lanreotide) Injection 90 mg/0.3 mL

Somatuline® Depot
(lanreotide) Injection
90 mg/0.3 mL

For deep subcutaneous injection
For single use only. Discard unused portion.
Somatuline® Depot should be administered by a healthcare professional.
Leave at room temperature for 30 minutes before administration.



Somatuline® Depot
(lanreotide) Injection 90 mg/0.3 mL



Somatuline® Depot
(lanreotide) Injection 90 mg/0.3 mL

NDC 15054 0090 3



90 mg/0.3 mL

Somatuline® Depot
(lanreotide) Injection 90 mg/0.3 mL
Distributed by :
Ipsen Biopharmaceuticals, Inc. Basking Ridge, NJ 07920
USA

90 mg/0.3 mL

Couleurs		(b) (4)
Date Création	18 DECEMBRE 2012	
Client	IPSEN	(b) (4)
Produit	SOMATULINE DEPOT 120 MG 0.5 US	
Code Article	1031764	
Dimension	89 x 21 x 296	Points particuliers :
Mise à Jour	18 NOV 2014	

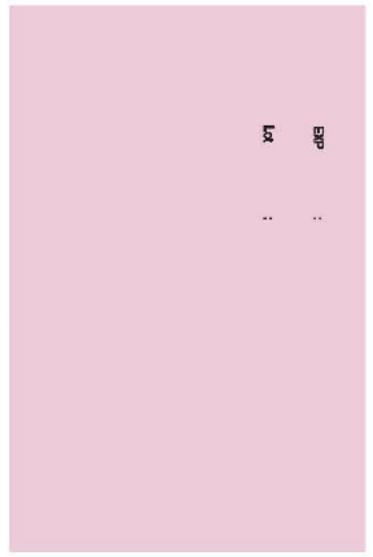


Somatuline® Depot
(lanreotide) Injection **120 mg/0.5 mL**

Manufactured by: Ipsen Pharma Biotech
83870 Signes
France

Distributed by: Ipsen Biopharmaceuticals Inc
Basking Ridge, NJ 07920
USA

If you have any questions about Somatuline® Depot, please call 1-888-980-2889



SRP :
Lr :

STORAGE: Refrigerate at 2°C - 8°C (36°F - 46°F) in its original package.
Protect from light
USUAL DOSAGE: see prescribing information.
Each syringe contains lanreotide acetate corresponding to 120 mg of lanreotide base per 0.5 mL solution, which is the equivalent of 120 mg lanreotide per syringe.

1031764

120 mg/0.5 mL



Somatuline® Depot
(lanreotide) Injection 120 mg/0.5 mL

Rx only

Somatuline® Depot
(lanreotide) Injection
120 mg/0.5 mL



For deep subcutaneous injection
For single use only. Discard unused portion.
Somatuline® Depot should be administered by a healthcare professional.
Leave at room temperature for 30 minutes before administration.
CONTENTS: This box contains one (1) pre-filled syringe.



Somatuline® Depot
(lanreotide) Injection 120 mg/0.5 mL



NDC 15054 0120 3



120 mg/0.5 mL

Somatuline® Depot
(lanreotide) Injection 120 mg/0.5 mL
Distributed by:
Ipsen Biopharmaceuticals, Inc. Basking Ridge, NJ 07920
USA

120 mg/0.5 mL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022074Orig1s004

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW # 5	1. ORGANIZATION	2. NDA NUMBER
	ONDQA/DNDQA III/Branch IX	N022074 (Approved 30-Aug-2007)
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Ipsen Pharma <u>Authorized Agent</u> : 65 quai Georges Gorse Biomeasure Incorporated 92100 Boulogne-Billancourt 27 Maple Street France Milford, MA 01757-3650		S-004, 03-May-2010 17-Jan-2014 Resubmission /After Action-Complete
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Somatulin® Depot	Lanreotide acetate	Amendment, 03-Oct-2011 User Validation Test Protocol, 02-Jul-2012 Amendment, 26-Dec-2012 Amendment, 25-Jan-2013 Amendment, 02-May-2013 Amendment, 17-Jan-2014 Amendment, 07-Apr-2014
8. SUPPLEMENT PROVIDES INFORMATION FOR		
Changes to manufacturing process steps for drug substance and drug product, and changes to container closure.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Somatostatin analog	Rx	DMF # 8974
12. DOSAGE FORM	13. POTENCY	
Injection	60 mg, 90 mg and 120 mg	
14. CHEMICAL NAME AND STRUCTURE		
<p>Lanreotide acetate is a synthetic cyclic octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl- L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Molecular weight of the base is 1096.34. Its amino acid sequence is:</p> $ \begin{array}{c} \text{S} \text{-----} \text{S} \\ \qquad \qquad \qquad \\ \text{D-}\beta\text{Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH}_2, \text{ x(CH}_3\text{COOH)} \end{array} $ <p>Current x (CH₃COOH) = 1.6 to 3.4 and Proposed x (CH₃COOH) = 1.0 to 2.0</p>		
15. COMMENTS		
<p>The FDA issued a CR letter on 25-May-2013 with comments on the Human Factors study and Labeling/Instructions For Use. There were no CMC related deficiencies identified in the CR letter. The Package Insert, Sachet labels and pouch labels for all three strengths and the Carton Labels for all three strengths submitted were reviewed, and the labeling information provided was found to be adequate from the CMC review perspective. The various sections in the PI namely, Highlights of prescribing information, Dosage and administration, Dosage forms and strengths, Description, and How supplied/storage and handling, were reviewed and found to be adequate from the CMC perspective.</p>		
16. CONCLUSION AND RECOMMENDATION		
<p>This is Review #5 for CMC information in the subject amended supplement. The information provided in the original submission as amended is satisfactory from CMC review standpoint. The responses provided in the resubmission are for addressing the deficiencies arising out of CDRH review. The supplement as amended is recommended for approval with the conclusion of a satisfactory CDRH review. This supplement is OND managed.</p>		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	28-Aug-2014
DISTRIBUTION: ORIGINAL JACKET CSO		REVIEWER DIVISION FILE
		DMEP

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/s/

PALLAIAH THAMMANA
08/28/2014

RAMESH RAGHAVACHARI
08/28/2014

CHEMISTRY REVIEW # 4	1. ORGANIZATION ONDQA/DNDQA III/Branch IX	2. NDA NUMBER N022074 (Approved 30-Aug-2007)
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Ipsen Pharma <u>Authorized Agent</u> : 65 quai Georges Gorse Biomeasure Incorporated 92100 Boulogne-Billancourt 27 Maple Street France Milford, MA 01757-3650		S-004, 03-May-2010 17-Jan-2014 Resubmission /After Action-Complete
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Somatulin® Depot	Lanreotide acetate	Amendment, 03-Oct-2011 User Validation Test Protocol, 02-Jul-2012 Amendment, 26-Dec-2012 Amendment, 25-Jan-2013 Amendment, 02-May-2013 Amendment, 17-Jan-2014 Amendment, 07-Apr-2014
8. SUPPLEMENT PROVIDES INFORMATION FOR		
Changes to manufacturing process steps for drug substance and drug product, and changes to container closure.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Somatostatin analog	Rx	DMF # 8974
12. DOSAGE FORM	13. POTENCY	
Injection	60 mg, 90 mg and 120 mg	
14. CHEMICAL NAME AND STRUCTURE		
<p>Lanreotide acetate is a synthetic cyclic octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl- L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Molecular weight of the base is 1096.34. Its amino acid sequence is:</p> $ \begin{array}{c} \text{S} \text{-----} \text{S} \\ \qquad \qquad \qquad \\ \text{D-}\beta\text{Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH}_2, \text{ x(CH}_3\text{COOH)} \end{array} $ <p>Current x (CH₃COOH) = 1.6 to 3.4 and Proposed x (CH₃COOH) = 1.0 to 2.0</p>		
15. COMMENTS		
<p>The FDA issued a CR letter on 25-May-2013 with comments on the Human Factor study and Labeling/Instructions For Use. There were no CMC related deficiencies identified in the CR letter</p> <p>The Labeling review of the Amendment dated 07-Apr-2014 concluded that the information provided was adequate (21-Apr-2014). The final CDRH review concluded that the information provided in the resubmission dated 17-Jan-2014 is adequate (28-Apr-2014).</p>		
16. CONCLUSION AND RECOMMENDATION		
<p>The information provided in the original submission as amended is satisfactory from CMC review standpoint. The responses provided in the resubmission are for addressing the deficiencies arising out of CDRH review only. The supplement as amended is recommended for approval with the conclusion of a satisfactory CDRH review. This supplement is OND managed.</p>		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	11-May-2014
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		
DMEP		

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/s/

PALLAIAH THAMMANA
05/14/2014

RAMESH RAGHAVACHARI
05/14/2014

CHEMISTRY REVIEW # 3	1. ORGANIZATION ONDQA/DNDQA III/Branch IX	2. NDA NUMBER N022074 (Approved 30-Aug-2007)
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Ipsen Pharma <u>Authorized Agent :</u> 65 quai Georges Gorse Biomeasure Incorporated 92100 Boulogne-Billancourt 27 Maple Street France Milford, MA 01757-3650		S-004, 03-May-2010
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Somatulin® Depot	Lanreotide acetate	Amendment, 03-Oct-2011 User Validation Test Protocol, 02-Jul-2012 Amendment, 26-Dec-2012
8. SUPPLEMENT PROVIDES INFORMATION FOR		
Changes to manufacturing process steps for drug substance and drug product, and changes to container closure.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Somatostatin analog	Rx	DMF # 8974
12. DOSAGE FORM	13. POTENCY	
Injection	60 mg, 90 mg and 120 mg	
14. CHEMICAL NAME AND STRUCTURE		
Lanreotide acetate is a synthetic cyclic octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl- L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Molecular weight of the base is 1096.34. Its amino acid sequence is:		
<pre> S-----S D-βNal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂, x(CH₃COOH) </pre>		
Current x (CH₃COOH) = 1.6 to 3.4 and Proposed x (CH₃COOH) = 1.0 to 2.0		
15. COMMENTS		
The subject supplement N022074/S-004 was issued a CR letter on 04-May-2011. The applicant submitted an amendment on 03-Oct-2011 and the responses provided in the resubmission were for addressing the deficiencies arising out of CDRH review only as there were no CMC related deficiencies identified in the CR letter. After review by CDRH, FDA issued a second CR letter on 03-Feb-2012, for which the Applicant submitted a revised User Validation Test Protocol and Instructions for Use on 02-Jul-2012, and requested for FDA's feedback prior to Study implementation. FDA issued a response advice letter on 17-Sep-2012. The current submission is Applicant's resubmission to the CR.		
The responses provided in the resubmission are for addressing the deficiencies arising out of CDRH review only as there were no CMC related deficiencies identified in the CR letter.		
16. CONCLUSION AND RECOMMENDATION		
The information provided in this paper submission as amended is satisfactory from CMC review standpoint. The supplement as amended is recommended for approval pending a satisfactory CDRH review. This supplement is OND managed.		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	15-Apr-2013
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DMEP		

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/s/

PALLAIAH THAMMANA
04/15/2013

RAMESH RAGHAVACHARI
04/15/2013

CHEMISTRY REVIEW # 2	1. ORGANIZATION ONDQA/DNDQA III/Branch IX	2. NDA NUMBER N022074 (Approved 30-Aug-2007)
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Ipsen Pharma <u>Authorized Agent</u> : 65 quai Georges Gorse Biomeasure Incorporated 92100 Boulogne-Billancourt 27 Maple Street France Milford, MA 01757-3650		S-004, 03-May-2010
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Somatulin® Depot	Lanreotide acetate	Amendment, 03-Oct-2011
8. SUPPLEMENT PROVIDES INFORMATION FOR		
Changes to manufacturing process steps for drug substance and drug product, and changes to container closure.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Somatostatin analog	Rx	DMF # 8974
12. DOSAGE FORM	13. POTENCY	
Injection	60 mg, 90 mg and 120 mg	
14. CHEMICAL NAME AND STRUCTURE		
Lanreotide acetate is a synthetic cyclic octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl- L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Molecular weight of the base is 1096.34. Its amino acid sequence is:		
$ \begin{array}{c} \text{S} \text{-----} \text{S} \\ \qquad \qquad \qquad \\ \text{D-}\beta\text{Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH}_2, \text{ x(CH}_3\text{COOH)} \end{array} $		
Current x (CH₃COOH) = 1.6 to 3.4 and Proposed x (CH₃COOH) = 1.0 to 2.0		
15. COMMENTS		
The subject amendment is a resubmission in response to the CR letter issued for N022074/S-004 on 04-May-2011. The responses provided in the resubmission are for addressing the deficiencies arising out of CDRH review only as there were no CMC related deficiencies identified in the CR letter.		
The applicant has provided revisions to the PI, and provided annotated and clean versions of the PI. The Description and How Supplied sections were previously reviewed in Review #1. The track changes proposed are acceptable. The amendment also provides draft container and carton labels which were found to be adequate.		
16. CONCLUSION AND RECOMMENDATION		
The information provided in this paper submission is satisfactory from the CMC review standpoint. The supplement as amended is recommended for approval pending a satisfactory CDRH review. This supplement is OND managed.		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	23-Jan-2012
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		
DMEP		

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/s/

PALLAIAH THAMMANA
01/27/2012

JAMES D VIDRA
01/27/2012

CHEMISTRY REVIEW	1. ORGANIZATION ONDQA/DNDQA III/Branch IX	2. NDA NUMBER N022074 (Approved 30-Aug-2007)
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Ipsen Pharma <u>Authorized Agent :</u> 65 quai Georges Gorse Biomeasure Incorporated 92100 Boulogne-Billancourt 27 Maple Street France Milford, MA 01757-3650		S-004, 03-May-2010
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Somatulin® Depot	Lanreotide acetate	
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Changes to manufacturing process steps for drug substance and drug product, and changes to container closure.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Somatostatin analog	Rx	DMF # 8974
12. DOSAGE FORM	13. POTENCY	
Injection	60 mg, 90 mg and 120 mg	
14. CHEMICAL NAME AND STRUCTURE		
See Chemist's review notes on next page		
15. COMMENTS		
<p>The proposed changes mainly include modification to drug substance manufacture process (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) In the proposed drug product manufacturing process, (b) (4) The drug substance from the proposed process was (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) were done on the drug substance derived from the proposed process. The physicochemical characterization demonstrated no observable changes to the drug substance. Extensive long-term stability and accelerated stability data on drug substance and drug product were submitted. Container closure changes were made to the primary secondary components of packaging which are described in the review.</p> <p>Revised package insert and container/carton labels were submitted. Upon review, the revisions to labeling were found satisfactory from CMC review standpoint. The Product Quality Microbiology reviewer found the relevant microbiology related steps in the manufacturing process and the product sterilization by (b) (4) to be satisfactory, and recommended the supplement for approval.</p>		
16. CONCLUSION AND RECOMMENDATION		
The information provided in this paper submission is extensive and satisfactory from the CMC review standpoint. The supplement is recommended for approval. Issue an Approval letter.		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	11-Aug-2010
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22074	SUPPL-4	BEAUFOUR IPSEN PHARMA	SOMATULINE DEPOT, 60,90,120 MG

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/s/

PALLAIAH THAMMANA
08/17/2010

JAMES D VIDRA
08/17/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022074Orig1s004

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products (DMEP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 022074/S-004

Name of Drug: Somatuline Depot (lanreotide) injection; 60 mg, 90 mg, 120 mg

Applicant: Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma

Labeling Reviewed

Submission Date:

October 15, 2014 (via email): Package insert/patient package insert (final agreed-upon Word)

June 18, 2014 (via email): Revised pouch (front/back) and carton labels; final agreed-upon pdf

May 15, 2014 (via email): Revised syringe labels; final agreed-upon pdf

May 15, 2014 (via email): Revised healthcare practitioner Instructions for Use (IFU); final agreed-upon pdf

January 16, 2014 (included in sNDA resubmission): Plunger protector label; final agreed-upon pdf

Receipt Date:

October 15, 2014 (via email): Package insert/patient package insert; final agreed-upon Word

June 18, 2014 (via email): Revised pouch (front/back) and carton labels; final agreed-upon pdf

May 15, 2014 (via email): Revised syringe labels; final agreed-upon pdf

May 15, 2014 (via email): Revised healthcare practitioner Instructions for Use (IFU); final agreed-upon pdf

January 17, 2014 (included in sNDA resubmission): Plunger protector label; final agreed-upon pdf

Material Referenced:

Complete Response letters dated May 4, 2011; February 3, 2012; and May 25, 2013

CMC reviews: August 17, 2010; January 27, 2012; April 15, 2013; May 14 and August 28, 2014

CDRH (device) reviews: February 22, 2011 and October 6, 2014

CDRH (human factors) reviews: February 3, 2012; September 10, 2012; April 26, 2013; April 28, 2014

DMEPA (labeling and human factors) review dated November 18, 2010

DMEPA (human factors and labeling) review dated April 13, 2012

**Note: comments from this review were conveyed in the February 3, 2012, CR letter.*

DMEPA (human factors/labeling) review dated September 11, 2012

DMEPA (labeling and human factors) review dated May 23, 2013

DMEPA (human factors and labeling) review dated April 21, 2014

DMEPA (labeling) review dated June 6, 2014

DMEPA (labeling) review dated October 2, 2014

Patient Labeling reviews: September 16, 2010 and November 17, 2011

Background and Summary Description:

Somatuline Depot Injection was approved on August 30, 2007, as a new molecular entity (NME) for the treatment of acromegaly (orphan indication). Up to this point it has been available as a pre-filled syringe fitted with a 20 mm needle covered by a dry natural rubber sheath; each pre-filled syringe is sealed in a laminated pouch and packed in a carton.

On April 29, 2010, the applicant submitted this CMC manufacturing supplement (with labeling, thus OND-managed) which provided for changes to the drug substance and drug product manufacturing processes, and to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. Also, the syringe dimensions for the three dosage strengths have been harmonized in order to have the three dosage strengths packaged with the same syringe and needle. A Complete Response letter issued on May 4, 2011, which cited device and medication error-related deficiencies, as well as requests for revisions to the carton and container labels.

The applicant resubmitted S-004 on October 3, 2011. This resubmission included a simulated user study report, as well as responses to the Complete Response letter dated May 4, 2011. On February 3, 2012, a Complete Response letter issued, citing deficiencies and advice related to the device and the usability validation study, as well as requests for revisions to the package insert, patient labeling, instructions for use, and carton/container labels. (On January 23, 2012, patient labeling comments and revision requests were sent by this RPM to the applicant, who responded via email on January 31, 2012.)

On July 2, 2012, the applicant submitted a revised draft user validation (human factors) study protocol for FDA feedback prior to beginning its user validation study (per the recommendation provided by FDA in the February 3, 2012, CR letter). A revised package insert, instructions for use and carton labels were also included in the submission. (A submission on August 23, 2012, contained a revised package insert.) DMEPA and CDRH (human factors) reviewers were consulted for advice, and on September 17, 2012, a letter issued which contained advice and further requests for revision of the protocol and IFU (and submission to FDA) prior to beginning the human factors study.

The applicant resubmitted S-004 on December 21, 2012. On January 28, 2013, an Acknowledge Incomplete Response letter issued, as the resubmission did not include the electronic labeling components as required per the regulations. The applicant submitted these required components on January 24, 2013, and then this submission was re-classified as a Complete Response submission to the February 3, 2012, CR letter. On April 24, 2013 (see communication dated April 26, 2013 in DARRTS), requests for additional information and product samples (on behalf of CDRH and DMEPA human factors reviewers) were conveyed to the applicant via email by this RPM, and on May 1, 2013, the applicant submitted an official response.) On May 25, 2013, a Complete Response letter issued, containing deficiencies related to the product design and human factors study (request to repeat the study) and requests for revision of the instructions for use.

The applicant resubmitted S-004 on January 16, 2014. On April 1, 2014, this RPM requested via email that the applicant submit color mock-ups of their syringe pouch sachet (back) labels, as only the draft instructions in French were provided in the electronic component of the resubmission. Product (device) samples were also requested. The applicant responded with an official submission on April 4, 2014. Both DMEPA and CDRH were consulted for review of the human factors study report and the applicant's revised instructions for use (directed to healthcare professionals administering Somatuline Depot to patients). In their reviews dated April 21 and April 28, 2014, respectively, the human factors study was deemed adequate, with no further revisions requested. The DMEPA review included requests for further revision to the instructions for use, package insert, syringe, pouch and carton labels. On May 12, 2014, this RPM sent these revision requests (except for the package insert) to the applicant via email, and the applicant responded with revised labels and instructions for use on May 15, 2014, via email. DMEPA reviewed these revised labels (refer to DMEPA email review dated June 6, 2014, in DARRTS) and further requests for revision (to the pouch and carton labeling) were sent to the applicant by the RPM via email on June 11, 2014. On June 18, 2014, the

applicant responded via email with revised labels as requested. (Refer to final DMEPA review dated October 2, 2014, and to CMC review indicating concurrence with labels and CMC sections of the labeling dated August 28, 2014.)

Note: it was realized during this final review cycle that a device review had never been received from CDRH. This RPM submitted a consult request (to both CDRH device and human factors reviewers) on January 20, 2012, but a response consult review of the device was never received. Therefore, this RPM contacted CDRH and initiated another consult request in DARRTS on July 28, 2014 (requesting review of the applicant's response from the October 4, 2011 resubmission to the two deficiencies from the CDRH device review dated February 22, 2011, and the CR letter dated May 4, 2011, that were never addressed). After much communication between this RPM and the relevant reviewers in CDRH and the applicant to retrieve the necessary information, including full study reports, a review indicating device acceptability was completed (refer to device review dated October 6, 2014 in DARRTS).

After review of the package insert by DMEP clinical reviewers and this RPM, a draft containing FDA comments and revisions (and indicated acceptability of the applicant's revisions) was sent to the applicant via email on October 14, 2014. The applicant responded via email on October 15, 2014, accepting all of FDA's revisions and comments.

Review of the Package Insert and Patient Package Insert

The revised labeling (PI and PPI) is being compared to the currently approved PI and PPI (approved with S-006 on November 27, 2013). The following revisions have been made to the PI, with the addition of text noted by underline and the deletion of text denoted by ~~strike through~~:

Highlights of Prescribing Information

-----**DOSAGE FORMS AND STRENGTHS**-----
Single use syringe: 60 mg, 90 mg and 120 mg (3)

Note: these additions are acceptable. Refer to Complete Response letter dated February 3, 2012, and to DMEPA review dated April 13, 2012. Concurrence by clinical reviewer Marina Zemskova and clinical team leader Dragos Roman via email on October 10, 2014.

Revision Date

The revision date has been changed from "~~Revised November 2013~~" to "Revised: 10/2014".

Note: this change in revision date is acceptable.

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dose for Renal and Hepatic Impairment

2.2 Instructions for Use

Note: the addition of these subsections is acceptable. Refer to Complete Response letter dated February 3, 2012, and to DMEPA review dated April 13, 2012. Concurrence by clinical reviewer Marina Zemskova and clinical team leader Dragos Roman via email on October 10, 2014.

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

Somatuline Depot should be administered by healthcare professionals. Please see enclosed Instructions for Use leaflet for administration of Somatuline Depot.

Patients should begin treatment with Somatuline Depot 90 mg given via the deep subcutaneous route, at 4-week intervals for 3 months.

After 3 months, dosage may be adjusted as follows:

- GH $>$ greater than 1 to \leq less than or equal to 2.5 ng/mL, IGF-1 normal and clinical symptoms controlled: maintain Somatuline Depot dose at 90 mg every 4 weeks.
- GH $>$ greater than 2.5 ng/mL, IGF-1 elevated and/or clinical symptoms uncontrolled, increase Somatuline Depot dose to 120 mg every 4 weeks.
- GH \leq less than or equal to 1 ng/mL, IGF-1 normal and clinical symptoms controlled: reduce Somatuline Depot dose to 60 mg every 4 weeks.

Thereafter, the dose should be adjusted according to the response of the patient as judged by a reduction in serum GH and /or IGF-1 levels; and/or changes in symptoms of acromegaly.

Patients who are controlled on Somatuline Depot 60 mg or 90 mg may be considered for an extended dosing interval of Somatuline Depot 120 mg every 6 or 8 weeks. GH and IGF-1 levels should be obtained 6 weeks after this change in dosing regimen to evaluate persistence of patient response.

Continued monitoring of patient response with dose adjustments for biochemical and clinical symptom control, as necessary, is recommended.

2.1 Dose for Renal and Hepatic Impairment

The starting dose in patients with moderate or severe renal impairment, or moderate or severe hepatic impairment should be 60 mg via the deep subcutaneous route, at 4-week intervals for 3 months followed by dose adjustment as described above [see Clinical Pharmacology (12.3)].

2.2 Instructions for Use

Somatuline Depot is provided in a single-dose, pre-filled syringe affixed with an automatic needle protection system. Somatuline Depot should be injected via the deep subcutaneous route in the superior external quadrant of the buttock. ~~The skin should not be folded and the needle should be inserted perpendicular to the skin, rapidly and to its full length.~~ The injection site should alternate between right and left sides from one injection to the next. Remove Somatuline Depot from the refrigerator 30 minutes prior to administration. Keep pouch sealed until just prior to injection.

~~The starting dose in patients with moderate or severe renal impairment, or moderate or severe hepatic impairment should be 60 mg via the deep subcutaneous route, at 4 week intervals for 3 months followed by dose adjustment as described above [see Clinical Pharmacology (12.3)].~~

Note: these changes are acceptable. Refer to Complete Response letter dated February 3, 2012, and to DMEPA reviews dated April 13, 2012 and April 21, 2014. Concurrence by clinical reviewer Marina Zemskova and clinical team leader Dragos Roman via email on October 10, 2014.

3 DOSAGE FORMS AND STRENGTHS

60 mg, 90 mg, and 120 mg sterile, single-use, pre-filled syringes fitted with an automatic needle guard. The pre-filled syringes contain a white to pale yellow, semi-solid formulation.

Note: these changes are acceptable. Refer to Complete Response letter dated February 3, 2012, to DMEPA review dated April 13, 2012, and to CMC reviews dated August 17, 2010, May 14, and August 28, 2014.

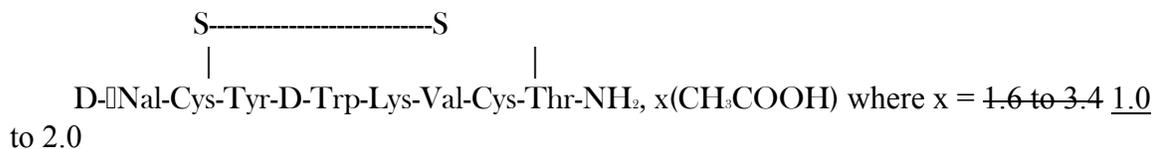
11 DESCRIPTION

Somatuline Depot (lanreotide) Injection 60 mg, 90 mg, and 120 mg is a prolonged-release formulation for deep subcutaneous injection containing the drug substance lanreotide acetate, a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin, water for injection, and acetic acid (for pH adjustment).

Somatuline Depot is available as sterile, ready-to-use, pre-filled syringes containing lanreotide supersaturated bulk solution of 24.6% w/w lanreotide base.

Each syringe contains:	Somatuline Depot 60 mg	Somatuline Depot 90 mg	Somatuline Depot 120 mg
Lanreotide acetate	79.8 <u>77.9</u> mg	116.4 <u>113.6</u> mg	155.5 <u>149.4</u> mg
<u>Acetic Acid</u>	<u>q.s.</u>	<u>q.s.</u>	<u>q.s.</u>
Water for injection	186.2 <u>186.6</u> mg	271.6 <u>272.3</u> mg	363 <u>357.8</u> mg
<u>Total Weight</u>	<u>266 mg</u>	<u>388 mg</u>	<u>510 mg</u>

Lanreotide acetate is a synthetic cyclical octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Its molecular weight is 1096.34 (base) and its amino acid sequence is:



For appearance of the formulation, see *Dosage Forms and Strengths (3)*.

Note: these changes are acceptable, given the proposed changes in this manufacturing supplement. Refer to the CMC reviews dated August 17, 2010; January 27, 2012; April 15, 2013; May 14 and August 28, 2014.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lanreotide, the active component of Somatuline Depot, is an octapeptide analog of natural somatostatin. The mechanism of action of lanreotide is believed to be similar to that of natural somatostatin.

12.2 Pharmacodynamics

12.3 Pharmacokinetics

Somatuline Depot is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids. The most likely mechanism of drug release is a passive diffusion of the precipitated drug from the depot towards the surrounding tissues, followed by the absorption into the blood stream.

After a single deep, subcutaneous administration, the mean absolute bioavailability of Somatuline Depot in healthy subjects was 73.4, 69.0, and 78.4%, for the 60 mg, 90 mg, and 120 mg doses, respectively. Mean C_{max} values ranged from 4.3 to 8.4 ng/mL during the first day. Single-dose linearity was demonstrated with respect to AUC and C_{max} , and showed high inter-subject variability. Somatuline Depot showed sustained release of lanreotide with a half-life of 23 to 30 days. Mean serum concentrations were > 1 ng/mL throughout 28 days at 90 mg and 120 mg and > 0.9 ng/mL with 60 mg.

In a repeat-dose administration pharmacokinetics (PK) study in acromegalic patients, rapid initial release was seen giving peak levels during the first day after administration. At doses of Somatuline Depot between 60 and 120 mg, linear pharmacokinetics were observed in acromegalic patients. At steady state, mean C_{max} values were 3.8 ± 0.5 , 5.7 ± 1.7 , and 7.7 ± 2.5 ng/mL, increasing linearly with dose. The mean accumulation ratio index was 2.7 which is in line with the range of values for the half-life of Somatuline Depot. The steady-state trough serum lanreotide concentrations in patients receiving Somatuline Depot every 28 days were 1.8 ± 0.3 ; 2.5 ± 0.9 , and 3.8 ± 1.0 ng/mL at 60 mg, 90 mg, and 120 mg doses, respectively. A limited initial burst effect and a low peak-to-trough fluctuation (81% to 108%) of the serum concentration at the plateau were observed.

For the same doses, similar values were obtained in clinical studies after at least four administrations (2.3 ± 0.9 , 3.2 ± 1.1 , and 4.0 ± 1.4 ng/mL, respectively).

Pharmacokinetic data from studies evaluating extended dosing use of Somatuline Depot 120 mg demonstrated mean steady state, C_{min} values between 1.6 and 2.3 ng/mL for the 8- and 6-week treatment interval, respectively.

Note: these clarifying additions of “mg” are acceptable. Refer to Complete Response letter dated February 3, 2012 and to DMEPA review dated April 13, 2012. Concurrence by clinical reviewer Marina Zemskova and clinical team leader Dragos Roman via email on October 10, 2014.

14 CLINICAL STUDIES

The effect of Somatuline Depot on reducing GH and IGF-levels and control of symptoms in patients with acromegaly was studied in two long-term, multiple-dose, randomized multicenter studies.

Study 1

This one-year study included a 4-week double-blind, placebo-controlled phase, a 16-week single-blind, fixed-dose phase, and a 32-week open-label dose-titration phase. Patients with active acromegaly based on biochemical tests and medical history entered a 12-week washout period if there was previous treatment with a somatostatin analog or a dopaminergic agonist.

Upon entry, patients were randomly allocated to receive a single deep subcutaneous injection of Somatuline Depot 60 mg, 90 mg, or 120 mg or placebo. Four weeks later, patients entered a fixed-dose phase where they received 4 injections of Somatuline Depot followed by a dose-titration phase of 8 injections for a total of 13 injections over 52 weeks (including the placebo phase). Injections were given at 4-week intervals. During the dose-titration phase of the study, the dose was titrated twice (every fourth injection), as needed, according to individual GH and IGF-1 levels.

A total of 108 patients (51 males, 57 females) were enrolled in the initial placebo-controlled phase of the study. Half (54/108) of the patients had never been treated with a somatostatin analog or dopamine agonist, or had stopped treatment for at least 3 months prior to their participation in the study and were required to have a mean GH level > 5 ng/mL at their first visit. The other half of the patients had received prior treatment with a somatostatin analog or a dopamine agonist before study entry and at study entry were to have a mean GH concentration > 3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication.

One hundred and seven (107) patients completed the placebo-controlled phase, 105 patients completed the fixed-dose phase, and 99 patients completed the dose-titration phase. Patients not completing withdrew due to adverse events (5) or lack of efficacy (4).

In the double-blind phase of study 1, a total of 52 (63%) of the 83 lanreotide-treated patients had a > 50% decrease in mean GH from baseline to Week 4 including 52%, 44%, and 90% of patients in the 60 mg, 90 mg, and 120 mg groups, respectively, compared to placebo (0%, 0/25). In the fixed-dose phase at Week 16, 72% of all 107 lanreotide-treated patients had a decrease from baseline in mean GH of > 50% including 68% (23/34), 64% (23/36), and 84% (31/37) of patients in the 60 mg, 90 mg, and 120 mg lanreotide treatment groups, respectively. Efficacy achieved in the first 16 weeks was maintained for the duration of the study (see Table 3).

Note: these clarifying additions of “mg” are acceptable. Refer to Complete Response letter dated February 3, 2012 and to DMEPA review dated April 13, 2012. Concurrence by clinical reviewer Marina Zemskova and clinical team leader Dragos Roman via email on October 10, 2014.

16 HOW SUPPLIED/STORAGE AND HANDLING

Somatuline Depot is supplied in strengths of 60 mg, 90 mg, and 120 mg in a single, sterile, pre-filled, ready-to-use, polypropylene syringe (fitted with an automatic needle guard) fitted with a 20 mm needle covered by a ~~dry natural rubber~~ low density polyethylene sheath.

Each pre-filled syringe is sealed in a laminated pouch and packed in a carton.

NDC 15054-0060- 13	60-mg, sterile, pre-filled syringe
NDC 15054-0090- 13	90-mg, sterile, pre-filled syringe
NDC 15054-0120- 13	120-mg, sterile, pre-filled syringe

Storage and Handling

Somatuline Depot 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. Thirty (30) minutes prior to injection, remove sealed pouch of Somatuline Depot from refrigerator and allow it to come to room temperature. Keep pouch sealed until injection.

Each syringe is intended for single use. Do not use beyond the expiration date on the packaging.

Note: these changes are acceptable, given the proposed changes in this manufacturing supplement. Refer to the CMC reviews dated August 17, 2010; January 27, 2012; April 15, 2013; May 14 and August 28, 2014.

Patient Package Insert

Patient Information

Somatuline® Depot (So-mah-tu-leen Dee-Poh)
(lanreotide) Injection

Read this Patient Information before you receive your first Somatuline® Depot injection and before each injection. There may be new information. This information does not take the place of talking with your ~~doctor~~ healthcare professional about your medical condition or your treatment.

What is Somatuline® Depot?

Somatuline® Depot is a prescription medicine used for the long-term treatment of people with acromegaly when:

- surgery or radiotherapy have not worked well enough or
- they are not able to have surgery or radiotherapy

It is not known if Somatuline® Depot is safe and effective in children.

What should I tell my ~~doctor~~ healthcare professional before receiving Somatuline® Depot?

Before you receive Somatuline® Depot, tell your ~~doctor~~ healthcare professional if you have:

- gallbladder problems
- diabetes
- thyroid problems
- heart problems
- kidney problems
- liver problems
- ~~are allergic to latex or natural dry rubber. The pre-filled syringe needle cover contains rubber.~~
- are pregnant or plan to become pregnant. It is not known if Somatuline® Depot will harm your unborn baby. Talk to your ~~doctor~~ healthcare professional if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if Somatuline® Depot passes into your breast milk. Talk to your ~~doctor~~ healthcare professional about the best way to feed your baby if you receive Somatuline® Depot.

Tell your ~~doctor~~ healthcare professional about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Somatuline® Depot and other medicines may affect each other causing side effects.

Somatuline® Depot may affect the way other medicines work, and other medicines may affect how Somatuline® Depot works. Your dose of Somatuline® Depot or your other medicines may need to be adjusted.

Especially tell your ~~doctor~~ healthcare professional if you take:

- insulin or other diabetes medicines
- a cyclosporine (Gengraf, Neoral, or Sandimmune)
- a medicine called bromocriptine (Parlodel)
- medicines that lower your heart rate such as beta blockers

Know the medicines you take. Keep a list of them to show your ~~doctor and pharmacist~~ healthcare professional when you get a new medicine.

How will I receive Somatuline® Depot?

- You will receive a Somatuline® Depot injection every 4 weeks ~~as directed by your doctor~~ in your doctor's office. Your ~~doctor~~ prescriber may change your dose of Somatuline® Depot or the length of time between your injections. Your ~~doctor~~ healthcare provider will tell you how long you need to receive Somatuline® Depot.
- Somatuline® Depot is injected deep under the skin of the upper outer area of your buttock.
- Your injection site should change (alternate) between your right and left buttock each time you receive an injection of Somatuline® Depot.
- During your treatment with Somatuline® Depot, your ~~doctor~~ healthcare professional may do certain blood tests to see if Somatuline® Depot is working. Your ~~doctor~~ healthcare professional may change your dose, or length of time between your Somatuline® Depot injections as needed.

Please see enclosed Instructions for Use leaflet.

What are the possible side effects of Somatuline® Depot?

Somatuline® Depot may cause serious side effects, including:

- **gallstones.** Tell your ~~doctor~~ healthcare professional if you have any of these symptoms:
 - sudden pain in your upper right stomach area (abdomen)
 - sudden pain in your right shoulder or between your shoulder blades
 - yellowing of your skin and whites of your eyes
 - fever with chills
 - nausea
- **changes in your blood sugar** (high blood sugar or low blood sugar). If you have diabetes, test your blood sugar as your ~~doctor~~ healthcare professional tells you to. Your ~~doctor~~ healthcare professional may change your dose of diabetes medicine especially when you first start receiving Somatuline® Depot or if your dose of Somatuline® Depot changes.
- **slow heart rate**
- **high blood pressure**

The most common side effects of Somatuline® Depot include:

- diarrhea
- stomach area (abdominal) pain
- nausea
- pain, itching or a lump at the injection site

Tell your ~~doctor~~ healthcare professional if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Somatuline® Depot. For more information, ask your ~~doctor or pharmacist~~ healthcare professional.

Call your ~~doctor~~ healthcare professional for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch.

General information about the safe and effective use of Somatuline® Depot.

Medicines are sometimes prescribed for conditions other than those listed in the patient leaflet. This Patient Information leaflet summarizes the most important information about Somatuline® Depot. If you would like more information about Somatuline® Depot, talk with your ~~doctor~~ healthcare professional. You can ask your ~~pharmacist or doctor~~ healthcare professional for information about Somatuline® Depot that is written for health professionals.

For more information, go to www.somatulinedepot.com or call Ipsen ~~Pharmaceuticals, Inc.~~ Biopharmaceuticals at 1-866-837-2422.

This Patient Information has been approved by the U.S. Food and Drug Administration.

~~Issued August 2007~~
~~Revised February 2012~~

Somatuline® Depot is manufactured by Ipsen Pharma Biotech SAS-~~BP~~, Parc d'Activites du Plateau de Signes, 707 83870 Signes, 83030 Toulon Cedex 9 France for ~~Ipsen Pharma SAS, 65 quai Georges Gorse, 92650, Boulogne Billancourt Cedex, France~~ for Ipsen Biopharmaceuticals, Inc., 106 Allen Road, Basking Ridge, NJ 07920 USA

Revised 10/2014

Note: these changes (including change of placement of revision date, change in manufacturing information, change from “doctor” and “pharmacist” to “healthcare professional”, addition of contact information for reporting side effects) are acceptable. The bullet point about allergies to latex or dry rubber (under the section entitled “What should I tell my healthcare professional

before receiving Somatuline® Depot?") no longer applies and has been removed due to the provisions of this manufacturing supplement. Clinical concurrence by clinical reviewer Marina Zemskova and clinical team leader Dragos Roman via email on October 10, 2014. Also refer to Patient Labeling review dated November 17, 2011.

Review of the Healthcare Provider Instructions for Use (IFU)

Note: there is no previously approved IFU to which a comparison can be made (i.e., the IFU has been developed over the course of extensive review of S-004 across numerous review cycles and feedback given to the applicant by FDA, and is being approved with this supplement). The final agreed-upon IFU is acceptable to DMEPA (per email dated July 25, 2014) and CDRH (per email dated August 1, 2014) human factors reviewers; also refer to DMEPA reviews dated April 21 and June 6, 2014, and to CDRH (human factors) review dated April 28, 2014. Clinical concurrence (clinical reviewer Marina Zemskova and clinical team leader Dragos Roman) via email on October 10, 2014.

Review of the Packaging/Carton and Container Labels

The revised packaging (carton and container labels) are being compared to the currently approved packaging, submitted with the post-approval final printed labeling (FPL) amendment on October 30, 2007, as requested in the approval letter for the original NDA dated August 30, 2007 (which contained requests for revisions to the carton/container labels). The following revisions have been made to the labels and are described briefly below, and where appropriate, deleted text is denoted by ~~striketrough~~ and added text is denoted by underline.

Plunger Protector label

Note: there is no previously approved plunger protector label to which a comparison can be made (i.e., the label is being approved with this S-004). However, it is acceptable to DMEPA and CMC reviewers; refer to DMEPA reviews dated May 23, 2013 and April 21, 2014, and to CMC review dated August 28, 2014.

Syringe labels

Changes made to the syringe labels previously approved on August 30, 2007, and submitted via final printed labeling (FPL) amendment dated October 30, 2007, include:

1. Previously, the manufacturer information appeared on the left-hand side of the syringe label sticker, and the drug product information and expiration date/lot number appeared on the right-hand side, with the sides being separated by a thin colored stripe down the middle (green for 60 mg strength, blue for 90 mg strength and purple for 120 mg strength). Now, the label information appears on the left-hand side of the label, beginning with the drug product information, followed by the manufacturer information, expiration date and lot number.

2. The statement “**Warning: Needle Sheath Contains Dry Natural Rubber**” has been removed given the provisions of this manufacturing supplement.
3. The following statement has been added to the lower right quadrant of the syringe label:
FOR SINGLE USE ONLY
DISCARD UNUSED
PORTION

Note: these changes are acceptable. Refer to DMEPA reviews dated April 21 and June 6, 2014, and to CMC review dated August 28, 2014.

Pouch labels

Changes made to the pouch labels previously approved on August 30, 2007, and submitted via final printed labeling (FPL) amendment dated October 30, 2007, include:

1. The NDC number has changed as follows:
 - a. From 1505406001 to 1505400603 (60 mg strength)
 - b. From 1505409001 to 1505400903 (90 mg strength)
 - c. From 1505412002 to 1505401203 (120 mg strength)
2. The identifier has changed as follows:
 - a. From 5187.01 to 1039707 (60 mg strength)
 - b. From 5188.01 to 1039708 (90 mg strength)
 - c. From 5189.01 to 1039709 (120 mg strength)
3. The instruction “Tear Here” has been added above the perforated line below the red arrow, just above the NDC number/bar code.
4. The colored illustration below the NDC number/bar code (showing how to pull the syringe open) has been removed.
5. The product strength expression (in white font on a colored background) has changed as follows:
 - a. 60 mg to 60 mg per 0.2 mL (green background)
 - b. 90 mg to 90 mg per 0.3 mL (blue background)
 - c. 120 mg to 120 mg per 0.5 mL (purple background)
6. The following text has been added to the front of the pouch, in the white space in the center:

Somatuline® Depot (lanreotide) Injection

For deep subcutaneous injection.

IMPORTANT Somatuline® Depot should be administered by a healthcare professional. Call 1-888-980-2889 and request training that includes delivering a practice injection.

REMEMBER Read both sides of the yellow instructions for use and prescribing information for complete instructions.
STORAGE Refrigerate at 2°C-8°C (36°F-46°F) in its original package. Protect from light.

Keep device out of reach of children.

7. The pouch labels (stickers) formerly appeared on the front of the pouch at the bottom, and now appear on the back of the pouch. The text appearing on the label has changed as follows:

Somatuline® Depot (lanreotide) Injection
~~(lanreotide) Injection-60 mg/0.2 mL~~
~~Rx only~~
FOR SINGLE USE ONLY. DISCARD UNUSED PORTION
~~Manufactured by~~ **Manufacturer: Ipsen Pharma Biotech, Signes France**
~~Warning: Needle Sheath Contains~~
~~Dry Natural Rubber~~

Leave at room temperature for 30 minutes before administration

EXP: 00/0000
Lot: ~~00~~ X00000 (Y00000)

Note: for the other two strengths, the product strength expression is 90 mg/0.3 mL and 120 mg/0.5 mL.

The label identifiers are: ES628 (60 mg strength), ES930 (90 mg strength) and ES1234 (120 mg strength).

Note: these changes are acceptable. Refer to DMEPA reviews dated April 21, June 6 and October 2, 2014, and to CMC review dated August 28, 2014.

Carton labels

Changes made to the carton labels previously approved on August 30, 2007, and submitted via final printed labeling (FPL) amendment dated October 30, 2007, include:

Front (principal) display panel

1. “**Rx only**” now appears in the upper left-hand corner.
2. The company name has changed from “IPSEN Tercica” to “IPSEN”.

3. The NDC number has been moved from the center right of the panel further to the right, now has a bar code above it, and has changed as follows:
 - a. From 15054 060 01 to 15054 0060 3 (60 mg strength)
 - b. From 15054 090 01 to 15054 0090 3 (90 mg strength)
 - c. From 15054 120 02 to 15054 0120 3 (120 mg strength)
4. The product strength expression (lower right corner) has changed as follows:
 - a. 60 mg to 60 mg/0.2 mL (white font on green background)
 - b. 90 mg to 90 mg/0.3 mL (white font on blue background)
 - c. 120 mg to 120 mg/0.5 mL (white font on purple background)
5. The text in the center of the panel has been modified as follows:

Somatuline® Depot

(lanreotide) Injection ~~60 mg/0.2 mL~~

60 mg/0.2 mL

For deep subcutaneous injection

~~Rx only. For single use only. Sterile. Discard unused portion.~~

~~Warning: Needle Sheath Contains Dry Natural Rubber~~

Somatuline® Depot should be administered by a healthcare professional.

Leave at room temperature for 30 minutes before administration.

CONTENTS: This box contains one (1) pre-filled syringe. ~~Each syringe contains lanreotide acetate corresponding to 60 mg of lanreotide base per 0.2 mL solution, which is the equivalent of 60 mg lanreotide per syringe.~~

Note: for the other two strengths, the product strength expression is 90 mg/0.3 mL and 120 mg/0.5 mL.

Back display panel

6. The label identifier has been moved from the lower left-hand corner to the upper right-hand corner, and has changed as follows:
 - a. 5730.01 to 1031767 (60 mg strength)
 - b. 5740.01 to 1031768 (90 mg strength)
 - c. 5750.01 to 1031764 (120 mg strength)
7. The NDC number has been removed.
8. “Rx only” has been removed.
9. The distributor information has changed as follows:

Distributed by: ~~Tereiea Inc.~~ Ipsen Biopharmaceuticals Inc.
~~Brisbane, CA 94005~~ Basking Ridge, NJ 07920
USA
10. The contact telephone number has changed from 1-866-837-2422 to 1-888-980-2889.

11. The phrase “Protect from light” has been added to the storage conditions description.
12. The USUAL DOSAGE statement has changed from “see enclosed leaflet” to “see prescribing information”.
13. The following statement (b) (4): Each syringe contains lanreotide acetate corresponding to 60 mg of lanreotide base per 0.2 mL solution, which is the equivalent of 60 mg lanreotide per syringe.
Note: this statement (b) (4) for the other two product strengths (90 mg of lanreotide base per 0.3 mL solution, and 120 mg of lanreotide base per 0.5 mL solution).

Side flaps/panels

14. The product strength expression has changed from 60 mg to 60 mg/0.2 mL, from 90 mg to 90 mg/0.3 mL and 120 mg to 120 mg/0.5 mL.
15. The distributor information has changed as follows:
Distributed by: ~~Tereiea Inc.~~ Ipsen Biopharmaceuticals Inc.
Brisbane, CA 94005 Basking Ridge, NJ 07920 USA
16. The company name has changed from “IPSEN Tercica” to “IPSEN”.
17. The expiration date and lot number information have been removed (i.e., now appear on the back display panel instead).
18. The following statement has been removed:
WARNING: NEEDLE SHEATH CONTAINS DRY NATURAL RUBBER.
USE ONLY AS DIRECTED BY YOUR DOCTOR.

Note: these changes to the carton labels are acceptable. Refer to DMEPA reviews dated April 21, June 6 and October 2, 2014, and to CMC review dated August 28, 2014.

Recommendations

An approval letter should issue for this supplement.

Jennifer Johnson	October 24, 2014
Regulatory Project Manager	Date
Pamela Lucarelli	October 27, 2014
Chief, Project Management Staff	Date

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/s/

JENNIFER L JOHNSON
10/27/2014



Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

ICC1400480

Date: October 2, 2014

To: Jennifer Johnson
Division of Metabolism and Endocrinology Products (DMEP),
Office of Drug Evaluation II (ODEII),
CDER

From: Nicholas W. Werner
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
CDRH

I. Issue

The Center for Drug Evaluation and Research (CDER) requested a consult from CDRH in regards to NDA 22074/S004, which is a combination product (sponsored by Ipsen) consisting of a pre-filled syringe that delivers Somatuline Depot. Dr. Jacqueline Ryan conducted a consult on the device component of the product and noted deficiencies that needed to be addressed by the sponsor. The following performance deficiencies were sent to the sponsor:

1. You have not performed any testing to demonstrate that the hazards associated with use of this sharps injury prevention device have been successfully mitigated. For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. Please review CDRH's Guidances, "Medical Devices with Sharps Injury Prevention Features" when evaluating device performance. This guidance can be located on FDA's website at the following location:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>
2. You have not performed any testing to demonstrate that the auto-injector utilized as part of this combination product is safe and effective for its intended use. Please provide performance data to demonstrate through bench testing that your device is safe and effective for its intended use. You should review FDA's Guidance Document "Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products, when developing the necessary bench testing to demonstrate the performance for your device. This Guidance document is located at:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

On October 4, 2011 a response was received from the sponsor in which the aforementioned performance deficiencies were addressed.

II. Deficiency Response Review

First Deficiency Response

In response to the first deficiency, the sponsor indicated that a risk analysis was performed to identify and assess the hazards associated with the use of the proposed injection system with the integrated sharps injury prevention feature.

The sponsor provided a table that lists how the sections of the referenced guidance document were applied to the design of the sharps injury prevention feature. This table can be seen as follows.

Section number	Title	Applicability (A: Applicable N/A: Non Applicable)	Comments
1	Introduction	A	Pre-filled Syringe fitted with a sharp injury prevention features
2	Background	N/A	Drug product application
3	Content & format of un abbreviated 510k submission	N/A	Drug product application
4	Scope	A	Pre-filled Syringe fitted with a sharp injury prevention features
5	Device Design	A	ISO13485 compliant for supplier of the syringe with the needle safety system - REXAM.
5.1	Device design - The user should be able to easily tell whether the sharps injury prevention feature is activated.	A	Activated device visually recognisable from non activated one as needle is retracted and it can be seen through the transparent material. Tested as part of the user simulated study RX24-01
5.2	Device design - Once activated, the sharps injury prevention feature cannot be deactivated and should remain protective through disposal.	A	Bench testing performed such as Override – Design review report RX20-01
5.3	Device Design – Active feature	N/A	Passive system
5.4	Device Design - Needle shield	N/A	See item 5.5
5.5	Device Design – Retractable sharp	A	Simulated user study RX24-01 is verifying full retraction of the needle
5.6	Device Design – Fixed recessed needle	N/A	See item 5.5
5.7	Device Design – coloured features	N/A	Non colored coded
6	Device description	A	Drug product application - Refer to section 3.2.P.7
7	Risk to Health	A	Risk analysis using FMEA tools of the device from a user point of view and a product design point of view has been carried out and rated following the ISO 14971 standard. Report RA-05003201
8	Bench Testing	A	Comparative study with two commercialised products – DSY05003201 01 01 24months Stability studies, Aging tests & stress tests - Design Verification Testing report – RX20-04
8.1	Force to attach detach connection	A	QP 41003 - Needle sheath removal; Finger holder connection; Stacked needle connection
8.2	Force to activate and deactivate the safety feature	A	Single use activation only; Override test ensuring impossible reactivation Design Verification Testing report –RX20-04
8.3	Reaction force generated by the activation mechanism,	A	Design Verification Testing report –RX20-04
8.4	Number of activations to failure	N/A	Single use, disposable device
8.5	Puncture resistance of shield or sheath	A	Crush & Drop testing performed

Section number	Title	Applicability (A: Applicable N/A: Non Applicable)	Comments
			Design Verification Testing report –RX20-04
8.6	Rate of fluid flow simulating extremes of pressure (e.g., the maximum force applied to the piston or maximum flow through an access port)	N/A	Disposable Pre-filled syringe by Ipsen with an unique highly viscous drug semi-solid. Not intended for use with other type of drug product. Refer to section 3.2 P.2 Rheology study
8.7	Accuracy of the dose administrated, if your device has atypical or unusual markings, e.g., inverted syringe markings.	N/A	No marking Full dose delivered in one shot; x3 dose strengths available Part of batch Release testing
8.8	Strength of joints, bonds, connections, hinges, valves, locking mechanisms	A	Needle bond test report – QP 41003 Drop testing & Crush testing - Design Verification Testing report –RX20-04
9	Microbial Ingress Tests	N/A	Single use, Full dose delivered in one shot Stacked needle syringe
10	Simulated Clinical Use Testing	A	Simulated user study report RX24-01 Refer to section 3.2 P.2.7.3 of the drug product application
10.1	Study design	A	Simulated user study report RX24-01
10.2	Evaluator Training	A	Simulated user study report RX24-01
10.3	Report Forms	A	Simulated user study report RX24-01
10.3	Failed Tests	A	Simulated user study report RX24-01
10.4	Sample Size Determination	A	Simulated user study report RX24-01
11	Sterilization	N/A	Drug product application – See section 3.2 P.3.5
12 ²	Biocompatibility	A	Drug product application – See section 3.2.P.2 Material in contact with hand of user are either Food grade material or Class VI USP Design review report RX20-01
13	Labelling		
13.1	Intended Use	N/A	Disposable Pre-filled syringe by Ipsen with an unique highly viscous drug semi-solid. Not intended for use with other type of drug product.
13.2	Directions for Use	A	Refer to proposed Full prescribing information in Section 2.1 Instruction For Use.
13.3	Precautions	N/A	Simulated studies has not shown any limitations for hand size for HCP
13.4	Warnings	N/A	Highly viscous semi-solid drug product with Injection Force comprised between (b) (4)
13.5	Description of the Device	A	Refer to proposed Full prescribing information in Section 2.1 Instruction For Use. Carton labelling
13.6	Accessories	N/A	Ready to use drug product, no accessories

The reports identified within the comments section of the previous table were reviewed to ensure that the information included was adequate to address the associated section of the guidance document. An overview of the relevant reports (including only the relevant sections of each report) can be seen as follows.

DSY-05003201 – Safe 'N Sound 3 in 1 Comparative Study with Substantial Equivalent Devices

This report provided a comparative study of bench testing conducted on the subject syringe with two identified comparative devices. The two devices that the syringe was compared to are the Ultrasafe Passive 0.5mL long Luer Lock and the Arixtra 1.0mL long. The following tests were conducted in this report:

Test & protocol reference	Test acceptance criteria	Test main characteristic
Drop test before use without locker (P002-04)	(b) (4)	
Drop test after use (P003-04)		
Safety system activation (P011-04)		

Test & protocol reference	Test acceptance criteria	Test main characteristic
Crush test after use (P005-04)		(b) (4)
Override test : push on Finger holder (P006-04)		
Override test : push on slider (P007-04)		
Override test : pull on slider (P008-04)		
Override test : pull on tube (P009-04)		

The results indicated that the device performed as well as or better than the other tested devices in all of the tests conducted. The subject device was tested per the Design Verification Testing Report (RX20-04), in which the results can be found in the test overview as provided below.

RX20-04 – 3 in 1 Safety Syringe – Design Verification Testing

This report outlines the design verification tests that were conducted by physically testing the syringe against set specifications as set forth in the Design Verification Tests. Additionally, these tests were done to verify that minor design changes to the device (defined as iterations) did not affect the ability of the device to pass physical tests. The review will focus only on the final iteration of the device and the verification testing done on the final version. The device was tested in a normal and accelerated aging (simulated 3 years) condition. The following tests were conducted:

Test Number	Test description
1	Drop test before use with Cap and Locker
2	Drop test before use with Cap but without Locker
3	Crush test before use with Cap and Locker
4	Activation and reaction forces
5	Drop test after use (safety feature activated)
6	Crush test after use (safety feature activated)
7	Override test by pushing on Plunger (safety feature activated)
8	Override test by pushing on Slider (safety feature activated)

9	Override test by pulling on Slider (safety feature activated)
10	Override test by pulling on Tubing (safety feature activated)
11	Pull test on Finger Holder

The results of these tests can be seen in the following table.

Aging	No aging	Aging
(b) (4)	(b) (4)	
Temperature conditions	Room temp	Room temp
Drop test before activation	(b) (4)	
Drop test before activation without locker	(b) (4)	
Drop test after activation	(b) (4)	
Crush test before activation with locker	(b) (4)	
Crush test after activation	(b) (4)	
Force to override by pushing on plunger rod (b) (4)	(b) (4)	
Force to override by pushing on slider (b) (4)	(b) (4)	
Force to override by pulling on slider (b) (4)	(b) (4)	
Force to override by pulling on tube (b) (4)	(b) (4)	
Safety feature activation force (b) (4)	(b) (4)	
Safety feature reaction force generated by spring	(b) (4)	
Functionality testing	(b) (4)	
Withstand of the finger holder on the plunger rod (b) (4)	(b) (4)	
Force to remove locker (hand user, limited study)	(b) (4)	

It can be seen in the table above, that the device passed all tests set forth in this report. The values not provided were tests only included in the simulated use study.

RX20-01 – Final Design Review

This report is designed to cover the actual User and Functional Requirements against set specifications. This report is a comprehensive review of all requirements for the device and includes the methods utilized for verification, the design output, and an indication if that specific requirement was verified. All requirements were indicated to have been verified.

QP41003 – Performance Qualification of the Manufacture of 3 in 1 Safe’N Sound Rexam Healthcare Syringes for Somatuline Autogel

This report (qualification) was done to show that the industrial manufacturing process utilized by Rexam could allow for a reproducible syringe that is compliant with the specifications set forth by the sponsor (Ipsen). The following production tests were included as part of the qualification:

Sample	Sample manager	Analysis/Test	Test Manager	Acceptance criteria
(b) (4)				

The report indicated that the syringes tested passed all of the production tests.

RX24-01 – 3 In 1 Device Large Scale User Study in the USA

The sponsor also performed a simulated use study utilizing 946 placebo filled syringes with the sharps injury prevention feature. The study included 69 nurses and 17 doctors, with each having previous experience with injectable treatments and each had given at least 5 injections per week. The primary objectives of the study were to establish that:

- The needle safety system consistently works as intended, when used by a variety of health care professionals following the instructions for use; and
- The assembly process is robust and yields syringes with a needle safety system that has a low failure rate across a sufficiently large number of units based on a statistical approach.

Pre-determined Pass/Fail criteria was set forth in the protocol, with a failed device being one that, in the hands of trained user, demonstrated one or more of the failure criteria presented in the following table.

ID	Failure Criterion	Acceptable Occurrence (n/946 devices)	Primary Assessment Method
1	Trained user <i>unable</i> to remove plunger protector	Zero	Observation of trained users
2	Trained user <i>unable</i> to remove needle cap	Zero	Observation of trained users
3	Trained user <i>unable</i> to complete injection	Zero	Observation of trained users
4	Trained user <i>unable</i> to activate safety feature	Zero	Observation of trained users
5	Trained user able to re-expose the needle after the safety feature has been activated (without abuse)	Zero	Observation of trained users
6	Trained user inadvertently activates safety feature prematurely - i.e. before completing injection	Zero	Observation of trained users
7	Plunger breaks during use by trained user	Zero	Observation of trained users / check device after use
8	Finger holder breaks during use by trained user	Zero	Observation of trained users / check device after use
9	Safety feature breaks during use by trained user	Zero	Observation of trained users / check device after use
10	Part of syringe breaks leaving trained user unable to use the syringe	Zero	Observation of trained users / check device after use
11	Safety feature fails to lock out after activation	Zero	Observation of trained users / check device after use

A summary of the results of the simulated use study can be seen in the following table.

Failure Criterion	Observed occurrences (x/946 devices)	95% Adjust Wald confidence interval for failure rate		99% Adjust Wald confidence interval for failure rate	
		Lower limit	Higher limit	Lower limit	Higher limit
Trained user unable to remove plunger protector	0	0.00%	0.35%	0.00%	0.69%
Trained user unable to remove needle cap	0	0.00%	0.35%	0.00%	0.69%
Trained user unable to complete injection	0	0.00%	0.35%	0.00%	0.69%
Trained user unable to activate the safety feature	1	<0,01%	0.66%	<0,01%	1.00%
Trained user able to re-exposed the needle after the safety feature has been activated (without abuse)	0	0.00%	0.35%	0.00%	0.69%
Trained user inadvertently activates safety feature prematurely – i.e. before completing injection	0	0.00%	0.35%	0.00%	0.69%
Plunger breaks during use by trained user	1	<0,01%	0.66%	<0,01%	1.00%
Finger holder breaks during use by trained user	0	0.00%	0.35%	0.00%	0.69%
Safety feature breaks during use by trained user	0	0.00%	0.35%	0.00%	0.69%
Part of syringe breaks leaving trained user enable to use the syringe	0	0.00%	0.35%	0.00%	0.69%
Overall	2	0.00%	0.82%	0%	1.18%

These results indicate a high level of performance and demonstrate the ease of use for the device after appropriate training. This study helps to verify many of the design features of the device as being functional for the end user.

Second Deficiency Response

In response to the second deficiency, the sponsor indicated that this device is not an autoinjector. The device is a manual syringe utilized for injection. The sponsor provided information to show how any applicable sections of the reference guidance document for auto injectors were addressed.

III. Recommendation

Response to First Deficiency

The sponsor provided an adequate response to the first deficiency. The response provided information and testing that was able to demonstrate that the hazards associated with the sharps injury prevention feature have been mitigated. The referenced guidance document was appropriately used and device performance was adequately characterized.

Response to Second Deficiency

The sponsor provided an adequate response to the second deficiency. The device is not an auto injector and therefore the performance data requested in the deficiency is not relevant to this device.

The overall response by the sponsor should be considered acceptable.

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/s/

JENNIFER L JOHNSON

10/06/2014

CDRH device review (in response to 1/20/12 and 7/28/14 consult requests) completed on 10/2/14 and sent to RPM via email on 10/3/14

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 29, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 22074/S-004
Product Name and Strength: Somatuline Depot (lanreotide) injection, 60 mg/0.2 mL,
90 mg/0.3 mL, 120/0.5 mL
Submission Date: July 14, 2014
Applicant/Sponsor Name: Ipsen Biopharmaceuticals, Inc
OSE RCM #: 2014-457-2
DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised pouch and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised pouch and carton labeling is acceptable from a medication error perspective.

¹ Mistry M. Label and Labeling Review for Somatuline (NDA 22074/S-004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Jun 06. 3 p. OSE RCM No.: 2014-475-1.

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/s/

MISHALE P MISTRY
09/29/2014

YELENA L MASLOV
10/02/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

*** This document contains proprietary information that cannot be released to the public***

DATE: April 15, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Jennifer Johnson, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 22074 S004 (Resubmission Dated 1/16/2014)**
Applicant: Ispen Pharma
Drug Constituent: Somatuline Depot (lanreotide 60mg, 90mg, 120mg)
Device Constituent: Prefilled Syringe
Intended Use: the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy (acromegaly)
CDRH CTS Tracking No.: 1400135

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

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CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 22074 S004 (Resubmission Dated 1/16/2014)

Applicant: Ispen Pharma

Drug Constituent: Somatuline Depot (lanreotide 60mg, 90mg, 120mg)

Device Constituent: Prefilled Syringe

Intended Use: the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy (acromegaly)

CDRH Human Factors Involvement History

- 2-Feb-2012: CDRH HF was requested to provide a review a Human Factors protocol contained in the NDA. CDRH provided 6 deficiencies to CDER to transmit the Sponsor.
- 25-July-2012: CDRH HF was requested to provide a review the revised Human Factors protocol contained in the NDA
- 14-Jan-2013: CDRH HF was requested to provide a review of a Human Factors study report contained in the NDA resubmission
- 18-Apr-2013: CDRH HF provided review recommendations to CDER with a request that additional mitigations are needed to effectively reduce use errors and that an additional HF study with 15 HCP and patients combined should be submitted.
- 26-Feb-2014: CDRH HF was requested to provide a review of a Human Factor study report contained in the resubmission of the NDA
- 25-April-2014: CDRH HF provided review recommendation to CDER indicating that the study report was found acceptable.

Overview and Recommendations

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, requested a Human Factors consultative review of the resubmission of NDA 22074 S004 submitted by Ispen Pharma. The resubmission included a Human Factors study report for review.

The product is a single-use, fixed-dose, prefilled syringe with an integrated sharps injury prevention feature. The drug product, Somatuline, once delivered subcutaneously, is indicated for long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.

Previous CDRH HF review of a previously conducted human factors study identified several pattern of use errors associated with the following tasks: verification of dose/expiration date, inserting at 90 degrees angle, and compressing the plunger to the button for full dose. While there was not a pattern of use error seen in identifying the correct injection site, the clinical impact of incorrectly injecting into the upper/middle buttock can be significant i.e. paralysis. Our review of the Sponsor's Instructions for Use indicated that additional information and emphasis should be considered for more adequately communicating to the users and that Ispen should provide results of a supplemental study with 15 representative users.

As a result, Ispen implemented one device related change (adding a label onto the outside of the plunger protector prompting users to remove before use) and several instructions for use related changes, which:

1. Specified that the user has to check that dose and expiration date in three locations (on the actual syringe, the pouch, the box/carton)
2. Specified to insert the needle at 90° angle
3. Included safety information regarding selecting injection site and insert the needle to full depth
4. Increased emphasis on the removal plunger protector, depressing the plunger to the bottom for full dose, maintaining pressure on plunger, allowing needle retract

Subsequent to implementing design, and IFU changes, Ispen conducted a human factors validation study with 15 healthcare providers to evaluate the effectiveness of the changes. The study results showed in comparison with the previous validation study results, only one type of use error was observed with two participants, which was to maintain pressure on the plunger after delivery of dose. However, upon further analysis, the Sponsor indicated that because a full dose was delivered, the needle retraction mechanism was activated even without maintaining pressure on the plunger.

The results of this human factors validation study demonstrated that use errors have been effectively reduced and that the product can be used safely and effectively by the intended users for its intended uses and use environments. This consultant does not have any further concerns.

Appendix 1: Prior CDRH Human Factors Review of Study Report (dated 4/18/2013)

Summary of Study Report

Intended Users/Uses/Use Environments: The proposed product is intended for use by trained users from two user groups: healthcare providers (HCP) and non-professional caregivers (NPC) who have been trained by an HCP. Content of training includes familiarizing product components, reviewing IFU, discussing key steps, demonstrating and practicing product use, and answering questions (Appendix C provides detailed description of training). Treatment frequency is typically monthly or longer as directed by the prescriber. The intended use environment for the product is physician's office or patient's home.

User Interface: The product is a single use 0.5mL prefilled syringe with a sharp injury prevention feature. The product contains lanreotide (somatostatin analog) in 3 alternative fill levels: 60mg/0.2mL, 90mg/0.3mL, or 120mg/0.5mL. Operation of the product includes 3 steps: preparation, administration, and retraction.

Summary of Known Problems and Formative Evaluations: The prefilled syringe has been designed to address known problems associated with needle retraction, injecting viscous drug product, and premature needle activation. Six formative studies were performed during product development phases, and product design and Instructions for Use have been iteratively modified to address observed use-related problems.

Validation Study: The study was conducted with 32 trained users (HCP and NPC), and 32 untrained users (HCP and NPC). Each participant performed a total of 9 injections: the first injection was used to assess safe and effective use, and injections 2-9 were used to assess whether the sharp prevention feature works as intended. Since training is a requirement for use with this product, this reviewer evaluated study results associated with trained study participants. The study results for the first injection are:

- 1 trained participant selected an incorrect injection site (patient's arm versus upper outer quadrant of the buttocks). Participant indicated that she recalled the injection site from training but did not remember if it was the only indicated injection site. According to the sponsor, the worst location is the upper/middle of buttocks (sciatic nerve) then paralysis could result.
- 10 trained participants did not verify the expiration date /dosage on the primary container. However, the root cause analysis was provided with trained and untrained participant identifications combined, so it was not clear which root cause was associated with which participant. According to the Sponsor, these errors have no measurable clinical impact.
- 2 trained participants did not insert the needle at 90 degrees angle. However, the root cause analysis was provided with trained and untrained participant identifications combined, so it was not clear which root cause was associated with which participant. According to the Sponsor, failure to insert the needle at the specified angle can reduce therapeutic duration.
- 1 trained participant did not insert the needle to the full depth. According to the Sponsor, failure to insert the needle to the full depth can reduce therapeutic duration.
- 5 trained participants did not compress the plunger to the button for full dose delivery. However, the root cause analysis was provided with trained and untrained participant identifications combined, so it was not clear which root cause was associated with

which participant. According to the Sponsor, failure to fully compress the plunger can result in underdosing, which has no clinical impact.

- 1 trained participant did not maintain pressure on the plunger while withdrawing the needle, which according to the Sponsor has no clinical impact.

Review Comments:

While the Sponsor concluded that these errors lead to minor acceptable and residual risks, the reviewer believes that the study results identified several pattern of use errors associated with the following tasks: verification of dose/expiration date, inserting at 90 degrees angle, and compressing the plunger to the button for full dose. While there was not a pattern of use error seen in identifying the correct injection site, the clinical impact of incorrectly injecting into the upper/middle buttock can be significant. In reviewing both the product design, and the product labeling, the reviewer believes that further emphasis of these steps in the product labeling and training to reduce the use errors. For example, the proposed IFU does not specify that the user has to check the dose/expiration date on the primary container closure. Also the proposed IFU states (b) (4) inserting the needle at 90 degrees angle. In addition, the IFU should include safety information emphasizing on the importance of selecting the correct injection site, and inserting the needle at full depth.

Deficiencies to be Transmitted to Ispen

Our review of your Human Factors study report identified several pattern of use errors associated with the following tasks: verification of dose/expiration date, inserting at 90 degrees angle, and compressing the plunger to the button for full dose. While there was not a pattern of use error seen in identifying the correct injection site, the clinical impact of incorrectly injecting into the upper/middle buttock can be significant i.e. paralysis. Our review of your Instructions for Use indicated that additional information and emphasis should be considered for more adequately communicating to the users. For example, the proposed IFU does not specify that the user has to check the dose/expiration date on the primary container closure. Also the proposed IFU states (b) (4) inserting the needle at 90 degrees angle. In addition, the IFU should include safety information emphasizing on the importance of selecting the correct injection site, and inserting the needle at full depth. We recommend that you modify your Instructions for Use, and provide us data of a supplemental study with 15 representative users (HCP and NPC) combined.

Appendix 2: Prior CDRH Human Factors Review of Study Protocol (dated 7/2/2012)

Overview and Recommendation

The Applicant seeks FDA's review for a new protocol titled "Simulated-Use Design Validation Testing of Somatuline Depot" (dated July 2, 2012). Overall, the protocol appears adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. This reviewer recommends that the following comments/deficiencies (blue) be transmitted to the Sponsor.

Overall, the protocol appeared adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. Please address the following:

1. You identified to unique user groups: Healthcare providers (HCP), and Non-professional caregivers (NPC) who have been trained by a HCP. You also specified the content and duration of training. However, your protocol was not whether the healthcare provider group will also receive training on the use of the device. It appeared that only the NPC group will receive training. Please clarify and justify that the training level that will be provided in the study is representative of training in realistic use.
2. You reported that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. You also included a user task analysis and along with a use FMEA in the protocol. While both analyses are comprehensive, the clinical impact/consequence was not included such that we are clear on which tasks should be prioritized in the testing. Please add to both analyses some discussions with respect to the clinical impact/consequence for all hazards/potential use errors, and clarify which tasks (critical and essential) will be prioritized in the study. Please note the following:
 - a. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Please ensure that you clearly identify and include all critical and essential tasks associated with safe and effective use of the device. Please note that criteria for determining whether a task has been completed successfully should be defined in advance. We consider task failure as action/lack of action that could lead to clinical harm. Furthermore, use errors that can be corrected should be discussed in detail with respect to how users were able to recognize the potential failures and what steps they took correct themselves and how the design of the device and its labeling influenced the patient's behavior for self-correction.
 - b. Depending on your response on the clinical impact/consequences, we might have clarification on your rationale on the severity rating of the hazards identified in your use FMEA. Please ensure that the severity rating for all hazards corresponds appropriately to the clinical impact/consequences.
3. You indicated that the study design will consist one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. It was not clear why the testing specified that each participant performs 10 injections. Please provide a rationale for the 10 injections, or alternatively, the number of injections that will be evaluated in the study should represent realistic use.

4. You stated that both observational data and subjective evaluations will be collected. It should be noted that the follow-up questions ask the participants whether or not they recall any use errors, close calls, or operational difficulties. It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have been considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that you may observe.
5. It is not clear how you will validate the instructions for use. You should validate the instructions to ensure that the end users will be able to correctly understand and follow them and to assess the extent to which the instructions support safe and effective use of your system by the intended users. If any other elements of labeling (e.g., packaging, inserts) are critical to use, include them in your validation testing as well. You may conduct these assessments in a separate study (with different participants, prior to the device validation study) or include them in your validation testing (following the device validation portion). To assess user understanding of critical messages in the labeling that cannot be assessed through observation of participant behavior, you can ask explicit, detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e. don't make the correct responses obvious) and for this reason, we discourage use of forced-choice responses. The participants should also provide subjective feedback regarding any wording in the labeling they found confusing, misleading or incomplete. Additionally, the clarity of the IFU/DHA should be evaluated with respect to findings on task failures/use errors observed in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

For more information on human factors, you might want to visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of human factors consultants that can assist in conducting a human factors study.

Review Material

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_2f198

Summary of Study Protocol and Reviewer Comments

The product is a single-use 0.5mL prefilled syringe with an integrated sharps injury prevention feature. The product will contain lanreotide in 3 alternative fill levels: 60mg/0.2mL, 90mg/0.3mL, or 120mg/0.5mL.

Figure 1: Device User Interface



Operation of the product requires 3 steps:

1. Preparation: Remove Plunger Protector and Needle Cap.
2. Administration: Insert the needle to its full length perpendicular (90°) to the skin and inject the full dose until the plunger cannot be depressed any further.
3. Retraction: Release pressure on the plunger to allow the sharps injury prevention feature to automatically retract the needle into the Sleeve where it will be locked permanently.

The product has 4 primary states:

1. New and unused;
2. Plunger Protector and Needle Guard removed;
3. Plunger fully depressed; and
4. Needle retracted and locked into Sleeve.

Figure 2: Four Primary States of the Product



The sponsor identified to unique user groups:

- Healthcare providers (HCP), 30 participants
- Non-professional caregivers (NPC) who have been trained by a HCP, 20 participants

The sponsor specified that the training will include:

- the trainer familiarizing the user with the components of the product
- the trainer resent through the instructions for use with the user

- the trainer and the user discussing the steps required for use
- the trainer demonstrating these are the product
- the trainer watching and correcting the user using the product
- the trainer answering any questions that the user may have

However, the protocol was not whether the healthcare provider group will also receive training on the use of the device.

The protocol stated that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. Additionally, the user task analysis and characterization provided detailed discussion on all use related hazards associated with the use of this product. The analysis provided a breakdown of the user interaction into three user performance requirements: perceptual, cognitive, and physical. In addition, a use FMEA was provided, which included this likelihood and severity, along with consequences and prevention control measures. *While both analyses appeared comprehensive, the clinical impact/consequence were not included such that it is to the reviewer which tasks should be prioritized in the testing.*

The study design consisted of one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. *It was not clear to the reviewer why the testing specified that each participant performs 10 injections. It did not appear that 10 injections are realistic use. The Sponsor should be asked to provide a rationale for the 10 injections, or alternatively, the number of injections that will be evaluated in the study should represent realistic use.*

Both observational data and subjective evaluations will be collected. The protocol states that if the safety feature has not been triggered, the Sponsor will verify under a microscope the distance between the end of the syringe and the front face of the plunger rubber stopper to verify the volume of potential drug left. The estimated calculated weight of the drug remaining can therefore be evaluated. Finally a sampling will be performed to verify if no residual drug is left into the syringes. It should be noted that the follow-up questions ask the participants whether not they recall any use errors, close calls, or operational difficulties. *It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that the Sponsor may observe.*

Appendix 3: Previous CDRH Human Factors Review (dated 2/2/2012)

DATE: February 2, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ODE/CDRH
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Reasol Agustin, CDER/DMEPA
Jennifer Johnson, CDER/OND/ODEII/DMEP
SUBJECT: NDA 22074 S-004, Ipsen Pharma (Biomeasure Inc.), Somatuline Depot
Human Factors/Usability Review, GEN1200091

Overview

On 5/4/2011, a complete response letter was issued to Ipsen Pharma with specific request for conducting a Human Factors/usability validation study. The Applicant provided a report titled “3 in 1 Device Large Scale User Study in the US.”

Review Comments and Discussion - User Study Report

The study report focused on providing data that demonstrates acceptable device performance. The study was conducted in March 2009 per Ipsen protocol # EX24-01. This protocol was not submitted for review.

The study recruited 86 HCPs (17 doctors and 69 nurses). All HCPs have experience in performing injections, at least 5 injections per week. All participants were trained. However, there was no analysis of the intended user population for the proposed device. A rationale that the participants recruited for the study are representative the overall population of users for the device was not provided. For a Human Factors/usability validation study, FDA expects that study participants should not be the Applicant’s own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.

It was not clear if the study participants had an opportunity to assess the clarity of the instructions for use and whether or not the Applicant assessed the extent to which the instructions support safe and effective use of the device. These assessments should be included in the validation testing or can be conducted in a separate study. The participants could use the instructions as they perform an actual or simulated procedure or verbally describe what they would do as they read the instructions. Afterward, the Applicant should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.

The study results focused on device performance rather the necessary performance and subjective data that FDA requires in a Human Factors/usability validation study. It appears that there is a number of device robustness/performance issues that should were identified and should be addressed. In addition, as a result of this study, the sponsor identified some potential areas where the device user interface could be further optimized (section 7.2. page 14). The Applicant

should complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.

In addition, on page 11 of the study report, the reviewer notes that in 8 instances, the moderators encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, FDA expects that there will be no test moderator, and the users are expected to use the device on their own. Instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures. The study conclusions indicated improvement in device performance. However, FDA expects that for a Human Factors/usability validation study, the conclusions should be based on how the sponsor performs their evaluation and how the evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

There were device modifications implemented post study and a retest was conducted with employees of Ispen Pharmaceuticals Development Department. This was not found acceptable.

Requests to be transmitted to the Sponsor

1. Please provide a complete analysis of the intended user population for the proposed device and provide a rationale that the participants recruited for the study are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.
2. In the Human Factors/usability validation study, participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.
3. We believe that your retesting participants and testing environments/conditions did not provide a valid representation of actual use. We expect that retesting could be conducted in the same manner as how you would conduct a Human Factors/usability validation study i.e. this testing should involve representative users performing tasks during simulated use/user scenarios that emphasize highest priority user tasks, and include a summary of user subjective assessment and findings with respect to the safety of the use of your device, and assessment of the effectiveness of device modifications in terms of how the final product has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users.
4. Your study data focused on device performance rather the necessary performance and subjective data that we require in a Human Factors/usability validation study. It appears

that there are a number of device robustness/performance issues that should be addressed. In addition, as a result of this study, you identified some potential areas where the device user interface could be further optimized (section 7.2. page 14). FDA recommends that you complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.

5. On page 11 of the study report, we note that in 8 instances, the moderator encouraged or prompt the users to push harder/further. This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Please note that instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures.
6. Your study conclusions indicated improvement in device performance. We expect that for a Human Factors/usability validation study, the conclusions should be based on how your evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

Based on the deficiencies stated above, we do not deem this study adequate to demonstrate that the proposed Somatuline Depot prefilled syringe can be used safely and effectively.

Therefore, we request you perform provide results of a Human Factors/usability validation study following these recommendations as well as those from the original CR Letter dated May 4, 2011. We strongly recommend that you submit your protocol, draft carton and container labeling, and proposed package insert labeling **prior to implementation** to ensure that your methods and the resulting data will be acceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

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/s/

JENNIFER L JOHNSON

04/28/2014

CDRH Human Factors Study and IFU review completed 4/25/14 and received by RPM on 4/28/14

HUMAN FACTOR STUDY, LABEL, AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 21, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology (DMEP)
Application Type and Number: NDA 22074/S-004
Product Name and Strength: Somatuline Depot (lanreotide) injection, 60 mg/0.2 mL,
90 mg/0.3 mL, 120/0.5 mL
Product Type: Combination Product (Drug-Device)
Rx or OTC: Rx
Applicant/Sponsor Name: Ipsen Biopharmaceuticals, Inc
Submission Date: January 17, 2014
OSE RCM #: 2014-457
DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the results of the Human Factor study (HFS), revisions made to the proposed container label, carton, and professional labeling, and instructions for use (IFU) for Somatuline Depot (lanreotide) injection, NDA # 22074/S-004, in response to our previous recommendations provided in OSE reviews #2013-497 (dated May 23, 2013), #2012-1657 (dated September 10, 2012), #2011-4429 (dated April 6, 2012), and #2010-1569 (dated November 16, 2010).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this HUMAN FACTOR STUDY, Label, and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	E

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Based upon the results of the Human Factor Study, the product appears to be safe and effective when used by healthcare professionals (HCPs) who have reviewed the Instructions for Use (IFU), as the study was designed in such a way that HCPs used the device only after reading the IFU.

One type of error occurred during the HF study: two participants failed to maintain pressure on the plunger after delivery of the dose. However, these errors did not have a measurable clinical impact nor affected the safe use of the product because both participants successfully continued to compress the plunger to the bottom and allowed the needle to retract, thus delivering a full dose and placing the device in a safe state. Additionally, DMEPA notes that

there are currently marketed products with similar type of needle protection systems (i.e., single-dose, pre-filled syringe affixed with a retractable needle) such as Arixtra and Lovenox. Because this container closure system is not a *novel* feature being introduced into the market, we expect that HCPs are familiar with this type of device. Nevertheless, DMEPA will provide recommendations in Section 4 to revise the IFU to address the error mentioned above.

In addition to the HF study evaluation, DMEPA analyzed medication errors cases that occurred with the marketed Somatuline Depot. Although medication errors cases reported wrong frequency of drug administration, wrong route of administration, and wrong technique related to the use of the product, a review of the labels and labeling demonstrates that product contains clear information regarding the frequency, route of administration, and injection administration of Somatuline Depot. See Appendix B for additional details regarding medication error cases and our analysis of the cases.

Additionally, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted that the proposed labels and labeling can be improved to highlight the recommendation that the product should be administered by health care professionals and increase the prominence of important information. Furthermore, the Instructions for Use can be improved to reduce repetitive information. Thus, DMEPA will provide its usual recommendations Section 4 to increase readability and prominence of important information on the proposed labels and labeling.

In summary, DMEPA expects that healthcare professionals who have read the Instructions for Use will be able to use Somatuline Depot safely and effectively.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors Study demonstrated that healthcare professionals are able to use the product safely and effectively when used after review of the Instructions for Use.

Additionally, the proposed labels and labeling can be improved to increase the readability and prominence of important information to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this Supplement:

- A. Section 2 Dosage and Administration in Full Prescribing Information:

1. Relocate the statement “Please see enclosed Instructions for Use leaflet for administration of Somatuline Depot” to the beginning of Section 2 Dosage and Administration in Full Prescribing Information and increase its prominence by using bold text. Relocating this statement may increase awareness to the importance of reviewing the Instructions for Use leaflet prior to administration as such actions may promote the safe and effective use of the product by healthcare professionals. Suggested bold text language may include:
“Somatuline Depot should be administered by healthcare professionals. Please see enclosed Instructions for Use leaflet for administration of Somatuline Depot.”

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

Based on this review, DMEPA recommends the following be implemented prior to the approval of this Supplement:

A. Instructions for Use

- a. Remove Step [REDACTED] (b) (4). It’s important that the patient remains as still as possible during the injection” as this information is repeated from Step B6.
- b. Consider revising the statement, [REDACTED] (b) (4) in Step C9 to read:
“Remove the syringe from the injection site WHILE keeping your finger on the plunger rod” in order to clarify the intended meaning of the instruction.

B. Syringe label

- a. Revise the spelling of the word “Manufacturer” on the proposed syringe label for the 120 mg/0.5 mL strength.
- b. Include the following statement regarding package type, “Discard unused portion” as this is important information that may be overlooked by the user if the carton labeling is discarded. Suggested text may include: “For single use only – Discard unused portion” as stated on your carton labeling.

C. Pouch labeling

- a. We recommend the labels and labeling should conform with the United States Pharmacopeia (USP) General Chapter <1> Injections. Revise statements of strength when listed anywhere on the labeling so that strengths are expressed in terms of total strength per total amount of milliliters. For example, revise “60 mg” to “60 mg/0.2 mL” or “60 mg per 0.2 mL”.

- b. Include storage information on the pouch labeling per Guidance: Container Labels and Carton Labeling, April 2013 as this is important information that may be overlooked by the user if the carton labeling is discarded.¹ Suggested text may include: “Storage: Refrigerate at 2°C-8°C (36°F-46°F) in its original package. Protect from light.”
- c. Include route of administration, “For deep subcutaneous injection”, as this is important information that may be overlooked by the user if the carton labeling is discarded.
- d. Include the following statement regarding package type, “Discard unused portion” as this is important information that may be overlooked by the user if the carton labeling is discarded. Suggested text may include: “For single use only – Discard unused portion” as stated on your carton labeling.
- e. Reorient the product barcode and NDC number in the same direction and field of vision as other text on the pouch labeling (i.e., readable without having to turn or rotate the pouch) in accordance with 21 CFR 201.15.
- f. Revise the following statement (b) (4) as this statement is contradictory to information in Section 2 Dosage and Administration of the Full Prescribing Information, where it states that Somatuline Depot should be administered by a healthcare professional. Suggested text may include: “Important: Somatuline Depot should be administered by a healthcare professional. Call 1-(800)-XXX-XXXX and request training that includes delivering a practice injection.”

D. Carton labeling

- a. See C.a.
- b. Relocate the NDC number from the back panel to appear prominently in the top third of the principal display panel in accordance with 21 CFR 207.35(3)(iii).
- c. Consider relocating the following sentence “Each syringe contains lanreotide acetate corresponding to 60 mg of lanreotide base per 0.2 mL solution, which is the equivalent of 60 mg lanreotide per syringe” from the principal display panel to the back panel as this information is repetitive of other information on the principal display panel and creates clutter.

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

- d. In addition to the storage information listed on the back panel, add the following statement, “Protect from light”, per Guidance: Container Labels and Carton Labeling, April 2013 as this is important information listed in Section 16 How Supplied/Storage and Handling of the Full Prescribing Information that may be overlooked by the user.¹
- e. Remove the following statement [REDACTED] (b) (4) [REDACTED] as this statement is contradictory to information in Section 2 Dosage and Administration of the Full Prescribing Information, where it states that Somatuline Depot should be administered by a healthcare professional.
- f. Include the following statement, “Somatuline Depot should be administered by a healthcare professional”, as both the product and Instructions for Use were validated through a Human Factors Study with healthcare professionals as the end users.

If you have further questions or need clarification, please contact Terrolyn Thomas, OSE Project Manager, at 240-402-3981.

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Somatuline Depot that Ipsen Pharmaceuticals, Inc submitted on January 17, 2014.

Table 2. Relevant Product Information for Somatuline Depot	
Active Ingredient	Lanreotide acetate
Indication	Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy
Route of Administration	Deep subcutaneous injection
Dosage Form	Injection
Strength	<ul style="list-style-type: none"> • 60 mg/0.2 mL • 90 mg/0.3 mL • 120/0.5 mL
Dose and Frequency	<ul style="list-style-type: none"> • The recommended dose is 90 mg every 4 weeks for 3 months. • In moderate and severe renal or hepatic impairment, the initial dose is 60 mg every 4 weeks for 3 months. • The dose should be adjusted thereafter based on growth hormone (GH) and/or IGF-1 levels.
How Supplied	<ul style="list-style-type: none"> • Single, sterile, pre-filled, ready-to-use, polypropylene syringe (fitted with an automatic needle guard) fitted with a 20 mm needle covered by a low density polyethylene sheath. • Each pre-filled syringe is sealed in a laminated pouch and packed in a carton.
Storage	<ul style="list-style-type: none"> • Store in a refrigerator at 2 °C to 8 °C (36 °F ° to 46 °F) and protected from light in its original package. • Thirty (30) minutes prior to injection, remove sealed pouch of Somatuline Depot from refrigerator and allow it to come to room temperature.
Container Closure	<ul style="list-style-type: none"> • The three strengths are provided in syringes including a sharps protection system and fitted with a (b) (4) external diameter needle. • The primary packaging consists of a (b) (4) polypropylene syringe, (b) (4) rubber plunger stopper, and (b) (4) stainless-steel needle. • The secondary packaging consists of a needle sheath, sharps protection system, laminated pouch, and cardboard carton.

Table 3 presents a comparative summary between the initial and new container-closure system for Somatuline Depot.

Table 3. Comparative Summary Between Initial and New Container-Closure System			
		Initial System (NDA 22-074)	New System (NDA 22-074, S-004)
Primary Packaging Components	Components	<ul style="list-style-type: none"> • (b) (4) polypropylene syringe • (b) (4) rubber plunger stopper • (b) (4) stainless-steel needle 	<ul style="list-style-type: none"> • (b) (4) polypropylene syringe • (b) (4) rubber plunger stopper • (b) (4) stainless-steel needle
	Syringe Volume	<ul style="list-style-type: none"> • 60 mg, 90 mg dose strength: 0.3 mL • 120 mg dose strength: 0.5 mL 	0.5 mL
	Syringe external shape	Square	Round
	Needle external diameter	<ul style="list-style-type: none"> • 60 mg, 90 mg dose strength: (b) (4) • 120 mg dose strength: (b) (4) 	(b) (4)
Secondary Packaging Components	Components	<ul style="list-style-type: none"> • Needle sheath • Finger –grip • Plunger rod • Cylinder protector (around the plunger rod) • Laminated pouch • Cardboard carton 	<ul style="list-style-type: none"> • Needle sheath • Sharp protection system • Laminated pouch • Cardboard carton
	Needle sheath material	Rubber	Plastic (LDPE)
	Laminated Pouch Material	<ul style="list-style-type: none"> • (b) (4) laminate • Thickness of (b) (4) 	<ul style="list-style-type: none"> • (b) (4) laminate • Thickness of (b) (4)
	Non-Functional Secondary Components	Finger grip, cylinder protector	Sharp protection system components

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

DMEPA previously performed an FDA Adverse Event Reporting System (AERS) to determine medication errors related to the use of this product and have been reported in RCM #2010-1569 (dated August 13, 2010), RCM #2011-4229 (dated April 6, 2012) and RCM #2012-1657 (dated September 10, 2012). Therefore, for this review, we conducted a search of the database (currently known as FAERS) on March 24, 2014 using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.¹

Table 4. FAERS Search Strategy	
Date Range	August 3, 2012 to March 1, 2014
Drug Names	Product Name: Somatuline Depot Product Active Ingredient: lanreotide; lanreotide acetate; lanreotide\lanreotide acetate
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

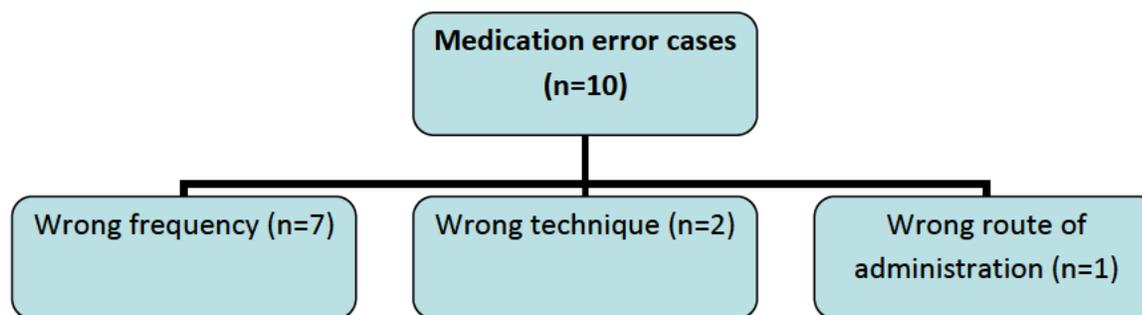
B.2 Results

Our search identified 36 cases, all of which described errors that need further analysis to determine whether they can be attributed to the proposed labels and labeling for Somatuline Depot. Of the 36 identified cases, we excluded 24 cases because they described errors outside of United States where there may be differences in use and/or labeling of the product. Additionally, one case was excluded because according to the patient, no medication error had actually occurred. Following exclusions, 11 medication error cases remained for our detailed analysis. Duplicates were merged into a single case.

Figure 1 provides a stratification of the number of cases included in the review by type of error.

¹ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Figure 1. Somatuline Depot Medication Errors (n=10), categorized by type of error



Wrong frequency of drug administration (n=7)

- Four cases (FAERS Case #9095439 [v1], #9327159 [v2], #9344168/#9556929 [v2], #9893745 [v2]) reported patients being treated with Somatuline 120 mg subcutaneously every 14 days instead of every 28 days. None of these cases provided additional details regarding contributing factors. One case (#9327159) reported occasional diarrhea, stomach pain, and flatulence as a resulting patient outcome. The remaining three cases did not report patient outcomes.
- One case, FAERS Case #9669666 (v2), reported that the patient began treatment with Somatuline 90 mg injected subcutaneously every six weeks. No additional details provided regarding contributing factors or patient outcome as a result of the medication error.
- One case, FAERS Case #9688098 (v1), reported that the patient began treatment with Somatuline 90 mg injected subcutaneously every six to eight weeks. No additional details provided regarding contributing factors or patient outcome as a result of the medication error.
- One case, FAERS Case #9826254 (v2), reported that the patient began treatment with Somatuline 120 mg injected subcutaneously every 28 days, but therapy frequency was later changed to every 21 days. No additional details provided regarding contributing factors or patient outcome as a result of the medication error.

Although we identified seven medication errors reporting wrong frequency of drug administration, a review of the Dosage and Administration section within the Prescribing Information labeling indicates that the labeling contains clear information regarding dosing frequency of Somatuline Depot. As a result, we do not believe further revisions to the labeling are needed at this time given the fact that this product has been marketed since 2007.

Wrong technique (n=2)

- One case, FAERS Case #9485761 (v1), reported that the patient began treatment with Somatuline Depot 120 mg injected every 28 days. The patient's daughter reported that her father had been administering the Somatuline injection incorrectly as he was not paying attention to the needle bevel and has been pinching the skin rather than stretching it out when inserting the needle. As a result, the patient developed scar tissue at injection site (buttocks). It was also reported that patient had difficulty performing Somatuline injections due to his skin being so tough, requiring him to apply additional force than typically required.

Per proposed Prescribing Information and Instructions for Use labeling, we note that it is recommended that this product should no longer be administered by patients and should only be administered by HCPs, which may mitigate the risk of errors related to wrong technique of injection.

- One case, FAERS Case #9792220 (v2), reported that the patient began treatment with Somatuline 120 mg injected subcutaneously every 28 days. On one occasion, approximately three months following initiation of therapy, a nurse administered Somatuline Depot injection in the patient's back, above her buttocks, in the hip. The patient experienced bumps and painful "big balls", located at the injection site, which lasted for several months. On a separate occasion, the patient self-administered Somatuline Depot injection under the surface of the skin, rather than as a deep subcutaneous injection, which resulted in an underdose as the patient was unable to administer the entire dose. No additional details provided regarding contributing factors to the medication errors.

In this case, it appears the health care professional attempted to alternate injection sites, which resulted in an injection administered in an incorrect location in one instance. However, our analysis indicates that the proposed Instructions for Use provide clear written instructions, along with diagrams, to demonstrate appropriate injection sites. With regard to the second situation within the reported case, per proposed Prescribing Information and Instructions for Use labeling, we note that it is recommended that this product should no longer be administered by patients and should only be administered by HCPs, which may mitigate the risk of errors related to wrong technique of injection and any subsequent underdosing that may result from the error.

Wrong route of administration (n=1)

- One case, FAERS Case #9528560 (v1), reported that the patient began treatment with Somatuline 60 mg injected intramuscularly every 28 days. No additional details provided regarding contributing factors or patient outcome as a result of the medication error.

Although we identified one medication error reporting wrong route of administration, a review of the Dosage and Administration section within the Prescribing Information labeling indicates that the labeling as well as the proposed Instructions for Use contain clear information regarding route of administration for Somatuline Depot. As a result, we do not believe further revisions to the labeling are needed at this time.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Table 5. Identified FAERS Case Numbers and Corresponding Manufacturer Control Numbers Summarized in Review		
FAERS Case Number	FAERS Case Version	Manufacturer Control Number
9095439	1	2013-0276
9327159	2	2013-0684
9344168, 9556929	2	2013-2423
9485761	1	2013-3273
9528560	1	2011-4287
9669666	2	2013-4802
9688098	1	2013-4513
9792220	2	2013-4524
9826254	2	2014-0155
9893745	2	2014-0769

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched an internal FDA database on March 24, 2014 using the terms, Somatuline to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA previously reviewed the Human Factor Study protocol and results, proposed container label, carton and professional labeling, and Instructions for Use in the following reviews:

- OSE review #2013-497 on May 23, 2013
- OSE review #2012-1657 on September 10, 2012
- OSE review #2011-4429 on April 6, 2012
- OSE review #2010-1569 on November 16, 2010

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

The Human Factor Study Results and IFU submitted on January 17, 2014 were evaluated. Below is a brief overview of the study objectives, descriptions of the study participants, study design, data collection, and data analysis.

Study Objective:

Evaluate the changes (to both the device and the Instructions for Use [IFU]) that were made following the validation study, submitted in December 2012, to demonstrate that the hazards associated with the use of the product have been successfully controlled, and new hazards have not been introduced, such that the product is reasonably safe and effective for the intended users, uses, and use environment.

Study Participants:

Sixteen (16) participants were enrolled in the study. All participants were healthcare providers (HCPs).

Training and Test Sessions:

Participants received the prefilled syringe with integrated sharps injury prevention feature, the IFU, the outer packaging (the box), the inner packaging (the pouch) and the drug facts information. Participants were asked to read the IFU but received no other training from the moderator prior to their initial use of the device. Participants performed one injection each, in on-one-on testing sessions lasting up to 30 minutes each.

Data Collection:

The study collected both empirical and qualitative data sufficient and appropriate to facilitate identification and understanding of the root causes of all use events, including use errors, near misses, and operational difficulties.

Empirical data: Participants were given an opportunity to use the product independently and in a manner that was as realistic as possible without guidance, coaching, praise, or critique from the Moderator. Data, such as successful or failed performance of key tasks, was measured directly. The Moderator observed participant behavior during the test to assess participants' adherence to protocol and proper technique, and to assess and understand the nature of any errors or problems that occurred.

Qualitative data: The Moderator asked open-ended questions of participants at the end of the study, such as, "What was your experience like of using the product?" "Did you have any difficulty using this product? [If so] can you tell me about that?"

Data Analysis:

The analysis included user performance failures, where failure of a task is defined as an action, lack of action, close call, or operational difficulty that could lead to clinical harm. In addition, study results included successes and failures for all essential and critical tasks.

Each instance of task failure or overall scenario failure was evaluated to determine its cause. In addition, the evaluation included subjective assessments following the failure concerning the cause of the failure from the perspective of the participants involved.

D.2 Study Results

Task	Prior Study Results	Current Study Results
1. Choose injection site The revised IFU emphasizes the importance of selecting the correct injection site by the addition of text and the addition of markers (circles labeled "OK") on other images in the IFU.	All of the untrained HCPs (17/17, 100%) selected the correct injection site.	All of the untrained HCPs (16/16, 100%) selected the correct injection site.
2. Verify dose/date The revised IFU indicates to check the date/dosage in all 3 potential locations. Success criteria were defined as checking the dose/date in <i>one</i> of the 3 possible locations.	All of the untrained HCPs (14/14, 100%) checked the dose/date in at least one location.	All of the untrained HCPs (16/16, 100%) checked the dose/date in at least one location.
3. Twist and pull to remove plunger protector The revised IFU emphasizes the step of removing the plunger protector and there is now a sticker on the actual device further emphasizing this information.	Most of the untrained HCPs (16/18, 89%) removed the plunger protector.	All of the untrained HCPs (16/16, 100%) removed the plunger protector.
4. Insert needle at 90 degrees and penetrate to full length of needle The revised IFU specifies to insert the needle at a 90 degree angle and includes 2 additional images: one new image shows the orientation of the patient and the 2nd shows an example of inserting the needle incorrectly at an acute angle. The revised IFU emphasizes the importance of inserting the needle at full depth and includes an image showing an example of not inserting to full depth.	All of the untrained HCPs (18/18, 100%) inserted the needle at 90 degrees. All of the untrained HCPs (17/17, 100%) penetrated to the full length of the needle.	All of the untrained HCPs (16/16, 100%) inserted the needle at 90 degrees. All of the untrained HCPs (16/16, 100%) penetrated to the full length of the needle.

Task	Prior Study Results	Current Study Results
<p>5. Continue compressing plunger to bottom, maintain pressure on plunger, and allow the needle to retract</p> <p>The revised IFU emphasizes compressing the plunger to the bottom to inject all of the medication and was deemed successful in its improvements. The revised IFU also emphasizes the importance of maintaining pressure on the plunger upon completion of the dose delivery in order to keep the needle extended until the needle is removed from the patient’s body. The revised IFU further emphasizes retracting the needle.</p>	<p>Most of the untrained HCPs (15/18, 83%) compressed the plunger to the bottom.</p> <p>Many of the untrained HCPs (12/17, 65%) maintained pressure on the plunger.</p> <p>Most of the untrained HCPs (16/18, 89%) allowed the needle to retract.</p>	<p>All of the untrained HCPs (16/16, 100%) compressed the plunger to the bottom.</p> <p>Most of the untrained HCPs (14/16, 88%) maintained pressure on the plunger.*</p> <p>All of the untrained HCPs (16/16, 100%) allowed the needle to retract.</p>

*** The use errors related to maintaining pressure on the plunger are detailed below:**

1. One HCP indicated that she did not realize one needed to keep holding down on the plunger as one removed the needle from the patient. With the intramuscular injection devices she is accustomed to, one pulls out the needle and slides the safety mechanism at the same time. She therefore thought engaging this safety mechanism would be a simultaneous action as well. She was not expecting it to be so rapid (HCP 06).
2. One HCP reported that she felt the needle retraction was “pretty standard” but that she did not know what to expect or how the safety mechanism would feel using it for the first time (HCP 06).

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Somatuline Depot labels and labeling submitted by Ipsen Pharmaceutical, Inc on January 17, 2014.

- Syringe label
- Plunger Protector label
- Pouch labeling
- Carton labeling
- Prescribing Information
- Instructions for Use

E.2 Label and Labeling Images

Syringe Label



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Human Factor Study, Label, Labeling and Packaging Review

Date: May 23, 2013

Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Somatuline Depot (Lanreotide) Injection, 60 mg/0.2 mL,
90 mg/0.3 mL, and 120 mg/0.5 mL

Application Type/Number: NDA 022074/S-004

Applicant/sponsor: Ipsen Pharma

OSE RCM #: 2013-497

*** This document contains proprietary and confidential information that should not be released to the public.***

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DRAFT

1 INTRODUCTION

This review evaluates the results of the Human Factor Study (HFS) for Somatuline Depot (Lanreotide) Injection and revisions made to the container label, carton and professional labeling, and instructions for use (IFU) in response to our previous recommendations provided in OSE reviews #2012-1657 and #2011-4229, dated September 10, 2012 and April 6, 2012 respectively. Preliminary comments regarding the HFS protocol were communicated to the Applicant on September 17, 2012.

1.1 REGULATORY HISTORY

Somatuline Depot (Lanreotide) Injection was originally approved as prefilled syringes containing 60 mg, 90 mg, and 120 mg on August 30, 2007. On April 29, 2010, the Applicant submitted a prior approval supplement (S-004) that introduced changes to the drug product container closure. The Applicant has amended the labels and labeling to describe these revisions. After a series of Compete Responses due to concerns regarding the safe and effective use of the proposed device and subsequent review and requested revisions of the human factors study protocol, the Applicant resubmitted the supplement with label and labeling changes in addition to the results of the Human Factor Study conducted on December 13, 2012.

1.2 PRODUCT INFORMATION

- Active Ingredient: Lanreotide Acetate
- Indication of Use: Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- Route of administration: Deep subcutaneous injection
- Dosage form: Injection
- Strength: 60 mg/0.2 mL, 90 mg/0.3 mL, 120 mg/0.5 mL
- Dose: The recommended dose is 90 mg every 4 weeks for 3 months. For moderate and severe renal and hepatic impairment the initial dose is 60 mg every 4 weeks for 3 months for moderate and severe renal and hepatic impairment. The dose should be adjusted thereafter based on growth hormone (GH) and/or IGF-1 levels.
- How Supplied: Sterile, single-use pre-filled syringes fitted with a 20 mm needle covered by a low density polyethylene sheath.
- Storage: Store in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package
- Container and Closure systems: The three strengths are provided in syringes including a sharp protection system and fitted with a (b) (4) external diameter needle. The primary packaging consists of a (b) (4) polypropylene syringe, a (b) (4) plunger stopper and a (b) (4) stainless-steel needle. The secondary packaging consists of a needle sheath, a sharp protection system, a laminated pouch, and a cardboard carton.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted January 25, 2013 (Appendix B)
- Carton Labeling submitted January 25, 2013 (Appendix C)
- Professional Labeling submitted January 25, 2013
- Instructions for Use submitted January 25, 2013 (Appendix D)

Additionally, DMEPA ensured the recommendations pertaining to the HF Study Protocol and labels and labeling for Somatuline Depot in OSE Review #2012-1657, were implemented.

2.2 HUMAN FACTOR STUDY DESIGN

The Human Factor Study Results and IFU submitted December 21, 2012 were also evaluated. Below is a brief overview of the study objectives, descriptions of the study participants, study design and data analysis.

Study Objectives:

The purpose of this study was to conduct a Simulated-Use Test to:

1. Demonstrate that the hazards associated with the use of the product have been successfully controlled such that the product is reasonably safe and effective for the intended users, uses, and use environments.
2. Demonstrate that the sharps injury prevention feature with the latest modification meets the relevant guidance for error-free performance.

Study Participants:

65 participants (49 Health-care providers (HCP) and 16 non-professional caregivers (NPC))

- A. HCP n=16, trained
- B. NPC n=16, trained
- C. HCP n=15, untrained, optional use of IFU
- D. HCP n=18, untrained, required use of IFU

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Study Design: Training and Test sessions

1. Training included introduction to the product components, reading through IFU, discussion of key steps for use of the product, trainer demonstration of appropriate injection of the product, user demonstrating they can use the product (2 trials) with trainer watching and trainer feedback on the participant use.
2. Test sessions were performed after a one-week interval from the training to simulate real-life practice. Participants performed up to a total of 9 injections each, lasted up to 90 minutes.

Data Analysis:

The study collected both empirical and qualitative data sufficient and appropriate to facilitate identification and understanding of the root causes of all use events, including use errors, near misses and operational difficulties.

All the critical and essential tasks (outlined in Appendix D) were evaluated to ensure that the product is reasonably safe and effective for the intended users, uses, and use environments.

3 MEDICATION ERROR RISK ASSESSMENT

In this supplement, the Applicant is proposing changes to the drug substance and drug product manufacturing process. In addition, they are also proposing changes to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. The Applicant submitted the revised label and labeling and IFU based on our previous recommendations, along with the results from the Human Factor Study. The revised container label, carton and insert labeling adequately addressed our concerns from a medication error perspective, thus the proposed container label, carton and insert labeling are acceptable.

The HFS results demonstrate failures in multiple tasks varying from low to high priority and resulting in minimal to higher clinical impact. The following tasks were considered failures because one or more than one participant failed to complete the task with success, as defined in the protocol. However, the failures noted are not new risks but risks that exist with the current device.

- Choosing an injection site: One trained HCP failed this step because she injected into the subcutaneous area of the arm. She further clarified that she recalled injecting in the upper outer quadrants of the buttocks in the training but she believed that she could inject into the subcutaneous tissue of the arm, thigh or buttocks as per patient preference.
- Remove PI and IFU: Two untrained HCP failed to remove all contents in the box. One participant did remove the IFU and the other participant did not remove either the IFU or the PI. The second participant was able to perform all the critical tasks without reading the IFU and only by relying on the device for proper use.

- Verify dose/date on primary container: 16 trained and untrained HCP and NCP failed this step. Upon questioning, most participants checked the date and dosage on the box or pouch but not on the primary container.
- Rapidly insert needle at 90 degrees (perpendicular): Two trained and one untrained participant failed this step. Two participants believed that the 90 degree angle meant a 45 degree angle. The third participant believed that she thought she performed in correctly.

Failures were noted in 3 critical tasks, removal of the plunger protector, compression of the plunger, allowing the needle to retract. Failure to follow these critical tasks may result in improper dose delivery, specifically underdose, or an accidental needle stick. These failures reveal that the instructions for use (IFU) may still require further clarification or revisions to the actual device design may be needed. A description of the critical task failures noted in the HF study appear below;

1. Twist and Pull to remove plunger protector:
2 untrained HCP who were required to read the IFU failed to remove the plunger protector prior to injection. One participant noted that it looked like the plunger protector was supposed to be there. The second participant removed the plunger protector when she realized the needle was not retracting. Failure to remove the plunger protector prior to injection may not allow the delivery of the full dose of the medication nor allow the needle to retract, resulting in underdose and accidental needle stick, respectively.
2. Continue compressing plunger to bottom:
5 trained and 5 untrained HCP participants failed to compress the plunger to bottom meaning the full dose was not delivered. Eight participants thought they had compressed the plunger all the way to the bottom. Two participants had previously failed to remove the plunger protector (see bullet above). One participant injected less than 85% of the medication and recognized she failed to inject all the medication immediately. The other seven participants injected at least 95% of the medication. Failure to compress the plunger to the bottom prevents the delivery of the full dose of the medication or may prevent the needle from retracting, resulting in underdose and accidental needle stick, respectively.
3. Allow needle to retract:
3 untrained HCP failed to engage the safety mechanism which may result in an accidental needle stick. All three participants noted that were unaware that the device had a needle retraction mechanism. One of these participants had failed to remove the plunger protector. The Applicant acknowledged that the IFU and the visual design of the device fail to convey that the device contains a needle retraction mechanism.

Failures 1 and 3, described above, occurred in the study arm that relied solely on the IFU to perform the assigned tasks. The Applicant concluded that these tasks are not problematic because it only occurred in a limited number of participants and all were

untrained participants. Thus they concluded that the risk is limited because all participants will be trained. However, we do not agree with their rationale because there may be times when a healthcare provider or patient may not receive training or decline training because they have used the device previously especially since the visual design of the device fails to convey the difference this device offers over the currently marketed device. Failure to perform these critical tasks correctly negates the addition of the sharps protection system. The primary reason for this device redesign was to help prevent needle stick injury after use.

We note that the proposed plunger protector appears to be part of the syringe, and it is also possible to depress the syringe plunger with the plunger protector in place. As such it may be difficult for the user to identify that the plunger protector needs to be removed prior to administration of the injection. We recommend adding a statement or a marking on the plunger protector that prompts the user to remove it prior to use. Alternately the plunger protector can be redesigned such that the plunger cannot be reached without the removal of the plunger protector (as seen in the current design of the marketed product).

Failure 2 occurred in both trained and untrained study groups. The Applicant stated that this would result in a single missed dose with no measurable clinical impact. However, we do not agree with their rationale because 8 of the 10 participants thought that they compressed the plunger all the way to bottom which means that this can be a repeated event, resulting in underdose each time the patient injected the medication. In addition, the Applicant stated that the medication is thicker and harder to push than expected which may have resulted in this failure. We recommend adding a statement in the IFU to emphasize that that medication may be thicker and thus harder to push and that pressure should be maintained to ensure that the entire content of the syringe is administered.

4 CONCLUSIONS

We find the revised container label, carton and professional labeling adequately addresses our concerns from a medication error perspective. However, the instructions for use (IFU) require additional revisions prior to approval of this supplement to address critical failures demonstrated in the Human Factors Study. Additionally we also propose changes to the plunger protector design to mitigate some of the risks that were identified in the HFS. We provide recommendations in Section 5.

5 RECOMMENDATIONS

1. Instruction for Use

We recommend revising the IFU to increase the importance of the following critical tasks:

1. Removal of the plunger and maintaining pressure on the plunger in order to activate needle retraction. We request you increase the emphasis of this task by bolding this step or adding a statement similar to C1 of the IFU (b) (4) important (b) (4) ...” This will act as a reminder to the end users to make sure that the step was done correctly.
2. Continue compressing plunger to bottom. We request you increase in the emphasis of this task by bolding the statement “The medication is

thicker and harder to push than you might expect” and relocate this statement so that it is presented as a new paragraph in C8 of the IFU.

3. Allow needle to retract. We request you increase the emphasis of this task by bolding the statement “If needle does not retract, push plunger again to engage safety mechanism” located in C10 of the IFU.

2. Product Design

1. We note that the proposed plunger protector appears to be part of the syringe, and the plunger can be depressed with the plunger protector in place. As such it may be difficult for the user to identify that the plunger protector needs to be removed prior to administration of the injection. We recommend adding a statement or a marking on the plunger protector that prompts the user to remove it prior to use. Alternately the plunger protector can be redesigned such that the plunger cannot be reached without the removal of the plunger protector (as seen in the current design of the marketed product).
2. Repeat the Human Factor Study incorporating our recommendations above with untrained participants (HCP and NCP). These participants should be provided the IFU and proceed with performing the tasks without assistance. This will help determine if the revision to the plunger protector design and the IFU mitigated the risks identified in your study.

If you have further questions or need clarifications, please contact Ermias Zerislassie, OSE Regulatory Project Manager, at 301-796-0097.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

/s/

LUBNA A MERCHANT
05/23/2013

CAROL A HOLQUIST
05/23/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: April 18, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Jennifer Johnson, Regulator Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: NDA 22074/S-004, Ispen Pharma, Somatuline Depot (lanreotide) injection, 60mg, 90mg, 120mg (CTS: ICC 1300020/CON131145)

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

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CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 22074/S-004

Applicant: Ispen Pharma

Drug Constituent: Somatuline Depot (lanreotide) Injection, 60mg, 90mg, and 120mg for treatment of excess growth hormone secretion (acromegaly)

Device Constituent: prefilled syringe

CDRH Human Factors Involvement History

- 14-Jan-2013: CDRH HF was requested to provide a review of the Human Factors study report contained in the NDA resubmission
- 25-July-2012: CDRH HF was requested to provide a review the revised Human Factors protocol contained in the NDA
- 2-Feb-2012: CDRH HF was requested to provide a review a Human Factors protocol contained in the NDA. CDRH provided 6 deficiencies to CDER to transmit the Sponsor.

Overview and Recommendations

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, requested a Human Factors consultative review of the resubmission of NDA 22074 S004 submitted by Ispen Pharma. The resubmission included a Human Factors study report and use-related risk analysis for review.

The product is a single-use, fixed-dose, prefilled syringe with an integrated sharps injury prevention feature. The drug product, Somatuline, once delivered subcutaneously, is indicated for long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.

We have identified one deficiency that should be transmitted to Ispen Pharma:

Our review of your Human Factors study report identified several pattern of use errors associated with the following tasks: verification of dose/expiration date, inserting at 90 degrees angle, and compressing the plunger to the button for full dose. While there was not a pattern of use error seen in identifying the correct injection site, the clinical impact of incorrectly injecting into the upper/middle buttock can be significant i.e. paralysis. Our review of your Instructions for Use indicated that additional information and emphasis should be considered for more adequately communicating to the users. For example, the proposed IFU does not specify that the user has to check the dose/expiration date on the primary container closure. Also the proposed IFU states to (b) (4) rather inserting the needle at 90 degrees angle. In addition, the IFU should include safety information emphasizing on the importance of selecting the correct injection site, and inserting the needle at full depth. We recommend that you modify your Instructions for Use, and provide us data of a supplemental study with 15 representative users (HCP and NPC) combined.

Review Material

Hardcopy

Summary of Study Report and Reviewer Comments

Intended Users/Uses/Use Environments: The proposed product is intended for use by trained users from two user groups: healthcare providers (HCP) and non-professional caregivers (NPC) who have been trained by an HCP. Content of training includes familiarizing product components, reviewing IFU, discussing key steps, demonstrating and practicing product use, and answering questions (Appendix C provides detailed description of training). Treatment frequency is typically monthly or longer as directed by the prescriber. The intended use environment for the product is physician's office or patient's home.

User Interface: The product is a single use 0.5mL prefilled syringe with a sharp injury prevention feature. The product contains lanreotide (somatostatin analogue) in 3 alternative fill levels: 60mg/0.2mL, 90mg/0.3mL, or 120mg/0.5mL. Operation of the product includes 3 steps: preparation, administration, and retraction.

Summary of Known Problems and Formative Evaluations: The prefilled syringe has been designed to address known problems associated with needle retraction, injecting viscous drug product, and premature needle activation. Six formative studies were performed during product development phases, and product design and Instructions for Use have been iteratively modified to address observed use-related problems.

Validation Study: The study was conducted with 32 trained users (HCP and NPC), and 32 untrained users (HCP and NPC). Each participant performed a total of 9 injections: the first injection was used to assess safe and effective use, and injections 2-9 were used to assess whether the sharp prevention feature works as intended. Since training is a requirement for use with this product, this reviewer evaluated study results associated with trained study participants. The study results for the first injection are:

- 1 trained participant selected an incorrect injection site (patient's arm versus upper outer quadrant of the buttocks). Participant indicated that she recalled the injection site from training but did not remember if it was the only indicated injection site. According to the sponsor, the worst location is the upper/middle of buttocks (sciatic nerve) then paralysis could result.
- 10 trained participants did not verify the expiration date /dosage on the primary container. However, the root cause analysis was provided with trained and untrained participant identifications combined, so it was not clear which root cause was associated with which participant. According to the Sponsor, these errors have no measurable clinical impact.
- 2 trained participants did not insert the needle at 90 degrees angle. However, the root cause analysis was provided with trained and untrained participant identifications combined, so it was not clear which root cause was associated with which participant. According to the Sponsor, failure to insert the needle at the specified angle can reduce therapeutic duration.
- 1 trained participant did not insert the needle to the full depth. According to the Sponsor, failure to insert the needle to the full depth can reduce therapeutic duration.
- 5 trained participants did not compress the plunger to the button for full dose delivery. However, the root cause analysis was provided with trained and untrained participant identifications combined, so it was not clear which root cause was associated with

which participant. According to the Sponsor, failure to fully compress the plunger can result in underdosing, which has no clinical impact.

- 1 trained participants did not maintain pressure on the plunger while withdrawing the needle, which according to the Sponsor has no clinical impact.

Review Comments:

While the Sponsor concluded that these errors lead to minor acceptable and residual risks, the reviewer believes that the study results identified several pattern of use errors associated with the following tasks: verification of dose/expiration date, inserting at 90 degrees angle, and compressing the plunger to the button for full dose. While there was not a pattern of use error seen in identifying the correct injection site, the clinical impact of incorrectly injecting into the upper/middle buttock can be significant. In reviewing both the product design, and the product labeling, the reviewer believes that further emphasis of these steps in the product labeling and training to reduce the use errors. For example, the proposed IFU does not specify that the user has to check the dose/expiration date on the primary container closure. Also the proposed IFU states to [REDACTED] ^{(b) (4)} rather inserting the needle at 90 degrees angle. In addition, the IFU should include safety information emphasizing on the importance of selecting the correct injection site, and inserting the needle at full depth.

Appendix 1: Prior CDRH Human Factors Review of Study Protocol (dated July 2, 2012)

Overview and Recommendation

The Applicant seeks FDA's review for the a new protocol titled "Simulated-Use Design Validation Testing of Somatuline Depot" (dated July 2, 2012). Overall, the protocol appears adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. This reviewer recommends that the following comments/deficiencies (blue) be transmitted to the Sponsor.

Overall, the protocol appeared adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. Please address the following:

1. You identified to unique user groups: Healthcare providers (HCP), and Non-professional caregivers (NPC) who have been trained by a HCP. You also specified the content and duration of training. However, your protocol was not whether the healthcare provider group will also receive training on the use of the device. It appeared that only the NPC group will receive training. Please clarify and justify that the training level that will be provided in the study is representative of training in realistic use.
2. You reported that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. You also included a user task analysis and along with a use FMEA in the protocol. While both analyses are comprehensive, the clinical impact/consequence were not included such that we are clear on which tasks should be prioritized in the testing. Please add to both analyses some discussions with respect to the clinical impact/consequence for all hazards/potential use errors, and clarify which tasks (critical and essential) will be prioritized in the study. Please note the following:
 - a. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Please ensure that you clearly identify and include all critical and essential tasks associated with safe and effective use of the device. Please note that criteria for determining whether a task has been completed successfully should be defined in advance. We consider task failure as action/lack of action that could lead to clinical harm. Furthermore, use errors that can be corrected should be discussed in detail with respect to how users were able to recognize the potential failures and what steps they took correct themselves and how the design of the device and its labeling influenced the patient's behavior for self-correction.
 - b. Depending on your response on the clinical impact/consequences, we might have clarification on your rationale on the severity rating of the hazards identified in your use FMEA. Please ensure that the severity rating for all hazards corresponds appropriately to the clinical impact/consequences.
3. You indicated that the study design will consist one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. It was not clear why the testing specified that each participant performs 10 injections. Please provide a rationale for the 10 injections, or

alternatively, the number of injections that will be evaluated in the study should represent realistic use.

4. You stated that both observational data and subjective evaluations will be collected. It should be noted that the follow-up questions ask the participants whether not they recall any use errors, close calls, or operational difficulties. It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that you may observe.
5. It is not clear how you will validate the instructions for use. You should validate the instructions to ensure that the end users will be able to correctly understand and follow them and to assess the extent to which the instructions support safe and effective use of your system by the intended users. If any other elements of labeling (e.g., packaging, inserts) are critical to use, include them in your validation testing as well. You may conduct these assessments in a separate study (with different participants, prior to the device validation study) or include them in your validation testing (following the device validation portion). To assess user understanding of critical messages in the labeling that can not be assessed through observation of participant behavior, you can ask explicit, detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e. don't make the correct responses obvious) and for this reason, we discourage use of forced-choice responses. The participants should also provide subjective feedback regarding any wording in the labeling they found confusing, misleading or incomplete. Additionally, the clarity of the IFU/DHA should be evaluated with respect to findings on task failures/use errors observed in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

For more information on human factors, you might want to visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of human factors consultants that can assist in conducting a human factors study.

Review Material

Summary of Study Protocol and Reviewer Comments

The product is a single-use 0.5mL prefilled syringe with an integrated sharps injury prevention feature. The product will contain lanreotide in 3 alternative fill levels: 60mg/0.2mL, 90mg/0.3mL, or 120mg/0.5mL.

Figure 1: Device User Interface



Operation of the product requires 3 steps:

1. Preparation: Remove Plunger Protector and Needle Cap.
2. Administration: Insert the needle to its full length perpendicular (90°) to the skin and inject the full dose until the plunger cannot be depressed any further.
3. Retraction: Release pressure on the plunger to allow the sharps injury prevention feature to automatically retract the needle into the Sleeve where it will be locked permanently.

The product has 4 primary states:

1. New and unused;
2. Plunger Protector and Needle Guard removed;
3. Plunger fully depressed; and
4. Needle retracted and locked into Sleeve.

Figure 2: Four Primary States of the Product



The sponsor identified to unique user groups:

- Healthcare providers (HCP), 30 participants

- Non-professional caregivers (NPC) who have been trained by a HCP, 20 participants

The sponsor specified that the training will include:

- the trainer familiarizing the user with the components of the product
- the trainer resent through the instructions for use with the user
- the trainer and the user discussing the steps required for use
- the trainer demonstrating these are the product
- the trainer watching and correcting the user using the product
- the trainer answering any questions that the user may have

However, the protocol was not whether the healthcare provider group will also receive training on the use of the device.

The protocol stated that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. Additionally, the user task analysis and characterization provided detailed discussion on all use related hazards associated with the use of this product. The analysis provided a breakdown of the user interaction into three user performance requirements: perceptual, cognitive, and physical. In addition, a use FMEA was provided, which included this likelihood and severity, along with consequences and prevention control measures. *While both analyses appeared comprehensive, the clinical impact/consequence were not included such that it is to the reviewer which tasks should be prioritized in the testing.*

The study design consisted of one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. *It was not clear to the reviewer why the testing specified that each participant performs 10 injections. It did not appear that 10 injections are realistic use. The Sponsor should be asked to provide a rationale for the 10 injections, or alternatively, the number of injections that will be evaluated in the study should represent realistic use.*

Both observational data and subjective evaluations will be collected. The protocol states that if the safety feature has not been triggered, the Sponsor will verify under a microscope the distance between the end of the syringe and the front face of the plunger rubber stopper to verify the volume of potential drug left. The estimated calculated weight of the drug remaining can therefore be evaluated. Finally a sampling will be performed to verify if no residual drug is left into the syringes. It should be noted that the follow-up questions ask the participants whether not they recall any use errors, close calls, or operational difficulties. *It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that the Sponsor may observe.*

Appendix 2: Previous CDRH Human Factors Review

DATE: February 2, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ODE/CDRH
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Reasol Agustin, CDER/DMEPA
Jennifer Johnson, CDER/OND/ODEII/DMEP
SUBJECT: NDA 22074 S-004, Ipsen Pharma (Biomeasure Inc.), Somatuline Depot
Human Factors/Usability Review, GEN1200091

Overview

On 5/4/2011, a complete response letter was issued to Ipsen Pharma with specific request for conducting a Human Factors/usability validation study. The Applicant provided a report titled “3 in 1 Device Large Scale User Study in the US.”

Review Comments and Discussion - User Study Report

The study report focused on providing data that demonstrates acceptable device performance. The study was conducted in March 2009 per Ipsen protocol # EX24-01. This protocol was not submitted for review.

The study recruited 86 HCPs (17 doctors and 69 nurses). All HCPs have experience in performing injections, at least 5 injections per week. All participants were trained. However, there was no analysis of the intended user population for the proposed device. A rationale that the participants recruited for the study are representative the overall population of users for the device was not provided. For a Human Factors/usability validation study, FDA expects that study participants should not be the Applicant’s own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.

It was not clear if the study participants had an opportunity to assess the clarity of the instructions for use and whether or not the Applicant assessed the extent to which the instructions support safe and effective use of the device. These assessments should be included in the validation testing or can be conducted in a separate study. The participants could use the instructions as they perform an actual or simulated procedure or verbally describe what they would do as they read the instructions. Afterward, the Applicant should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.

The study results focused on device performance rather than the necessary performance and subjective data that FDA requires in a Human Factors/usability validation study. It appears that there is a number of device robustness/performance issues that should have been identified and should be addressed. In addition, as a result of this study, the sponsor identified some potential areas where the device user interface could be further optimized (section 7.2, page 14). The Applicant should complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.

In addition, on page 11 of the study report, the reviewer notes that in 8 instances, the moderators encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, FDA expects that there will be no test moderator, and the users are expected to use the device on their own. Instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures. The study conclusions indicated improvement in device performance. However, FDA expects that for a Human Factors/usability validation study, the conclusions should be based on how the sponsor performs their evaluation and how the evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

There were device modifications implemented post study and a retest was conducted with employees of Ipsen Pharmaceuticals Development Department. This was not found acceptable.

Requests to be transmitted to the Sponsor

1. Please provide a complete analysis of the intended user population for the proposed device and provide a rationale that the participants recruited for the study are representative of the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test be representative of the U.S. population and to reside in the U.S.
2. In the Human Factors/usability validation study, participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.
3. We believe that your retesting participants and testing environments/conditions did not provide a valid representation of actual use. We expect that retesting could be conducted in the same manner as how you would conduct a Human Factors/usability validation study i.e. this testing should involve representative users performing tasks during simulated use/user scenarios that emphasize highest priority user tasks, and include a summary of user subjective assessment and findings with respect to the safety of the use

of your device, and assessment of the effectiveness of device modifications in terms of how the final product has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users.

4. Your study data focused on device performance rather than the necessary performance and subjective data that we require in a Human Factors/usability validation study. It appears that there are a number of device robustness/performance issues that should be addressed. In addition, as a result of this study, you identified some potential areas where the device user interface could be further optimized (section 7.2, page 14). FDA recommends that you complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.
5. On page 11 of the study report, we note that in 8 instances, the moderator encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Please note that instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures.
6. Your study conclusions indicated improvement in device performance. We expect that for a Human Factors/usability validation study, the conclusions should be based on how your evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

Based on the deficiencies stated above, we do not deem this study adequate to demonstrate that the proposed Somatuline Depot prefilled syringe can be used safely and effectively.

Therefore, we request you provide results of a Human Factors/usability validation study following these recommendations as well as those from the original CR Letter dated May 4, 2011. We strongly recommend that you submit your protocol, draft carton and container labeling, and proposed package insert labeling **prior to implementation** to ensure that your methods and the resulting data will be acceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

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/s/

JENNIFER L JOHNSON

04/26/2013

CDRH Review by QuynhNhu Nguyen 4/19/13

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Human Factor Study and Label and Labeling Review

Date: September 10, 2012
Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis
Acting Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis
Deputy Division Director: Kellie Taylor, PharmD MPH
Division of Medication Error Prevention and Analysis
Drug Name and Strengths: Somatuline Depot (Lanreotide) Injection
60 mg, 90 mg, 120 mg
Application Type/Number: NDA 022074/S-004
Applicant: Ipsen Pharmaceuticals
OSE RCM #: 2012-1657

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised draft study protocol entitled “Simulated-Use Validation Testing of Somatuline Depot” and label and labeling, dated July 5, 2012 for Somatuline Depot (Lanreotide) Injection in response to a request from the Division of Metabolism and Endocrinology Products (DMEP).

1.1 REGULATORY HISTORY

Somatuline Depot (Lanreotide) Injection was originally approved on August 30, 2007, as 60 mg, 90 mg, and 120 mg injections in prefilled syringes. On April 29, 2010, the Applicant submitted a prior approval supplement (S-004) that introduced changes to the drug product container closure to add a sharps protection system to the prefilled syringe. To accommodate the changes, the Applicant has amended the labels and labeling. On May 4, 2011, a Complete Response (CR) letter was issued because of concerns regarding the safe and effective use of the proposed device. Subsequently, the Applicant resubmitted a response to the CR letter, dated October 3, 2011 in which the Applicant included the Human Factors Protocol related to the proposed changes. The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the protocol in OSE Review #2011-4229 and recommended revisions to the Applicant’s protocol. The supplement subsequently received a CR letter on February 1, 2012 because of new concerns regarding the device and usability validation protocol.

On July 5, 2012, the Applicant resubmitted the Supplement after the CR. In the same submission, the Applicant included a revised human factors protocol for review by DMEPA and The Center for Devices and Radiological Health (CDRH). On September 6, 2012, CDRH completed their evaluation and comments of the revised protocol. The majority of CDRH’s comments are in alignment with DMEPA’s comments or focus on different aspects of the protocol. See Section 3.1 Comments to the Applicant for DMEPA’s comments and Appendix C for CDRH’s comments.

1.2 PRODUCT INFORMATION

- Established Name: Lanreotide Acetate
- Indication of Use: Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- Route of administration: Deep subcutaneous injection
- Dosage form: Injection
- Strength: 60 mg, 90 mg, 120 mg
- Dose: The recommended dose is 90 mg every 4 weeks for 3 months. For moderate and severe renal and hepatic impairment the initial dose is 60 mg every 4 weeks for 3 months for moderate and severe renal and hepatic impairment. The dose should be adjusted thereafter based on growth hormone (GH) and/or IGF-1 levels.
- How Supplied: Sterile, single-use pre-filled syringes fitted with a 20 mm needle covered by a low density polyethylene sheath.
- Storage: Store in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package

- Container and Closure systems: The three strengths are provided in syringes including a sharp protection system and fitted with a (b) (4) external diameter needle. The primary packaging consists of a (b) (4) polypropylene syringe, a (b) (4) plunger stopper and a (b) (4) stainless-steel needle. The secondary packaging consists of a needle sheath, a sharp protection system, a laminated pouch, and a cardboard carton.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted August 23, 2012 (Appendix A)
- Carton Labeling submitted July 5, 2012 (Appendix B)
- Insert Labeling submitted July 5, 2012
- OSE RCM #2011-4229

DMEPA previously performed an FDA Adverse Event Reporting System (AERS) search to determine medication errors related to the use of this product and have been reported in RCM #2010-1569 dated August 13, 2010 and RCM #2011-4229, dated April 6, 2012. Therefore, for this review, we conducted a search of the database from April 6, 2012 to August 3, 2012 using the following search terms: active ingredient “lanreotide”, trade name “Somatuline Depot”, and verbatim terms “Somatu%” and “lanre%.” The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and (HLT) “Product Quality Issues NEC,” “Product Packaging Issues,” and “Product Label Issues.”

The AERS search retrieved a total of 3 reports. Each report was reviewed for relevancy and duplication. After individual review, all three case reports were not included in the final analysis for the following reasons:

- Overdose due to healthcare practitioner doubling patient dose (n=1)
- Dose omission due to noncompliance (n=2)

3 CONCLUSIONS AND RECOMMENDATIONS

The revised study protocol and the instructions for use contain additional deficiencies that require revision prior to implementation. We recommend additional revisions be implemented prior to approval of this NDA. We provide comments on the proposed protocol in Section 3.1 *Comments to the Applicant*. On September 6, 2012, CDRH completed their evaluation and comments of the revised protocol. The majority of CDRH’s comments are in alignment with DMEPA’s comments or focus on different aspects of the protocol.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 COMMENTS TO THE APPLICANT

HUMAN FACTORS STUDY

1. Study Population and Training

Your study population consists of 20 Non-professional caregivers (NPCs) who are all trained then tested and 30 Health-care providers (HCPs) divided into 3 arms: 1) Training + testing, 2) IFU + Testing, and 3) No IFU + Testing. Although the study population (HCPs and NPCs) is representative of Somatuline Depot end users, the number of HCP users per arm is insufficient. Additionally, you did not account for the fact that not all NCP users may receive training. Although you stated that most will be trained prior to first use and it is unlikely that patients will use the product without training unless they have used the currently marketed product and do not request training, the labeling of the product does not reflect this aspect; and thus, there may be circumstances where the product is received by the patient and/or caregiver before any training or education is provided. In this case, patients and/or caregiver may attempt to use the product without prior formal training. Therefore, we continue to recommend that not all participants in the NPC group receive formal training; participants should use the IFU as they desire while interacting with the device. Thus, the study should include at least 60 participants divided as follows:

- a. Verbal training of the participants (15 of HCPs and 15 of NPCs)
- b. Participants are provided with the kit containing the IFU, but not specifically instructed to refer to the IFU. Participants should use the IFU as they desire while interacting with the device and should not receive any training regarding use of the product (15 of HCPs and 15 of NPCs)

If you wish, you may exclude the arm where the kit is provided and the moderator prompts the participants to read the IFU prior to administration.

2. Study Design

- a. Overall Study Approach

The protocol states that each participant will complete 10 injections per session. Although we have no objection to this approach, we recommend that results regarding the first injection are reported separately from the results reported for second through tenth injections. We are most interested in the data validations from the first injection, since this is most reflective of the expected use of patients when first exposed to the product. Also, the performance of injections two through ten may be influenced by learning that occurs with repeated sequential use which is not reflective of actual use since your product is administered every 4 weeks.

- b. How the Session Represents Anticipated Use

The protocol states that the Moderator will ask the participant how he/she would position the patient for injection, then the moderator will orient the pad accordingly: either vertically (lying down) or horizontally (sitting or standing). Since your product should be administered by a health care professional or a caregiver, in order to

simulate real-life scenario, we recommend using a dummy and the participant can orient the dummy into the position he/she would want to position a person for injection. Then the participant should inject the drug into a dummy (or pad on a dummy). Since the IFU specifically states that only two areas can be used for deep subcutaneous injection, this will ensure that participants are knowledgeable regarding the proper location for the injection.

c. Data Collection and Coding

The standardized scoring A= Assisted defined as “Successful completion of the task was only possible with the assistance from the Moderator.” This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Thus, we will consider instances where the moderator intervenes/coaches/prompts the study participants as failures.

4. Study Report

DMEPA continues to recommend the use of open-ended questions from participants to obtain subjective feedback regarding any wording instructions that they found confusing, misleading or incomplete.

3.1.2 INSTRUCTIONS FOR USE

In Section B8, remove the “(b)(4)” because it may be interpreted as the proper location for the injection. The “(u)” usually represents the spot of injection; therefore we recommend only marking the areas that should be injected.

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

Appendix C: Comments from CDRH received on September 6, 2012 via electronic mail

Overall, the protocol appeared adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. Please address the following:

1. You identified two unique user groups: Healthcare providers (HCP), and Non-professional caregivers (NPC) who have been trained by a HCP. You also specified the content and duration of training. However, your protocol was not whether the healthcare provider group will also receive training on the use of the device. It appeared that only the NPC group will receive training. Please clarify and justify that the training level that will be provided in the study is representative of training in realistic use.
2. You reported that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. You also included a user task analysis and along with a use FMEA in the protocol. While both analyses are comprehensive, the clinical impact/consequence were not included such that we are clear on which tasks should be prioritized in the testing. Please add to both analyses some discussions with respect to the clinical impact/consequence for all hazards/potential use errors, and clarify which tasks (critical and essential) will be prioritized in the study. Please note the following:
 - a. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Please ensure that you clearly identify and include all critical and essential tasks associated with safe and effective use of the device. Please note that criteria for determining whether a task has been completed successfully should be defined in advance. We consider task failure as action/lack of action that could lead to clinical harm. Furthermore, use errors that can be corrected should be discussed in detail with respect to how users were able to recognize the potential failures and what steps they took correct themselves and how the design of the device and its labeling influenced the patient's behavior for self-correction.
 - b. Depending on your response on the clinical impact/consequences, we might have clarification on your rationale on the severity rating of the hazards identified in your use FMEA. Please ensure that the severity rating for all hazards corresponds appropriately to the clinical impact/consequences.
3. You indicated that the study design will consist one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. It was not clear why the testing specified that each participant performs 10 injections. Please provide a rationale for the 10 injections, or alternatively, the number of injections that will be evaluated in the study should represent realistic use.
4. You stated that both observational data and subjective evaluations will be collected. It should be noted that the follow-up questions ask the participants whether not they recall any use errors, close calls, or operational difficulties. It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that you may observe.

5. It is not clear how you will validate the instructions for use. You should validate the instructions to ensure that the end users will be able to correctly understand and follow them and to assess the extent to which the instructions support safe and effective use of your system by the intended users. If any other elements of labeling (e.g., packaging, inserts) are critical to use, include them in your validation testing as well. You may conduct these assessments in a separate study (with different participants, prior to the device validation study) or include them in your validation testing (following the device validation portion). To assess user understanding of critical messages in the labeling that cannot be assessed through observation of participant behavior, you can ask explicit, detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e. don't make the correct responses obvious) and for this reason, we discourage use of forced-choice responses. The participants should also provide subjective feedback regarding any wording in the labeling they found confusing, misleading or incomplete. Additionally, the clarity of the IFU/DHA should be evaluated with respect to findings on task failures/use errors observed in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

For more information on human factors, you might want to visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of human factors consultants that can assist in conducting a human factors study.

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

/s/

REASOL AGUSTIN
09/11/2012

YELENA L MASLOV
09/11/2012

KELLIE A TAYLOR
09/11/2012

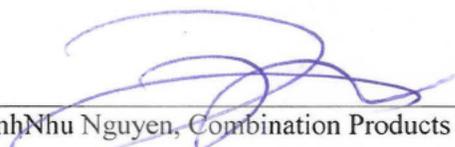


Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: September 5, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Jennifer Johnson, Regulator Project Manager, CDER/OND/ODEII/DMEP
SUBJECT: NDA 22074/S-004, Ispen Pharma, Somatuline Depot (lanreotide) injection, 60mg, 90mg, 120mg (CTS: ICC 1200117/CON1214291)

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

9/10/2012
Date



Ron Kaye, Human Factors and Device Use-Safety Team Leader

9/10/2012
Date

CDRH Human Factors Review

Overview and Recommendations

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, requested a Human Factors consultative review of the NDA 22074 S004 submitted by Ispen Pharma. The Applicant seeks FDA's review for the a new protocol titled "Simulated-Use Design Validation Testing of Somatuline Depot" (dated July 2, 2012). Overall, the protocol appears adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. This reviewer recommends that the following comments/deficiencies (blue) be transmitted to the Sponsor.

Overall, the protocol appeared adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. Please address the following:

1. You identified to unique user groups: Healthcare providers (HCP), and Non-professional caregivers (NPC) who have been trained by a HCP. You also specified the content and duration of training. However, your protocol was not whether the healthcare provider group will also receive training on the use of the device. It appeared that only the NPC group will receive training. Please clarify and justify that the training level that will be provided in the study is representative of training in realistic use.
2. You reported that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. You also included a user task analysis and along with a use FMEA in the protocol. While both analyses are comprehensive, the clinical impact/consequence were not included such that we are clear on which tasks should be prioritized in the testing. Please add to both analyses some discussions with respect to the clinical impact/consequence for all hazards/potential use errors, and clarify which tasks (critical and essential) will be prioritized in the study. Please note the following:
 - a. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Please ensure that you clearly identify and include all critical and essential tasks associated with safe and effective use of the device. Please note that criteria for determining whether a task has been completed successfully should be defined in advance. We consider task failure as action/lack of action that could lead to clinical harm. Furthermore, use errors that can be corrected should be discussed in detail with respect to how users were able to recognize the potential failures and what steps they took correct themselves and how the design of the device and its labeling influenced the patient's behavior for self-correction.
 - b. Depending on your response on the clinical impact/consequences, we might have clarification on your rationale on the severity rating of the hazards identified in your use FMEA. Please ensure that the severity rating for all hazards corresponds appropriately to the clinical impact/consequences.
3. You indicated that the study design will consist one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. It was not clear why the testing specified that each participant performs 10 injections. Please provide a rationale for the 10 injections, or

alternatively, the number of injections that will be evaluated in the study should represent realistic use.

4. You stated that both observational data and subjective evaluations will be collected. It should be noted that the follow-up questions ask the participants whether not they recall any use errors, close calls, or operational difficulties. It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have been considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that you may observe.
5. It is not clear how you will validate the instructions for use. You should validate the instructions to ensure that the end users will be able to correctly understand and follow them and to assess the extent to which the instructions support safe and effective use of your system by the intended users. If any other elements of labeling (e.g., packaging, inserts) are critical to use, include them in your validation testing as well. You may conduct these assessments in a separate study (with different participants, prior to the device validation study) or include them in your validation testing (following the device validation portion). To assess user understanding of critical messages in the labeling that can not be assessed through observation of participant behavior, you can ask explicit, detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e. don't make the correct responses obvious) and for this reason, we discourage use of forced-choice responses. The participants should also provide subjective feedback regarding any wording in the labeling they found confusing, misleading or incomplete. Additionally, the clarity of the IFU/DHA should be evaluated with respect to findings on task failures/use errors observed in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

For more information on human factors, you might want to visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of human factors consultants that can assist in conducting a human factors study.

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 22074/S-004

Applicant: Ispen Pharma

Drug Constituent: Somatuline Depot (lanreotide) Injection, 60mg, 90mg, and 120mg for treatment of excess growth hormone secretion (acromegaly)

Device Constituent: prefilled syringe

CDRH Human Factors Involvement History

- 25-July-2012: CDRH HF was requested to provide a review the revised Human Factors protocol contained in the NDA
- 2-Feb-2012: CDRH HF was requested to provide a review a Human Factors protocol contained in the NDA. CDRH provided 6 deficiencies to CDER to transmit the Sponsor.

Review of Human Factors Related Information

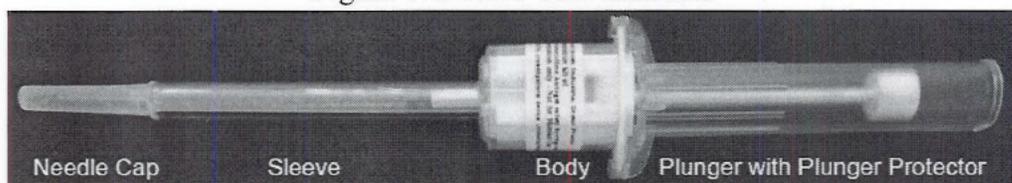
Review Material

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_2f198

Summary of Study Protocol and Reviewer Comments

The product is a single-use 0.5mL prefilled syringe with an integrated sharps injury prevention feature. The product will contain lanreotide in 3 alternative fill levels: 60mg/0.2mL, 90mg/0.3mL, or 120mg/0.5mL.

Figure 1: Device User Interface



Operation of the product requires 3 steps:

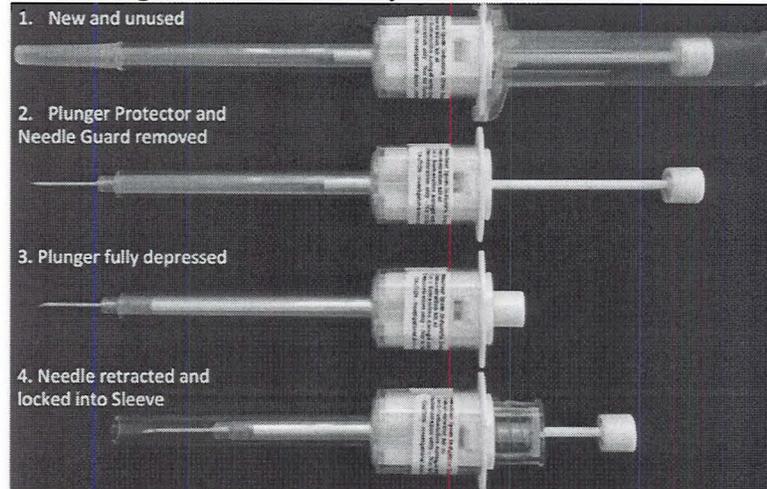
1. Preparation: Remove Plunger Protector and Needle Cap.
2. Administration: Insert the needle to its full length perpendicular (90°) to the skin and inject the full dose until the plunger cannot be depressed any further.
3. Retraction: Release pressure on the plunger to allow the sharps injury prevention feature to automatically retract the needle into the Sleeve where it will be locked permanently.

The product has 4 primary states:

1. New and unused;
2. Plunger Protector and Needle Guard removed;
3. Plunger fully depressed; and

4. Needle retracted and locked into Sleeve.

Figure 2: Four Primary States of the Product



The sponsor identified to unique user groups:

- Healthcare providers (HCP), 30 participants
- Non-professional caregivers (NPC) who have been trained by a HCP, 20 participants

The sponsor specified that the training will include:

- the trainer familiarizing the user with the components of the product
- the trainer resent through the instructions for use with the user
- the trainer and the user discussing the steps required for use
- the trainer demonstrating these are the product
- the trainer watching and correcting the user using the product
- the trainer answering any questions that the user may have

However, the protocol was not whether the healthcare provider group will also receive training on the use of the device.

The protocol stated that several formative evaluations were conducted on the proposed device. Observed use related issues were addressed by employing subsequent risk control measures. Additionally, the user task analysis and characterization provided detailed discussion on all use related hazards associated with the use of this product. The analysis provided a breakdown of the user interaction into three user performance requirements: perceptual, cognitive, and physical. In addition, a use FMEA was provided, which included this likelihood and severity, along with consequences and prevention control measures. *While both analyses appeared comprehensive, the clinical impact/consequence were not included such that it is to the reviewer which tasks should be prioritized in the testing.*

The study design consisted of one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. *It was not clear to the reviewer why the testing specified that each participant performs 10 injections. It did not appear that 10 injections are realistic use. The Sponsor should be asked to provide a rationale for the 10 injections, or alternatively, the number of injections that will be evaluated in the study should represent realistic use.*

Both observational data and subjective evaluations will be collected. The protocol states that if the safety feature has not been triggered, the Sponsor will verify under a microscope the distance between the end of the syringe and the front face of the plunger rubber stopper to verify the volume of potential drug left. The estimated calculated weight of the drug remaining can therefore be evaluated. Finally a sampling will be performed to verify if no residual drug is left into the syringes. It should be noted that the follow-up questions ask the participants whether not they recall any use errors, close calls, or operational difficulties. *It might be challenging for the participant to recall use-related issues. This reviewer recommends that the questions should include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that the Sponsor may observe.*

Appendix 1: Previous CDRH Human Factors Review Memo

DATE: February 2, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ODE/CDRH
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Reasol Agustin, CDER/DMEPA
Jennifer Johnson, CDER/OND/ODEII/DMEP
SUBJECT: NDA 22074 S-004, Ipsen Pharma (Biomeasure Inc.), Somatuline Depot
Human Factors/Usability Review, GEN1200091

Overview

On 5/4/2011, a complete response letter was issued to Ipsen Pharma with specific request for conducting a Human Factors/usability validation study. The Applicant provided a report titled "3 in 1 Device Large Scale User Study in the US."

Review Comments and Discussion - User Study Report

The study report focused on providing data that demonstrates acceptable device performance. The study was conducted in March 2009 per Ipsen protocol # EX24-01. This protocol was not submitted for review.

The study recruited 86 HCPs (17 doctors and 69 nurses). All HCPs have experience in performing injections, at least 5 injections per week. All participants were trained. However, there was no analysis of the intended user population for the proposed device. A rationale that the participants recruited for the study are representative the overall population of users for the device was not provided. For a Human Factors/usability validation study, FDA expects that study participants should not be the Applicant's own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.

It was not clear if the study participants had an opportunity to assess the clarity of the instructions for use and whether or not the Applicant assessed the extent to which the instructions support safe and effective use of the device. These assessments should be included in the validation testing or can be conducted in a separate study. The participants could use the instructions as they perform an actual or simulated procedure or verbally describe what they would do as they read the instructions. Afterward, the Applicant should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.

The study results focused on device performance rather the necessary performance and subjective data that FDA requires in a Human Factors/usability validation study. It appears that there is a number of device robustness/performance issues that should were identified and should be addressed. In addition, as a result of this study, the sponsor identified some potential areas

where the device user interface could be further optimized (section 7.2. page 14). The Applicant should complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.

In addition, on page 11 of the study report, the reviewer notes that in 8 instances, the moderators encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, FDA expects that there will be no test moderator, and the users are expected to use the device on their own. Instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures. The study conclusions indicated improvement in device performance. However, FDA expects that for a Human Factors/usability validation study, the conclusions should be based on how the sponsor performs their evaluation and how the evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

There were device modifications implemented post study and a retest was conducted with employees of Ipsen Pharmaceuticals Development Department. This was not found acceptable.

Requests to be transmitted to the Sponsor

1. Please provide a complete analysis of the intended user population for the proposed device and provide a rationale that the participants recruited for the study are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.
2. In the Human Factors/usability validation study, participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.
3. We believe that your retesting participants and testing environments/conditions did not provide a valid representation of actual use. We expect that retesting could be conducted in the same manner as how you would conduct a Human Factors/usability validation study i.e. this testing should involve representative users performing tasks during simulated use/user scenarios that emphasize highest priority user tasks, and include a summary of user subjective assessment and findings with respect to the safety of the use of your device, and assessment of the effectiveness of device modifications in terms of how the final product has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users.

4. Your study data focused on device performance rather than the necessary performance and subjective data that we require in a Human Factors/usability validation study. It appears that there are a number of device robustness/performance issues that should be addressed. In addition, as a result of this study, you identified some potential areas where the device user interface could be further optimized (section 7.2, page 14). FDA recommends that you complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.
5. On page 11 of the study report, we note that in 8 instances, the moderator encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Please note that instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures.
6. Your study conclusions indicated improvement in device performance. We expect that for a Human Factors/usability validation study, the conclusions should be based on how your evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

Based on the deficiencies stated above, we do not deem this study adequate to demonstrate that the proposed Somatuline Depot prefilled syringe can be used safely and effectively.

Therefore, we request you perform provide results of a Human Factors/usability validation study following these recommendations as well as those from the original CR Letter dated May 4, 2011. We strongly recommend that you submit your protocol, draft carton and container labeling, and proposed package insert labeling **prior to implementation** to ensure that your methods and the resulting data will be acceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

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/s/

JENNIFER L JOHNSON

09/10/2012

Signed on behalf of QuynhNhu Nguyen, CDRH

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Human Factor Study and Label and Labeling Review**

Date: April 6, 2012

Reviewer(s): Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Deputy Division Director: Kellie Taylor, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Somatuline Depot (Lanreotide) Injection
60 mg, 90 mg, 120 mg

Application Type/Number: NDA 022074/S-004

Applicant: Ipsen Pharmaceuticals

OSE RCM #: 2011-4229

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the study protocol entitled “3in1 Device Large Scale User Study” and label and labeling, dated October 3, 2011 for Somatuline Depot (Lanreotide) Injection in response to a request from the Division of Metabolism and Endocrinology Products (DMEP).

1.1 REGULATORY HISTORY

Somatuline Depot (Lanreotide) Injection was originally approved on August 30, 2007, as 60 mg, 90 mg, and 120 mg injections in prefilled syringes. On April 29, 2010, the Applicant submitted a prior approval supplement (S-004) that introduced changes to the drug product container closure to add a sharps protection system to the pre-filled syringe. To accommodate the changes, the Applicant has amended the labels and labeling. Additionally, the supplement introduced changes in the manufacturing process, which were evaluated by Office of New Drug Quality Assessment. On May 4, 2011, a Complete Response (CR) letter was issued because of concerns regarding the safe and effective use of the proposed device. Subsequently, the Applicant resubmitted a response to the CR letter, dated October 3, 2011.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 3, 2011 submission.

- Established Name: Lanreotide
- Indication of Use: Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- Route of administration: Deep subcutaneous injection
- Dosage form: Injection
- Strength: 60 mg, 90 mg, 120 mg
- Dose: The recommended dose is 90 mg every 4 weeks for 3 months. For moderate and severe renal and hepatic impairment the initial dose is 60 mg every 4 weeks for 3 months for moderate and severe renal and hepatic impairment. The dose should be adjusted thereafter based on GH and/or IGF-1 levels.
- How Supplied: Sterile, single-use pre-filled syringes fitted with a 20 mm needle covered by a low density polyethylene sheath.
- Storage: Store in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package
- Container and Closure systems: The three doses are provided in a syringe including a sharp protection system and fitted with a (b) (4) external diameter needle. The primary packaging consists of a (b) (4) polypropylene syringe, a (b) (4) (b) (4) plunger stopper and a (b) (4) stainless-steel needle. The secondary packaging consists of a needle sheath, a sharp protection system, a laminated pouch, and a cardboard carton.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted October 3, 2011 (Appendix A)
- Carton Labeling submitted October 3, 2011 (Appendix B)
- Insert Labeling submitted October 3, 2011

DMEPA previously performed an FDA Adverse Event Reporting System (AERS) search to determine medication errors related to the use of this product and have been reported in RCM #2010-1569 dated August 13, 2010. Therefore, for this review, we conducted a search of the database from August 13, 2010 to January 3, 2012 using the following search terms: active ingredient “lanreotide”, trade name “Somatuline Depot”, and verbatim terms “Somatu%” and “lanre%.” The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues.”

The AERS search retrieved a total of 9 reports. Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when provided by the reporter. After individual review, 5 case reports were not included in the final analysis because all 5 reports are of an adverse event without a medication error.

Following exclusions, 4 medication error cases were relevant to this review

In addition, DMEPA reviewed the results of the 3in1 Device Large Scale User Study submitted by the Applicant in response to the CR letter issued on May 4, 2011.

3 DISCUSSION

3.1 AERS CASES

DMEPA retrieved a total of nine reports from the FDA Adverse Event Reporting System (AERS) database. After excluding cases as described in Section 2, four cases remained. Of the 4 cases, one was from the United States (US) and all others were foreign cases. In all of these cases, no significant adverse events were reported

- Wrong Route (n=2)
 1. The first case (ISR # 7103011-8) is a US case received from a nurse regarding a 59-year old, female patient. The patient was initiated with Somatuline Depot and was trained to inject herself via deep subcutaneous injection into her thigh at dose of 60 mg for the treatment of acromegaly. On an unreported date, the patient developed a nodule at the injection site after receiving her first injection but reported that nodules occurred regardless of injection technique. Two days later, the patient developed mild to moderate pain after the first injection and was advised to talk to her healthcare professional regarding injection technique. The patient was also concern about her injection technique and stated that due to her weight (49 kg) the injection was pushing through her muscle and the plunger was bending.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. The second (ISR # 7450341-9) is a case from France reported by a physician regarding an 83-year old male patient. This report was reported because of adverse events but it was noted that the injections were being given via intramuscular route.

The submitted labels and labeling adequately convey that the intended route of administration is for deep subcutaneous injection.

- Improper storage (n=2)
 1. The first case (ISR # 7468931-6) is from the United Kingdom and received from a nurse regarding a 77 year old male patient. The patient reported adverse events like malaise, raised blood pressure and was eventually hospitalized. The patient who is also a physician believed that the product had not been refrigerated for a week prior and on collection. The nurse and patient believed that the adverse events may have been caused by the possible incorrect storage of the product.
 2. The second case (ISR # 7725601-4) is also from the United Kingdom and received from a consumer regarding a male patient. The patient experienced an infection at the injection site after initial treatment. The patient speculated that the infection may be due to the fact that he left the Somatuline out for two hours, rather than for the recommended thirty minutes. The patient felt it was easier to give when it wasn't as cold and that it stayed as a "lump" at the injection site until it dissipated. The patient was given antibiotics and has recovered from the infection but not from the "lump."

The submitted labels and labeling adequately convey that Somatuline Depot must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and be removed from the refrigerator 30 minutes prior to administration.

4 CONCLUSIONS AND RECOMMENDATIONS

The study protocol contains deficiencies that require revision prior to implementation and the proposed labels and labeling introduce vulnerability that can lead to medication errors. We recommend the following be implemented prior to approval of this NDA. We provide comments on the proposed protocol in Section 4.1 *Comments to the Applicant*.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

4.1 COMMENTS TO THE APPLICANT

The following sections provide the consolidated DMEPA/CDRH comments to the Applicant submitted in the CR Letter issued on May 4, 2011.

DEVICE/USABILITY VALIDATION STUDY

4.2.1 STUDY OBJECTIVES

Your simulated study protocol objective was in alignment with device performance rather than demonstrating the safe and effective use of the device. The primary objective of a summative human factor study should be to demonstrate the safe and effective use of the

device by representative user under simulated use conditions (refer to original CR Issue 4 dated May 4, 2011).

4.2.2 STUDY POPULATION

Your study population only consisted of Health Care Providers (HCPs) experienced in the administration of deep subcutaneous injections to patients. This is not representative of all Somatuline Depot end users.

The study population should represent all end users, including HCPs, and patients/caregivers experienced in the administration of deep subcutaneous injection, as well as naïve subjects (i.e., with no experience in the administration of deep subcutaneous injection). In our Adverse Events Reporting Systems (AERS) search, we identified a case of a patient self-injecting Somatuline Depot which indicates the need to include patients/caregivers as representative end users. Provide a complete analysis of the intended user population for the proposed device and provide a rationale that the participants recruited for the study are representative of the overall population of users for your device. Note that study participants should not be your own employees, or those who have been exposed to the product prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test be representative of the U.S. population and reside in the U.S.

4.2.3 TRAINING

The training provided during the study included a training video that you state will not be available in the U.S. In addition, your study required that participants confirm understanding of the instructions for use (IFU) before proceeding with the testing. This is not representative of actual end user training.

- In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording instructions that they found confusing, misleading or incomplete.
- We recommend that you include at least two arms in the study: participants in one arm are required to read the IFU prior to simulating the injection, and participants in the second arm are provided the product and the IFU without being asked or required to read the IFU prior to simulating the injection. Ensure that these two arms include representative end users (i.e., HCPs, caregivers/patients, experienced and naïve).

4.2.4 RETESTING AFTER DIMENSIONAL MODIFICATION

We acknowledge that retesting after device modification is necessary to demonstrate that the failures have been addressed adequately and that new failure modes have not been introduced. However, we noted the following deficiencies in your retesting: users were employees of Ipsen Pharmaceuticals Development Department; all users were trained to a point where they could demonstrate comprehension, technique, and confidence in their

ability to attempt the testing of the devices; and the devices used in retesting were unfilled prefilled syringes which are not representative of the performance of filled devices. We believe that your retesting participants and testing environments/conditions did not provide a valid representation of actual use. We expect that retesting could be conducted in the same manner as how you would conduct a Human Factors/usability validation study (i.e., this testing should involve representative users performing tasks during simulated use/user scenarios that emphasize highest priority user tasks, and include a summary of user subjective assessment and findings with respect to the safety of the use of your device, and assessment of the effectiveness of device modifications in terms of how the final product has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users).

Retesting after device modification should follow all the requirements for human factors testing.

4.2.5 STUDY DATA

Your study data focused on device performance rather the necessary performance and subjective data that we require in a Human Factors/usability validation study. It appears that there are a number of device robustness/performance issues that should be addressed. In addition, as a result of this study, you identified some potential areas where the device user interface could be further optimized (section 7.2. page 14). We recommend that you complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.

4.2.5 STUDY REPORT

On page 11 of the study report, we note that in 8 instances, the moderator encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Note that instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures.

4.2.6 STUDY CONCLUSION

Your study conclusions indicated improvement in device performance. We expect that for a Human Factors/usability validation study, the conclusions should be based on how your evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

LABELING

A. Pouch Labeling

- a. Revise the statement “ (b) (4) ” to read:

(b) (4)

- b. Ensure that the expiration date and lot number are included.
- B. Carton Labeling
- a. Relocate the “Rx only” statement on the principal display panel toward the upper left portion of the carton.
 - b. For the 90 mg/0.3 mL carton labeling, revise the statement (b) (4) (b) (4) to read “For single use only - Discard unused portion”.
 - c. Revise the statement “(b) (4)” to read “Usual dosage: See prescribing information”.
 - d. There is no statement on the carton labeling that indicates you must leave the product at room temperature for 30 minutes prior to administration; therefore practitioners may not be aware of this necessary step which can result in delay of care. The container label and carton labeling of the current products and proposed product should prominently display a statement that conveys the duration for the product to be at room temperature prior to administration.
- C. Highlights of Prescribing Information
- a. Section 3 Dosage Forms and Strengths - add the unit “mg” to the strength to read: Single use syringe: 60 mg, 90 mg, and 120 mg.
- D. Full Prescribing Information
- a. Section 2 Dosage and Administration
 - i. Replace the symbols “>” and “<” with the words “greater than” and “less than”, respectively. These symbols (< and >) are considered dangerous abbreviations. They are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations¹. As part of a national campaign to avoid the use of dangerous abbreviations, symbols, and dose designations, FDA agreed not to approve such error-prone abbreviations in the approved labeling of products.
 - ii. Create a subsection for Dosing for Renal and Hepatic Impairment so that this dosing adjustment required for this patient population is prominent. Currently, the dosing instructions for renally and hepatically impaired patients appear at the bottom of the Dosage and Administration section and can be easily overlooked. Creating a subsection entitled *Dose for Renal and Hepatic Impairment* will make this information more noticeable. For example:
 - 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dose for Renal and Hepatic Impairment
 - 2.2 Instructions for Use
 - b. Section 2.1 Instructions for Use
 - i. Revise the statement (b) (4) to read (b) (4) (b) (4) (90 degree angle)”.

ii. Revise the statement

(b) (4)

” to read

(b) (4)

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

APPEARS THIS
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ORIGINAL

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/s/

REASOL AGUSTIN
04/06/2012

CARLOS M MENA-GRILLASCA
04/13/2012

KELLIE A TAYLOR
04/13/2012



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: February 2, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ODE/CDRH
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID
Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Reasol Agustin, CDER/DMEPA
Jennifer Johnson, CDER/OND/ODEII/DMEP
SUBJECT: NDA 22074 S-004, Ipsen Pharma (Biomeasure Inc.), Somatuline Depot
Human Factors/Usability Review, GEN1200091

[Handwritten signatures and dates: 2/2/2012, 2/12/2012]

Overview

On 5/4/2011, a complete response letter was issued to Ipsen Pharma with specific request for conducting a Human Factors/usability validation study. The Applicant provided a report titled "3 in 1 Device Large Scale User Study in the US."

Review Comments and Discussion - User Study Report

The study report focused on providing data that demonstrates acceptable device performance. The study was conducted in March 2009 per Ipsen protocol # EX24-01. This protocol was not submitted for review.

The study recruited 86 HCPs (17 doctors and 69 nurses). All HCPs have experience in performing injections, at least 5 injections per week. All participants were trained. However, there was no analysis of the intended user population for the proposed device. A rationale that the participants recruited for the study are representative the overall population of users for the device was not provided. For a Human Factors/usability validation study, FDA expects that study participants should not be the Applicant's own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.

It was not clear if the study participants had an opportunity to assess the clarity of the instructions for use and whether or not the Applicant assessed the extent to which the instructions support safe and effective use of the device. These assessments should be included in the validation testing or can be conducted in a separate study. The participants could use the instructions as they perform an actual or simulated procedure or verbally describe what they would do as they read the instructions. Afterward, the Applicant should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.

The study results focused on device performance rather the necessary performance and subjective data that FDA requires in a Human Factors/usability validation study. It appears that

there is a number of device robustness/performance issues that should were identified and should be addressed. In addition, as a result of this study, the sponsor identified some potential areas where the device user interface could be further optimized (section 7.2. page 14). The Applicant should complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.

In addition, on page 11 of the study report, the reviewer notes that in 8 instances, the moderators encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, FDA expects that there will be no test moderator, and the users are expected to use the device on their own. Instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures. The study conclusions indicated improvement in device performance. However, FDA expects that for a Human Factors/usability validation study, the conclusions should be based on how the sponsor performs their evaluation and how the evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

There were device modifications implemented post study and a retest was conducted with employees of Ipsen Pharmaceuticals Development Department. This was not found acceptable.

Requests to be transmitted to the Sponsor

1. Please provide a complete analysis of the intended user population for the proposed device and provide a rationale that the participants recruited for the study are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing. For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.
2. In the Human Factors/usability validation study, participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.
3. We believe that your retesting participants and testing environments/conditions did not provide a valid representation of actual use. We expect that retesting could be conducted in the same manner as how you would conduct a Human Factors/usability validation study i.e. this testing should involve representative users performing tasks during simulated use/user scenarios that emphasize highest priority user tasks, and include a summary of user subjective assessment and findings with respect to the safety of the use of your device, and assessment of the effectiveness of device modifications in terms of how the final product has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users.

4. Your study data focused on device performance rather than the necessary performance and subjective data that we require in a Human Factors/usability validation study. It appears that there are a number of device robustness/performance issues that should be addressed. In addition, as a result of this study, you identified some potential areas where the device user interface could be further optimized (section 7.2, page 14). FDA recommends that you complete all of the necessary testing to demonstrate acceptable device robustness/performance and optimize the device user interface prior to conducting the Human Factors/usability validation study.
5. On page 11 of the study report, we note that in 8 instances, the moderator encouraged or prompted the users to push harder/further. This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Please note that instances where the moderator intervenes/coaches/prompts the study participants should be considered as failures.
6. Your study conclusions indicated improvement in device performance. We expect that for a Human Factors/usability validation study, the conclusions should be based on how your evaluation demonstrates that the device is reasonably safe and effective for the intended users, uses and use conditions.

Based on the deficiencies stated above, we do not deem this study adequate to demonstrate that the proposed Somatuline Depot prefilled syringe can be used safely and effectively.

Therefore, we request you provide results of a Human Factors/usability validation study following these recommendations as well as those from the original CR Letter dated May 4, 2011. We strongly recommend that you submit your protocol, draft carton and container labeling, and proposed package insert labeling **prior to implementation** to ensure that your methods and the resulting data will be acceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

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/s/

JENNIFER L JOHNSON

02/03/2012

CDRH review completed by QuynhNhu Nguyen on 2/2/12

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **November 17, 2011**

To: **Mary Parks, MD, Director
Division of Products (DMEP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)**

**Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)**

From: **Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)**

Subject: **DMPP Review of Patient Labeling (PPI)**

Drug Name (established name): **SOMATULINE DEPOT (lanreotide)**

Dosage Form and Route: **Injection**

Application Type/Number: **NDA 22074**

Supplement number: **004**

Applicant: **Ipsen Pharmaceuticals**

1 INTRODUCTION

On October 03, 2011, the Applicant submitted Manufacturing (CMC) Supplement with a labeling resubmission in response to a Complete Response (CR) letter issued by the FDA on May 04, 2011. The re-submission included a revised package insert with a new Instructions for Use section in Section 2, Dosage and Administration, and a video demonstrating how to operate the device. The application was originally submitted on May 03, 2010.

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI), for Somatuline Depot (lanreotide) Injection.

2 MATERIAL REVIEWED

- Draft SOMATULINE DEPOT (lanreotide) Patient Package Insert (PPI), received on October 04, 2011 and received by DMPP on November 09, 2011.
- Draft SOMATULINE DEPOT (lanreotide) Prescribing Information (PI) received on October 04, 2011 and received by DMPP on November 09, 2011.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 DISCUSSION

We note the Instructions for Use in Section 2 of the PI. However, it is unclear in the PI if this injection is given only in a doctor's office by a healthcare provider. If it is only given in a doctor's office by a healthcare provider, it is acceptable to have the IFU in Section 2 of the PI. If there is a possibility of a family member/caregiver giving the injection, there should be a separate IFU for the patients and this should be stated in the PI.

5 CONCLUSIONS

The PPI is acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI. Please let us know if you have any questions.

7 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHAWNA L HUTCHINS
11/17/2011

MELISSA I HULETT
11/17/2011

LASHAWN M GRIFFITHS
11/17/2011

Johnson, Jennifer

From: Ryan, Jaqueline
Sent: Friday, January 28, 2011 12:34 PM
To: Johnson, Jennifer
Subject: RE: REVISED - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)
Follow Up Flag: Follow up
Due By: Friday, January 28, 2011 1:00 PM
Flag Status: Red
Attachments: NDA 20774 NThakur comments.doc

Jennifer,
Please accept the REVISED consult attached.
Thanks.
Jacqueline Ryan

From: Johnson, Jennifer
Sent: Wednesday, January 26, 2011 1:27 PM
To: Ryan, Jaqueline; Thakur, Nikhil
Cc: Milone, Joseph; Baker, Marsha *
Subject: RE: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Thanks so much for the update - we really appreciate it!

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: Ryan, Jaqueline
Sent: Wednesday, January 26, 2011 1:23 PM
To: Thakur, Nikhil
Cc: Milone, Joseph; Baker, Marsha *; Johnson, Jennifer
Subject: RE: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Will be done 1/27/10.
Jacqueline Ryan

From: Thakur, Nikhil
Sent: Wednesday, January 26, 2011 12:33 PM
To: Ryan, Jaqueline
Subject: FW: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Perhaps I missed something here... in a meeting... will catch up with you at 1:00 PM.

Sincerely,
Nikhil

Nikhil Thakur
LCDR, USPHS
Combination Products Team Leader

Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Anesthesiology, General Hospital, Dental and Infection Control Devices
General Hospital Devices Branch

Address:
1090 North Hinesville Ave
Reference ID: 2908608
Bldg: WO66, Rm 2562

2/18/2011

Darrts Login

Silver Spring, MD 20993

Telephone: (301) 796 - 5536

Fax: (301) 847 - 8109

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From: OC Combination Products
Sent: Wednesday, January 26, 2011 12:19 PM
To: Thakur, Nikhil; Ryan, Jaqueline
Cc: OC Combination Products; Baker, Marsha *
Subject: FW: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Hi Nikhil and Jaqueline,

Can you please provide CDER with a status update for this consult request? CDER had requested a completion date of 1/11/11. When do you expect this request to be completed?

Sincerely,
Joe

Joseph Milone, Ph.D.
Biologist
Office of Combination Products
Office of the Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
WO 32 Rm 5134

10903 New Hampshire Avenue
Silver Spring, MD 20996-0002
joseph.milone@fda.hhs.gov
Tel: 301-796-8939 Fax: 301-847-8619

<http://www.fda.gov/CombinationProducts/default.htm>

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From: Johnson, Jennifer
Sent: Friday, January 21, 2011 6:27 PM
To: OC Combination Products
Subject: RE: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Dear Marsha,

Thanks for checking in. No, we have not received comments regarding this consult request just yet.

If you wouldn't mind checking on the status of the consult, that would be great.

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: OC Combination Products
Sent: Thursday, January 20, 2011 1:32 PM
To: Jennifer Johnson
Subject: FW: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)
Reference ID: 2908608

2/18/2011

Dear Jennifer,

Have you received comments/a review for the below/attached consult request? It is still open in my tracking database. If you did receive comments, what date did you receive them? I need this information to close it out of the database. Also, please let me know if the due date listed on the consult was changed/re-negotiated prior to completion of the consult request. Thank you.

Sincerely,
 Marsha Baker
 OCP
 301-796-8935

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Thursday, December 09, 2010 7:08 PM
To: Thakur, Nikhil; OC Combination Products; Sharma, Khushboo; Johnson, Jennifer
Subject: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)



[Proceed to DARRTS Login](#)

Finalized - Intercenter/Combination Products Consult (FRM-CONSULT-02)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
FRM-CONSULT-02	CONSULT	Intercenter/Combination Products Consult

Linked Supporting Documents

Application Type	Application Number	Sponsor	Product Name (Preferred)	Submission Type	Submission Number	Group Id	Supporting Document Number	Category	Subcategory
NDA	22074	BEAUFOR IPSEN PHARMA	SOMATULINE DEPOT, 60,90,120 MG	SUPPL	4	204685	58	New	Supplement

Linked Submissions

Application Type	Application Number	Sponsor	Preferred Product Name	Submission Type	Submission Number	Submission Classif
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Signers

Signer	Proxy Signer	Signed Status	Signed Date
JOHNSON, JENNIFER L.		signed	12/09/2010

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["Confidential Information"](#)



Reference ID: 2908608

2/18/2011

Date: January 27, 2011

From: Jacqueline Ryan, Medical Officer, DAGID/GHDBR
To: **Jennifer Johnson**
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research

Subject: NDA 022074 Ipsen Pharma Somatuline Depot (Lanreotide) Injection
Syringe Re-design

Summary:

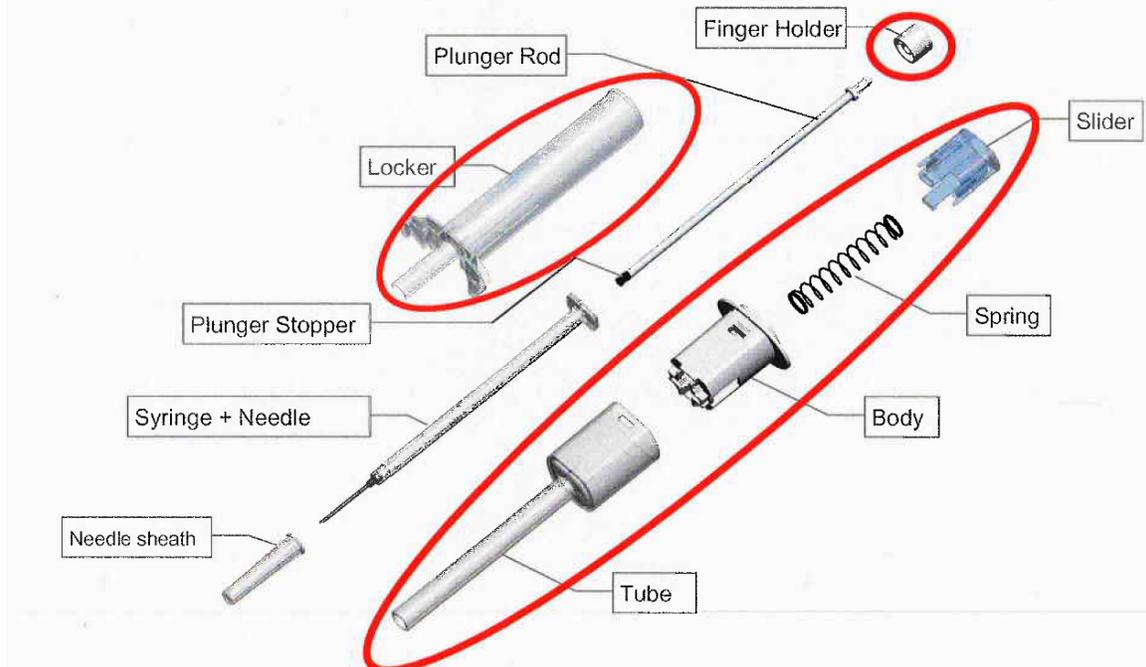
Center for Drug Evaluation and Research has requested a consult from the Center for Devices and Radiological Health, regarding the addition of a sharps protection feature for the Applicant's pre-filled Somatuline Depot syringes. Somatuline Depot (Lanreotide) Injection was originally approved on August 30, 2007, as 60 mg, 90 mg, and 120 mg injections in prefilled syringes. On April, 29, 2010, the Applicant submitted a prior approval supplement SLR-004 that introduces changes to the drug product container closure to add a sharps protection system to the syringe. To accommodate the changes, the Applicant has amended the labels and labeling.

Documents Reviewed:

NDA 002074 chemistry review and proposed labeling

Device Description:

The device consists of a single-dose, prefilled syringe with an affixed needle and with an affixed automatic needle protection system. The user must maintain pressure on the plunger of the device as it is withdrawn from the injection site to avoid activating the needle protection system.



CDRH Review:

Regarding Device Performance, we have reviewed the engineering drawings and device labeling. Based on the information provided in the submission, we have the following concerns.

Typically, devices with sharps injury prevention features are class II devices, subject to 21 CFR Part 820 Quality System Regulation, which include Design Controls. Design controls (21 CFR 820.30) are an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances. Design controls make systematic assessment of the design an integral part of a device's development. As a result, deficiencies in design input requirements, and discrepancies between the proposed designs and requirements, may be discovered and corrected earlier in the development process. We believe design controls increase the likelihood that the design transferred to production will translate into a device that is appropriate for its intended use.

The Applicant has not provided any performance data to demonstrate that the device is safe and effective for the intended use. CDRH typically requires bench testing and simulated clinical use testing for devices with sharps injury prevention features. If the Applicant's sharps injury prevention feature is currently legally marketed as a part of another device, the Applicant may identify that device in lieu of performing bench and simulated clinical use testing.

However, it should be noted that the proposed syringe and sharps protections system appears to differ from the usual method of administration for an injection. The user must use the thumb to maintain pressure on the plunger to avoid activation of the automatic needle shield safety system. If the user removes the thumb from the syringe plunger too early, the user may activate the safety system while the needle is still in the deep subcutaneous tissue. This activation may lead to early retraction of the needle and deposition of the drug in the superficial cutaneous tissue or improper dosing, thus raising concerns of safety and efficacy.

Recommendation

Based on our review of the submission, the following deficiency should be conveyed to the Applicant.

1. You have not performed any testing to demonstrate that the hazards associated with use of this sharps injury prevention device have been successfully mitigated. For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. Please review CDRH's Guidances, "Medical Devices with Sharps Injury Prevention Features" when evaluating device performance. This guidance can be located on FDA's website at the following location:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>

2. You have not performed any testing to demonstrate that the auto-injector utilized as part of this combination product is safe and effective for its intended use. Please provide performance data to demonstrate through bench testing that your device is safe and effective for its intended use. You should review FDA's Guidance Document "Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products, when developing the necessary bench testing to demonstrate the performance for your device. This Guidance document is located at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

3. You have not performed any human factors / simulated use testing to demonstrate that

you have mitigated the hazards associated with the use of your device.

Please conduct a design validation (human factors) study. We recommend that you review CDRH's Guidance "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management". This guidance is located on FDA's website at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>

We also encourage you to submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions, including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

4. Devices and Labeling Used
 - a. For design validation, the devices used in your testing should represent the final design, including the labeling.
 - b. Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.
5. User Tasks and Training
 - a. FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.
 - b. Please describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.
 - c. The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you provide and how it corresponded to realistic training levels.

6. Use Environment and Conditions
 - a. You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.
 - b. Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.
 - c. Please describe the testing environment and realism of the simulated use in sufficient detail for us to determine if they were appropriate for validation testing.
7. Study Participants
 - a. FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels) will use your device, you should include 15 from each group.
 - b. Regardless of the number of groups you test, please provide a rationale that these groups adequately represent the overall population of users for your device. Note that study participants should not be your own employees.
8. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

 - a. Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.
 - b. Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Please describe and provide a rationale for including each type of data you collect.

If you have any questions, please contact Dr. Jacqueline Ryan at (301) 796 – 9599.

Sincerely,

Jacqueline Ryan, MD
General Hospital Devices Branch
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

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/s/

JENNIFER L JOHNSON

02/22/2011

Consult review received by CDRH on January 28, 2011

**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: November 16, 2010

Application Type/Number: NDA 022074 SLR-004

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Somatuline Depot (Lanreotide) Injection
60 mg, 90 mg, and 120 mg syringe

Applicant: Ipsen Pharma

OSE RCM #: 2010-1569

1 INTRODUCTION

This review responds to a request from Division of Metabolism and Endocrinology Products (DMEP) for DMEPA review of the proposed labels and labeling of Somatuline Depot (Lanreotide) Injection, 60 mg, 90 mg, and 120 mg prefilled syringes for their vulnerability to medication errors.

Somatuline Depot (Lanreotide) Injection was originally approved on August 30, 2007, as 60 mg, 90 mg, and 120 mg injections in prefilled syringes. On April, 29, 2010, the Applicant submitted a prior approval supplement SLR-004 that introduces changes to the drug product container closure to add a sharps protection system to the syringe. To accommodate the changes, the Applicant has amended the labels and labeling. Additionally, the supplement introduces changes in the manufacturing process, which will be evaluated by Office of New Drug Quality Assessment.

2 METHODS, MATERIALS, AND RESULTS

Since Somatuline Depot is currently marketed, the Division of Medication Error Prevention and Analysis searched the Adverse Events Reporting System (AERS) database for any medication errors involving Somatuline Depot. This section describes the methods used for the AERS search as well as the methods used for evaluation of the labels for this review.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH STRATEGY

For this review, DMEPA performed an AERS search on August 13, 2010, for medication errors submitted for this product. The following criteria was used: active ingredient *Lanreotide*, trade name *Somatuline Depot*, and the verbatim terms *Lanre%* and *Somatu%*; and the MedDRA reactions *Medication Errors* (HLGT) and *Product Quality Issue* (PT) to identify medication errors that would be relevant to this review.

2.2 AERS RESULTS

The AERS search retrieved a total of 3 reports. Of these reports, one was excluded from further analysis because they were determined to adverse reactions not related to the product labeling issues. The remaining two reports involved errors with the use of Somatuline Depot (Lanreotide) Injection.

The first report involved errors of wrong route of administration and wrong duration that occurred in France. The patient was administered Somatuline LP (Lanreotide) intramuscularly every 3 months. Additionally, the product was stored at room temperature for two days, but based on information provided by Ipsen Pharma, the nurse decided to administer the injection. The patient suffered severe abdominal pain.

The second report involved an error of improper dose resulting in overdose. The patient was receiving Somatuline 90 mg and then 60 mg was added for a total dose of 150 mg over 5 months. The patient required surgery for cytolytic hepatitis with choledochal enlargement that required surgery. The relationship of Somatuline to the patient's diagnosis and surgery was considered dubious.

The carton labeling indicates on the principal display panel, *For deep subcutaneous injection*. The insert labeling provides clear instructions for dose and frequency of administration. Despite these errors, the labels and labeling for this product are sufficient.

2.3 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) and lessons learned from postmarketing experience to evaluate the labels and labeling that were submitted on April 29, 2010 (Appendices A and B; no image of insert labeling).

3 DISCUSSION

The Applicant proposes a new syringe with a sharps protection system. The proposed syringe requires a new technique for use that is different than the currently marketed syringe.

3.1 INTRODUCTION OF NEW SYRINGE

3.1.1 Sharps Protection System

The proposed syringe and sharps protections system differs from the usual method of administration for an injection. More specifically, after the user fully depresses the syringe plunger and the drug is administered, this system requires the user to maintain pressure on the syringe plunger after hearing the *click* sound. Maintaining thumb pressure on the syringe plunger after it is fully depressed and the drug is administered is not a usual step in the process of administering an injection. User removal of the thumb off the syringe plunger releases pressure and activates the sharps protection system. If the user removes their thumb too early, this activation may lead to retraction of the needle while it is in the patient's deep subcutaneous tissue.

DMEPA reviewed postmarketing medication error cases involving similarly designed pre-filled syringes in which the needle retracted while the nurse injected the drug. The nurse had difficulty injecting drug and attempted to reposition the needle, which led to needle retraction. This resulted in the patient not receiving the correct dose of medication. Since Somatuline Depot instructions for use state to slowly inject the drug and typically 20 seconds are needed to inject the full dose, DMEPA is concerned with the risk of the needle retracting prior to the patient receiving the full dose. The Applicant did not submit data that identifies or evaluates these risks.

This unique sharps protection system requires testing to demonstrate users can safely use this product. Additionally, this product was not approved by the Center for Devices and Radiological Health, Office of Device Evaluation (CDRH/ODE). We contacted CDRH/ODE and they confirmed this product requires their review prior to approval.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3.1.2 Non-latex Needle Sheath

Introduction of the non-latex sheath allows for safe use of Somatuline Depot for patients with latex allergy. The Applicant has removed the warning statement, “Warning: Needle Sheath Contains Dry Natural Rubber”, that appears on the insert and carton labeling. No additional safety measures are required.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation notes the proposed syringe and sharps protection system requires human factors usability testing to demonstrate that healthcare practitioners can safely use this product. Specifically, we are concerned with healthcare provider’s ability to keep the plunger depressed for the recommended time without activation of the sharps protections system. Additionally, DMEPA recommends DMEP consult CDRH/ODE for the evaluation of the proposed Somatuline Depot syringe and sharps protections system because this device has not been approved for use with this drug product.

Furthermore, our evaluation notes areas where information on the labels and labeling can be improved to minimize the potential for medication errors; however we reserve our final comments upon evaluation of human factors usability testing and completion of the consult from CDRH/ODE. We provide comments on the insert labeling in Section 4.1 *Comments to the Division*. Section 4.2 *Comments to the Applicant* contains our recommendations for the container pouch label and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Rita Tossa, OSE project manager, at 301-796-4053.

4.1 COMMENTS TO THE DIVISION

A. Section 2 – Dosage and Administration

1. Replace the symbols, > and <, with the words greater than and less than. These symbols (> and <) are considered dangerous abbreviations. They are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations². As part of a national campaign to avoid the use of dangerous abbreviations, symbols, and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 9/02/2010.

2. Create a subsection for Dosing for Renal and Hepatic Impairment so that this patient population is prominent. Currently, the dosing instructions for renally and hepatically impaired patients appear at the bottom of the dosage and administration section and can be easily overlooked. Creating a subsection entitled *Dose for Renal and Hepatic Impairment* will make this information more noticeable. For example:

2 DOSAGE AND ADMINISTRATION

2.1 (b) (4)

2.2 Dose for Renal and Hepatic Impairment

(b) (4) Instructions for Use

B. Section 2.1 – Instructions for use, (b) (4)

Revise the terms (b) (4) to read (b) (4) (90 degree angle).

C. Section 2.1 – Instructions for use, (b) (4)

Revise the sentence (b) (4), to read:

(b) (4)

D. Highlights of Prescribing Information - Dosage Forms and Strengths,

Section 3 – Dosage Forms and Strengths, Section 11 – Description, Section 12. 3 (b) (4), Section 14 – Clinical Studies

Revise the statement 60, 90 and 120 mg to read 60 mg, 90 mg, and 120 mg.

Note the addition of *mg* after each strength.

4.2 COMMENTS TO THE APPLICANT

A. Syringe and Sharps Protections System

We have two concerns with your proposed syringe and sharps protection system. The first concern relates to the requirement to maintain pressure on the syringe plunger after administering the drug to avoid retraction of the needle. DMEPA is concerned with the risk of the needle retracting while it is in the patient's deep subcutaneous tissue.

The second concern relates to the risk of needle retraction during the slow injection. Postmarketing medication error cases involving needle retraction have been reported with similarly designed pre-filled syringes. These cases describe the needle retracting while the user injected the drug and repositioned the needle during the slow injection, resulting in the patient not receiving the complete dose. Since Somatuline Depot instructions for use state to slowly inject the drug and typically 20 seconds are needed

to inject the full dose, DMEPA is concerned with the risk of the needle retracting prior to the patient receiving the full dose.

Have you conducted human factors usability studies to demonstrate safe use of this drug device product and addressed the above concerns? If so, please submit to the Agency for review. If not, we request you submit a protocol for review of usability study for this product.

B. Pouch Carton Labeling

1. Revise to include the proprietary and established names. Currently, the pouch container label displays only the strength of Somatuline Depot and a diagram illustrating removal of the plunger protector. The pouch container label must contain the name of the product for identification purposes should the pouch be removed from the carton.

2. [REDACTED] (b) (4) and add instructions for the user to read the package insert instructions. [REDACTED] (b) (4)

[REDACTED]

However, there are other important instructions the user must follow to ensure correct use of the product.

3. Add a statement such as “Tear here” to provide guidance on how to open the pouch and remove the syringe.

C. Carton Labeling

1. Revise the appearance of *ml* to read *mL*. For example *90 mg/0.3 ml* should read *90 mg/0.3 mL*.

2. Relocate the statement *Rx Only* toward the lower left portion of the carton labeling.

3. Revise the statement [REDACTED] (b) (4) to read:

For single use only - Discard unused portion.

Note deletion of [REDACTED] (b) (4).

REFERENCES

5 ADVERSE EVENTS REPORTING SYSTEM (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

JIBRIL ABDUS-SAMAD
11/16/2010

DENISE P TOYER
11/18/2010

CAROL A HOLQUIST
11/18/2010



**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: September 16, 2010

To: Mary Parks, M.D., Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Melissa Hulett RN, BSN, MSBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Somatuline Depot (lanreotide) Injection

Application Type/Number: NDA 22-074

Submission Number: S-004

Applicant/sponsor: Beaufour Ipsen Pharma

OSE RCM #: 2010-1575

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Somatuline Depot (lanreotide) Injection for deep subcutaneous injection.

On October 27, 2006 Somatuline Depot (lanreotide) Injection was originally submitted by Beaufour Ipsen Pharma and was granted Orphan status. Somatuline Depot (lanreotide) Injection received initial approval on August 30, 2007 for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. On May 3, 2010 Beaufour Ipsen Pharma submitted a CMC supplement addressing a change to the container closure system and harmonizing the dosage strengths with a single syringe type. OSE previously reviewed the proposed PPI for Somatuline Depot (lanreotide) on August 8, 2007. At the request of DMEP, DRISK is providing a comprehensive review of the PPI at this time.

2 MATERIAL REVIEWED

- Draft Somatuline Depot (lanreotide) Injection Prescribing Information (PI) submitted May 3, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on September 7, 2010.
- Draft Somatuline Depot (lanreotide) Injection Patient Package Insert (PPI) submitted on May 3, 2010, revised by the review division throughout the review cycle and received by DRISK on September 7, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- revised the PPI to be consistent with current patient labeling standards
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please send DRISK's comments to the Applicant and copy us on the correspondence. Let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22074	ORIG-1	BEAUFOR IPSEN PHARMA	SOMATULINE DEPOT, 60,90,120 MG
NDA-22074	SUPPL-4	BEAUFOR IPSEN PHARMA	SOMATULINE DEPOT, 60,90,120 MG

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/s/

MELISSA I HULETT
09/16/2010

LASHAWN M GRIFFITHS
09/16/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022074Orig1s004

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

December 29, 2014

This COR-SNDAIR-03 (General Advice Letter) was originally coded as a COR-SNDAACTION-05 (Approval). This letter contained duplicates of the 120-mg strength pouch labels instead of the 60 and 90-mg strength labels. This was the second copy of the Approval letter sent to the Applicant. The duplicate labels were created during the conversion of PDF. The conversion issue was corrected and a third copy of the letter was checked in on December 17, 2014. The letter was backdated to October 28, 2014 to maintain the original action date.

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/s/

JEAN-MARC P GUETTIER
10/28/2014

November 19, 2014

This COR-SNDAIR-03 (General Advice Letter) was originally coded as a COR-SNDACTION-05 (Approval). The letter included duplicates of the 120 mg strength pouch labels instead of the 60 mg and 90 mg labels. A corrected letter was checked in on November 14, 2014 and backdated to October 28, 2014 to maintain the original action date.

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/s/

JEAN-MARC P GUETTIER
10/28/2014

From: Johnson, Jennifer
To: "Mary Jane CHEAH"
Cc: Steven SCOTT; (b) (6)
Bcc: Johnson, Jennifer
Subject: NDA 22074/S-004 (Somatuline Depot): Final Agreed-Upon Labels and Labeling
Date: Monday, October 27, 2014 3:21:00 PM
Attachments: [2014-October CLEAN USPI - FINAL - 10 15 14.doc](#)
[1. IFU Somatuline Depot - Revised per FDA 2014-05-12.pdf](#)
[5. Plunger Protector Label.pdf](#)
[2. Syringe Labels for 60, 90, and 120 mg.pdf](#)
[Pouch Labels 60 mg, 90 mg, 120 mg on colored background - 2014-06-18.pdf](#)
[A. 60 mg pouch - 3 in 1 - 2014-06-18.pdf](#)
[A. 90 mg pouch - 3 in 1 - 2014-06-18.pdf](#)
[A. 120 mg pouch - 3 in 1 - 2014-06-18.pdf](#)
[C. 60 mg Carton for FDA Submission 2014-06-18.pdf](#)
[C. 90 mg Carton for FDA Submission 2014-06-18.pdf](#)
[C. 120 mg Carton for FDA Submission 2014-06-18.pdf](#)

Dear Mary Jane,

This email is to confirm that we have reviewed the clean Word version of the Somatuline Depot package insert/patient package insert you sent via email on October 15, 2014, and this version (attached again to this email) can be considered the final agreed-upon PI/PPI for the purpose of the S-004 action letter.

The other relevant (revised) pieces of labeling (also attached) can also be considered final/agreed-upon:

- Healthcare Provider Instructions for Use (IFU), submitted to me via email on May 15, 2014
- Plunger protector label, submitted with Complete Response submission on January 16, 2014
- Syringe labels, submitted to me via email on May 15, 2014
- Pouch (sachet) labels, submitted to me via email on June 18, 2014
- Carton labels, submitted to me via email on June 18, 2014

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Mary Jane CHEAH [mailto:mary.jane.cheah@ipsen.com]
Sent: Wednesday, October 15, 2014 2:24 PM
To: Johnson, Jennifer
Cc: Steven SCOTT; (b) (6)

Subject: NDA 22074/S-004 (Somatuline Depot): Ipsen Accepts All FDA Revisions to the PI

Dear Jennifer,

Re NDA 22074/S-004 (Somatuline Depot), we accept all FDA revisions to the Package Insert.

Attached is the PI as sent to us by you yesterday afternoon, showing all FDA comments in Track Changes, and a CLEAN version with all comments accepted.

Please let me know what I can do next to help bring this to a happy close.

Your efforts and attention are, as always, very much appreciated.

Best regards,
Mary Jane

Mary Jane Cheah
Associate Director, Regulatory Affairs
Ipsen Biopharmaceuticals, Inc.
Tel: 908-275-6471
Email: mary.jane.cheah@ipsen.com

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]

Sent: Tuesday, October 14, 2014 2:31 PM

To: Mary Jane CHEAH

Cc: Steven SCOTT; (b) (6)

Subject: NDA 22074/S-004 (Somatuline Depot): FDA comments on PI and Patient Instructions

Dear Mary Jane,

Please find attached our edits and comments on the Somatuline Depot PI and Patient Instructions. We have made our edits to the tracked changes Word version that you submitted to S-004 on January 16, 2014.

You may send your response draft back to me via email; an official submission (amendment) to your sNDA is not necessary at this time.

Let me know if you have any questions or concerns.
Thank you again for your patience.

Kind Regards,
Jennifer

Jennifer Johnson

Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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"Ipsen Biopharm Limited. Registered in Wales no. 1653765. Registered office: Ash Road, Wrexham Industrial Estate, Wrexham, UK, LL13 9UF." "This email (including any attachment) is intended only for the use by the recipients named above and contains proprietary information that may be confidential, copyrighted and/or privileged. Unauthorized disclosure, use or copying is prohibited. If this email was sent to you in error or if you are not an intended recipient, please notify the sender immediately and delete this email from your systems. Thank you."p>

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

/s/

JENNIFER L JOHNSON

10/27/2014

Email to applicant, confirming final agreed-upon labeling and labels for action on S-004

From: Johnson, Jennifer
To: ["Mary Jane CHEAH"](#)
Cc: [Steven SCOTT](#); (b) (6)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 22074/S-004 (Somatuline Depot): FDA comments on PI and Patient Instructions
Date: Tuesday, October 14, 2014 2:30:00 PM
Attachments: [FDA edits Somatuline Depot PI 14 Oct 2014 NDA 22074 S004.doc](#)

Dear Mary Jane,

Please find attached our edits and comments on the Somatuline Depot PI and Patient Instructions. We have made our edits to the tracked changes Word version that you submitted to S-004 on January 16, 2014.

You may send your response draft back to me via email; an official submission (amendment) to your sNDA is not necessary at this time.

Let me know if you have any questions or concerns.
Thank you again for your patience.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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

/s/

JENNIFER L JOHNSON

10/14/2014

FDA edits/comments on PI/PPI for NDA 22074/S-004; concurrence from clinical reviewer Marina Zemskova and clinical team leader Dragos Roman on 10/10/14, and from CMC reviewer Pallaiah Thammana (and TL/Branch Chief Ramesh Raghavachari) on 8/28/14

MANDATORY: Send a copy of the consult request form to the Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH/Office of Device Evaluation
Division: DAGID/GHDB
Mail Code: HF
Consulting Reviewer Name: LCDR Keith Marin
Building/Room #: WO66 Room 2567
Phone #: 301-796-2462
Fax #: 301-847-8109
Email Address: keith.marin@fda.hhs.gov
RPM/CSO Name and Mail Code: Branch Chief: Richard Chapman

From (Originating Center):

Center: CDER
Division: DMEP
Mail Code: HF D-510
Requesting Reviewer Name: Jennifer Johnson
Building/Room #: WO22 Room 3114
Phone #: 301-796-2194
Fax #: 301-796-9712
Email Address: jennifer.johnson@fda.hhs.gov
RPM/CSO Name and Mail Code: same as above
Requesting Reviewer's Concurring Supervisor's Name: Pam Lucarelli

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 28, 2014

Requested Completion Date: August 29, 2014

Submission/Application Number: NDA 22074/S-004
(Not Barcode Number)

Submission Type: sNDA (manufacturing suppleme
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: October 4, 2011

Official Submission Due Date: ASAP, see below

Name of Product: Somatuline Depot (lanreotide) injection: 60 m Name of Firm: Ipsen Pharma

Intended Use: Approved indication: long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

1) Complete Response resubmission (SDN 167) received 10/4/11 (2nd review cycle), 2) Complete Response letter issued 5/4/11 (1st review cycle), 3) CDRH (device) review dated 2/22/11 (includes deficiencies conveyed to applicant in 5/4/11 CR letter, which were addressed by applicant in 10/4/11 resubmission)

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

This CMC supplement S-004 (labeling included, thus OND-managed) was originally submitted on 4/29/10 and proposed changes to the drug substance and drug product manufacturing processes, and to the drug product container closure system, which includes addition of a sharps protection system to the syringe to help prevent needle stick injury after use. The syringe dimensions for the 3 dosage strengths have been harmonized to have the 3 dosage strengths packaged with the same syringe and needle. A Complete Response letter issued on 5/4/11. The applicant submitted a Complete Response resubmission on 10/4/11 to address the deficiencies conveyed in the 5/4/11 CR letter, including #2 and #3 regarding the device (which originated from the CDRH device review by Jacqueline Ryan dated 2/22/11). The DMEP RPM (Jennifer Johnson) submitted an intercenter consult request on 1/20/12, directed to Jacqueline Ryan (CDRH - device review) and Quynh Nguyen (CDRH - human factors study review). See next page ==>>

A human factors study review was completed by Quynh Nguyen on 2/3/12; however, a device review was never completed in response to this consult request. A Complete Response letter issued on 2/3/12. On 7/2/12, the applicant submitted a human factors study protocol for Agency review, which was consulted to CDRH (Quynh Nguyen) on 7/19/12, and the review was completed on 9/10/12. On 12/21/12, the applicant submitted a response to the 2/3/12 CR letter; however, because it did not contain the required electronic labeling components, an Acknowledge Complete Response letter issued. The applicant submitted the required missing components on 1/24/13 (so this submission was designated as the Complete Response resubmission). Another intercenter consult request was sent to Quynh Nguyen on 1/14/13, and the review was completed on 4/26/13. A Complete Response letter (3rd review cycle) issued on 5/25/13. The applicant submitted a response to the 5/25/13 CR letter (4th cycle) on 1/16/14. An intercenter consult request was sent to CDRH (Quynh Nguyen) on 2/26/14, and the review was completed on 4/28/14. This review included no deficiencies and stated that the human factors study and the Instructions for Use (IFU) incorporated in the HFS were acceptable. DMEPA also concurred with this assessment.

Therefore, the deficiencies related to the human factors study (protocol and report) across numerous review cycles have been communicated to the applicant and sufficiently addressed. However, we still need confirmation from CDRH that the following deficiencies pertaining to the device itself (refer to CR letter dated 5/4/11) have been sufficiently addressed before approving this supplement:

2. You have not performed any testing to demonstrate that the hazards associated with use of this sharps injury prevention device have been successfully mitigated. For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. We recommend that you review the Center for Devices and Radiological Health (CDRH) Guidance Document, “Medical Devices with Sharps Injury Prevention Features” when evaluating device performance. This document is located at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>
3. You have not performed any testing to demonstrate that the auto-injector utilized as part of this combination product is safe and effective for its intended use. Please provide performance data to demonstrate through bench testing that your device is safe and effective for its intended use. We recommend that you review FDA’s Guidance Document “Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products”, when developing the necessary bench testing to demonstrate the performance for your device. This document is located at:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

The relevant documents have been attached to this consult, and I am happy to provide any further information, reviews, etc., that may be helpful. Feel free to contact me with any questions.

Johnson, Jennifer

From: Ryan, Jaqueline
Sent: Friday, January 28, 2011 12:34 PM
To: Johnson, Jennifer
Subject: RE: REVISED - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)
Follow Up Flag: Follow up
Due By: Friday, January 28, 2011 1:00 PM
Flag Status: Red
Attachments: NDA 20774 NThakur comments.doc

Jennifer,
Please accept the REVISED consult attached.
Thanks.
Jacqueline Ryan

From: Johnson, Jennifer
Sent: Wednesday, January 26, 2011 1:27 PM
To: Ryan, Jaqueline; Thakur, Nikhil
Cc: Milone, Joseph; Baker, Marsha *
Subject: RE: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Thanks so much for the update - we really appreciate it!

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: Ryan, Jaqueline
Sent: Wednesday, January 26, 2011 1:23 PM
To: Thakur, Nikhil
Cc: Milone, Joseph; Baker, Marsha *; Johnson, Jennifer
Subject: RE: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Will be done 1/27/10.
Jacqueline Ryan

From: Thakur, Nikhil
Sent: Wednesday, January 26, 2011 12:33 PM
To: Ryan, Jaqueline
Subject: FW: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Perhaps I missed something here... in a meeting... will catch up with you at 1:00 PM.

Sincerely,
Nikhil

Nikhil Thakur
LCDR, USPHS
Combination Products Team Leader

Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Anesthesiology, General Hospital, Dental and Infection Control Devices
General Hospital Devices Branch

Address:
10903 New Hampshire Avenue,
Bldg: WO66, Rm 2562

Reference ID: 3600575
2/18/2011

Darrts Login

Silver Spring, MD 20993

Telephone: (301) 796 - 5536

Fax: (301) 847 - 8109

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From: OC Combination Products
Sent: Wednesday, January 26, 2011 12:19 PM
To: Thakur, Nikhil; Ryan, Jaqueline
Cc: OC Combination Products; Baker, Marsha *
Subject: FW: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Hi Nikhil and Jaqueline,

Can you please provide CDER with a status update for this consult request? CDER had requested a completion date of 1/11/11. When do you expect this request to be completed?

Sincerely,
Joe

Joseph Milone, Ph.D.
Biologist
Office of Combination Products
Office of the Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
WO 32 Rm 5134

10903 New Hampshire Avenue
Silver Spring, MD 20996-0002
joseph.milone@fda.hhs.gov
Tel: 301-796-8939 Fax: 301-847-8619

<http://www.fda.gov/CombinationProducts/default.htm>

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From: Johnson, Jennifer
Sent: Friday, January 21, 2011 6:27 PM
To: OC Combination Products
Subject: RE: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)

Dear Marsha,

Thanks for checking in. No, we have not received comments regarding this consult request just yet.

If you wouldn't mind checking on the status of the consult, that would be great.

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: OC Combination Products
Sent: Thursday, January 20, 2011 1:32 PM
To: Johnson, Jennifer
Subject: FW: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)
Reference ID: 3600575

2/18/2011

Dear Jennifer,

Have you received comments/a review for the below/attached consult request? It is still open in my tracking database. If you did receive comments, what date did you receive them? I need this information to close it out of the database. Also, please let me know if the due date listed on the consult was changed/re-negotiated prior to completion of the consult request. Thank you.

Sincerely,
Marsha Baker
OCP
301-796-8935

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Thursday, December 09, 2010 7:08 PM
To: Thakur, Nikhil; OC Combination Products; Sharma, Khushboo; Johnson, Jennifer
Subject: Finalized - NDA 22074 Intercenter/Combination Products Consult (FRM-CONSULT-02)



[Proceed to DARRTS Login](#)

Finalized - Intercenter/Combination Products Consult (FRM-CONSULT-02)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
FRM-CONSULT-02	CONSULT	Intercenter/Combination Products Consult

Linked Supporting Documents

Application Type	Application Number	Sponsor	Product Name (Preferred)	Submission Type	Submission Number	Group Id	Supporting Document Number	Category	Subcategory
NDA	22074	BEAUFOR IPSEN PHARMA	SOMATULINE DEPOT, 60,90,120 MG	SUPPL	4	204685	58	New	Supplement

Linked Submissions

Application Type	Application Number	Sponsor	Preferred Product Name	Submission Type	Submission Number	Submission Classif
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Signers

Signer	Proxy Signer	Signed Status	Signed Date
JOHNSON, JENNIFER L.		signed	12/09/2010

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["Confidential Information"](#)



Date: January 27, 2011

From: Jacqueline Ryan, Medical Officer, DAGID/GHDBR
To: **Jennifer Johnson**
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research

Subject: NDA 022074 Ipsen Pharma Somatuline Depot (Lanreotide) Injection
Syringe Re-design

Summary:

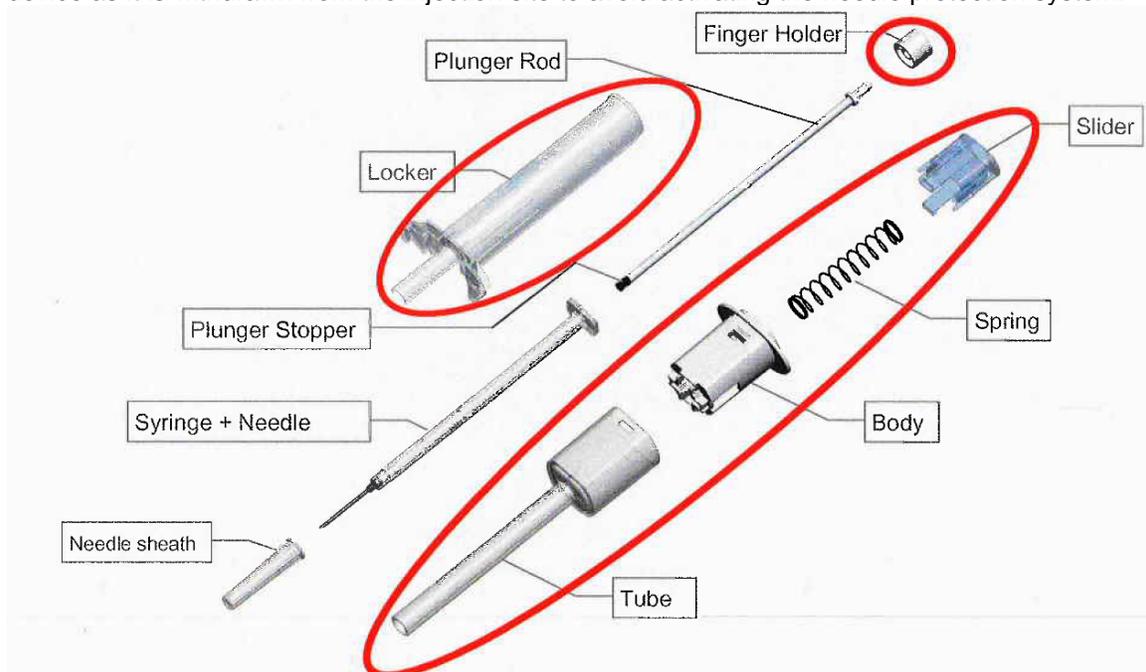
Center for Drug Evaluation and Research has requested a consult from the Center for Devices and Radiological Health, regarding the addition of a sharps protection feature for the Applicant's pre-filled Somatuline Depot syringes. Somatuline Depot (Lanreotide) Injection was originally approved on August 30, 2007, as 60 mg, 90 mg, and 120 mg injections in prefilled syringes. On April, 29, 2010, the Applicant submitted a prior approval supplement SLR-004 that introduces changes to the drug product container closure to add a sharps protection system to the syringe. To accommodate the changes, the Applicant has amended the labels and labeling.

Documents Reviewed:

NDA 002074 chemistry review and proposed labeling

Device Description:

The device consists of a single-dose, prefilled syringe with an affixed needle and with an affixed automatic needle protection system. The user must maintain pressure on the plunger of the device as it is withdrawn from the injection site to avoid activating the needle protection system.



CDRH Review:

Regarding Device Performance, we have reviewed the engineering drawings and device labeling. Based on the information provided in the submission, we have the following concerns.

Typically, devices with sharps injury prevention features are class II devices, subject to 21 CFR Part 820 Quality System Regulation, which include Design Controls. Design controls (21 CFR 820.30) are an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances. Design controls make systematic assessment of the design an integral part of a device's development. As a result, deficiencies in design input requirements, and discrepancies between the proposed designs and requirements, may be discovered and corrected earlier in the development process. We believe design controls increase the likelihood that the design transferred to production will translate into a device that is appropriate for its intended use.

The Applicant has not provided any performance data to demonstrate that the device is safe and effective for the intended use. CDRH typically requires bench testing and simulated clinical use testing for devices with sharps injury prevention features. If the Applicant's sharps injury prevention feature is currently legally marketed as a part of another device, the Applicant may identify that device in lieu of performing bench and simulated clinical use testing.

However, it should be noted that the proposed syringe and sharps protections system appears to differ from the usual method of administration for an injection. The user must use the thumb to maintain pressure on the plunger to avoid activation of the automatic needle shield safety system. If the user removes the thumb from the syringe plunger too early, the user may activate the safety system while the needle is still in the deep subcutaneous tissue. This activation may lead to early retraction of the needle and deposition of the drug in the superficial cutaneous tissue or improper dosing, thus raising concerns of safety and efficacy.

Recommendation

Based on our review of the submission, the following deficiency should be conveyed to the Applicant.

1. You have not performed any testing to demonstrate that the hazards associated with use of this sharps injury prevention device have been successfully mitigated. For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. Please review CDRH's Guidances, "Medical Devices with Sharps Injury Prevention Features" when evaluating device performance. This guidance can be located on FDA's website at the following location:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>

2. You have not performed any testing to demonstrate that the auto-injector utilized as part of this combination product is safe and effective for its intended use. Please provide performance data to demonstrate through bench testing that your device is safe and effective for its intended use. You should review FDA's Guidance Document "Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products, when developing the necessary bench testing to demonstrate the performance for your device. This Guidance document is located at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

3. You have not performed any human factors / simulated use testing to demonstrate that

you have mitigated the hazards associated with the use of your device.

Please conduct a design validation (human factors) study. We recommend that you review CDRH's Guidance "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management". This guidance is located on FDA's website at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>

We also encourage you to submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions, including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

4. Devices and Labeling Used
 - a. For design validation, the devices used in your testing should represent the final design, including the labeling.
 - b. Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

5. User Tasks and Training
 - a. FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.
 - b. Please describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.
 - c. The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you provide and how it corresponded to realistic training levels.

6. Use Environment and Conditions
 - a. You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.
 - b. Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.
 - c. Please describe the testing environment and realism of the simulated use in sufficient detail for us to determine if they were appropriate for validation testing.
7. Study Participants
 - a. FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels) will use your device, you should include 15 from each group.
 - b. Regardless of the number of groups you test, please provide a rationale that these groups adequately represent the overall population of users for your device. Note that study participants should not be your own employees.
8. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

 - a. Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.
 - b. Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Please describe and provide a rationale for including each type of data you collect.

If you have any questions, please contact Dr. Jacqueline Ryan at (301) 796 – 9599.

Sincerely,

Jacqueline Ryan, MD
General Hospital Devices Branch
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: Center for Devices and Radiological Health
Division: Div of Anesthesiology, Gen Hospital,
Infection Control & Dental Devices, Anesthesiology &
Respiratory Devices Branch/General Hospital Devices
Branch

Mail Code: HF_-

Consulting Reviewer Name: Jacqueline Ryan and
QuynhNhu Nguyen

Building/Room #: WO66 Room 1257 (JR)/WO66 Room
2531 (QN)

Phone #: 301-796-9599 (JR)/301-796-6273 (QN)

Fax #: N/A

Email Address: jacqueline.ryan@fda.hhs.gov and
quynht.nguyen@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Metabolic and Endocrine Products

Mail Code: HFD-510

Requesting Reviewer Name: Reasol Agustin, Division
of Medication Error Prevention and Analysis (DMEPA)

Building/Room #: WO 51 Room 2204

Phone#: 301-796-2932

Fax #:

Email Address: reasol.agustin@fda.hhs.gov

RPM/CSO Name and Mail Code: Jennifer Johnson,
HFD-510

Requesting Reviewer's Concurring Supervisor's Name:
Carlos Mena-Grillasca (DMEPA)

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: January 20, 2012 (original email
October 7, 2011)

Submission/Application Number: NDA 22074/S-004

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: October 4, 2011

Name of Product: Somatuline Depot (lanreotide)
Injection, 60 mg, 90 mg, 120 mg

Requested Completion Date: **PDUFA goal date
February 4, 2012**

Submission Type: NDA

Official Submission Due Date: February 4, 2012

Name of Firm: Ipsen Pharma (U.S. Agent: Biomeasure
Incorporated)

Intended Use: long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy (orphan indication)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): The original CMC supplement provided for changes to the drug product container closure system to add a sharps protection system to the syringe. (Refer to the Complete Response letter which issued on May 4, 2011, and contained mainly CDRH and DMEPA deficiencies.) Please review the device performance information (Jackie Ryan) and the human factors information (QuynhNhu Nguyen). Refer to CMC review dated August 17, 2010, to DMEPA review dated November 18, 2010 and to CDRH review dated February 22, 2011 (DARRTS date; actual review completed January 27, 2011, by Jackie Ryan). I have scanned the resubmission and uploaded it to the DMEP eRoom. Also, here is the direct EDR link to the electronic components, including an injection demonstration video: \\CDSESUB4\NONECTD\NDA022074\4941684. Feel free to contact me with any questions. Many thanks, Jennifer Johnson, RPM (WO22 Rm 3114, 301-796-2194, jennifer.johnson@fda.hhs.gov)

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

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/s/

JENNIFER L JOHNSON
07/28/2014

From: Johnson, Jennifer
To: "Mary Jane CHEAH"
Cc: (b) (6); Steven SCOTT; (b) (6)
Bcc: Johnson, Jennifer
Subject: NDA 22074/S-004 (Somatuline Depot): FDA Requested Revisions to Carton/Container Labels submitted May 15, 2014
Date: Wednesday, June 11, 2014 6:01:00 PM

Dear Mary Jane,

Our DMEPA colleagues have reviewed the revised IFU and carton/container labels that you sent to me via email on May 15th. In response, we have the following requests for further revision to the pouch and carton labeling prior to the approval of this sNDA:

A. Pouch labeling - Front

- a. Relocate the route of administration statement ("For deep subcutaneous injection") to be listed after the proprietary name, established name, and dosage form, on a separate line to reduce the risk of this important information from being overlooked. Additionally, please increase the prominence of the route of administration statement by using bold text.

Suggested order of information to be listed may include:

Somatuline Depot (lanreotide) Injection
For deep subcutaneous injection
IMPORTANT Somatuline Depot should be administered by a healthcare professional. Call 1-888-980-2889 and request training that includes delivering a practice injection.
REMEMBER Read both sides of the yellow instructions for use and prescribing information for complete instructions.
STORAGE Refrigerate at 2°C – 8°C (36°F – 46°F) in its original package.
Protect from light.
Keep device out of reach of children

- b. To increase the readability of important statements, increase the amount of white space between statements and/or increase the prominence of information.

B. Pouch labeling – Back

- a. On the pouch label (to be placed on the back side of the pouch), relocate the following statement "For single use only. Discard unused portion." to be listed on a separate line from the established name of the product to reduce the risk of this important information from being overlooked.

C. Carton labeling

- a. Relocate the statement of strength to be listed on a separate line from the established name and dosage form of the product to reduce the risk of this important information from being overlooked.
- b. Relocate the route of administration statement ("For deep subcutaneous injection") to be listed after the proprietary name, established name, and dosage form, on a separate line to reduce the risk of this important information from being

overlooked. Additionally, please increase the prominence of the route of administration statement by using bold text.

Suggested order of information to be listed may include:

Somatuline Depot
(lanreotide) Injection
60 mg/0.2 mL
For deep subcutaneous injection
For single use only. Discard unused portion.
Somatuline Depot should be administered by a healthcare professional.
Leave at room temperature for 30 minutes before administration.

- c. To increase the readability of important statements, increase the amount of white space between statements and/or increase the prominence of information.

The revised labels can be submitted to me via email.
Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Mary Jane CHEAH [mailto:mary.jane.cheah@ipsen.com]
Sent: Thursday, May 15, 2014 6:27 PM
To: Johnson, Jennifer
Cc: (b) (6) Steven SCOTT; (b) (6)
Subject: RE: NDA 22074/S-004 (Somatuline Depot): FDA Requested Revisions to IFU and Carton/Container Labels

Dear Jennifer,

Regarding Somatuline® Depot (lanreotide) Injection, NDA 22074/S-004:

We have revised all packaging to reflect the changes you communicated to us on Monday, May 12th.

The revised packaging is attached, and your email to us is below.

One extra change was made to the Instructions for Use (IFU) to carry over, for consistency, a

comment you made on the cartons.

The original IFU, page 1 had read on the top, left-hand portion, "2. [REDACTED] (b) (4)
[REDACTED] (b) (4)

That line now reads, "2. Somatuline Depot should be administered by a healthcare professional."

All other revisions were made exactly as directed.

Thank you very much for your input.

Please let us know if we can do anything further.

We look forward to receiving comments on our USPI.

Best regards,
Mary Jane

Mary Jane Cheah
Sr Manager, Postmarketing Regulatory Affairs
Ipsen Biopharmaceuticals, Inc.
Tel: 908-275-6471
Email: mary.jane.cheah@ipsen.com

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Monday, May 12, 2014 7:28 PM
To: Mary Jane CHEAH
Cc: [REDACTED] (b) (6); Steven SCOTT
Subject: NDA 22074/S-004 (Somatuline Depot): FDA Requested Revisions to IFU and Carton/Container Labels

Dear Mary Jane,

We have completed our review of your Instructions for Use (IFU) and carton/container labels submitted to NDA 22074/S-004, Somatuline Depot (lanreotide) injection on January 16 and April 4, 2014, and have the following recommendations and revisions:

1. Instructions for Use

a) Remove Step [REDACTED] (b) (4)
[REDACTED] It's important that the patient remains as still as possible during the injection" as this information is repeated from Step B6.

b) Consider revising the statement, [REDACTED] (b) (4)

(b) (4) in Step C9 to read:

“Remove the syringe from the injection site WHILE keeping your finger on the plunger rod” in order to clarify the intended meaning of the instruction.

2. Syringe label

a) Revise the spelling of the word “Manufacturer” on the proposed syringe label for the 120 mg/0.5 mL strength.

b) Include the following statement regarding package type, “Discard unused portion” as this is important information that may be overlooked by the user if the carton labeling is discarded. Suggested text may include: “For single use only – Discard unused portion” as stated on your carton labeling.

3. Pouch labeling

a) We recommend the labels and labeling should conform with the United States Pharmacopeia (USP) General Chapter <1> Injections. Revise statements of strength when listed anywhere on the labeling so that strengths are expressed in terms of total strength per total amount of milliliters. For example, revise “60 mg” to “60 mg/0.2 mL” or “60 mg per 0.2 mL”.

b) Include storage information on the pouch labeling per Guidance: Container Labels and Carton Labeling, April 2013 as this is important information that may be overlooked by the user if the carton labeling is discarded.¹ Suggested text may include: “Storage: Refrigerate at 2°C-8°C (36°F-46°F) in its original package. Protect from light.”

c) Include route of administration, “For deep subcutaneous injection”, as this is important information that may be overlooked by the user if the carton labeling is discarded.

d) Include the following statement regarding package type, “Discard unused portion” as this is important information that may be overlooked by the user if the carton labeling is discarded. Suggested text may include: “For single use only – Discard unused portion” as stated on your carton labeling.

e) Reorient the product barcode and NDC number in the same direction and field of vision as other text on the pouch labeling (i.e., readable without having to turn or rotate the pouch) in accordance with 21 CFR 201.15.

f) Revise the following statement (b) (4) as this statement is contradictory to information in Section 2 Dosage and Administration of the Full Prescribing Information, where it states that Somatuline Depot should be administered by a healthcare

professional. Suggested text may include: “Important: Somatuline Depot should be administered by a healthcare professional. Call 1-(800)-XXX-XXXX and request training that includes delivering a practice injection.”

4. Carton labeling

a) See comment 3(a) above.

b) Relocate the NDC number from the back panel to appear prominently in the top third of the principal display panel in accordance with 21 CFR 207.35(3)(iii).

c) Consider relocating the following sentence “Each syringe contains lanreotide acetate corresponding to 60 mg of lanreotide base per 0.2 mL solution, which is the equivalent of 60 mg lanreotide per syringe” from the principal display panel to the back panel as this information is repetitive of other information on the principal display panel and creates clutter.

d) In addition to the storage information listed on the back panel, add the following statement, “Protect from light”, per FDA Guidance: Container Labels and Carton Labeling, April 2013 as this is important information listed in Section 16 How Supplied/Storage and Handling of the Full Prescribing Information that may be overlooked by the user.¹

e) Remove the following statement (b) (4) as this statement is contradictory to information in Section 2 Dosage and Administration of the Full Prescribing Information, where it states that Somatuline Depot should be administered by a healthcare professional.

f) Include the following statement, “Somatuline Depot should be administered by a healthcare professional”, as both the product and Instructions for Use were validated through a Human Factors Study with healthcare professionals as the end users.

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

We request that the IFU and carton/container labels be revised in accordance with the above recommendations prior to approval of S-004. The revised IFU and labels can be submitted to me via email (i.e., no formal submission to the sNDA is needed at this time).

Revisions to the package insert will be sent via a separate email soon.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
06/11/2014

From: [Mistry, Mishale](#)
To: [Johnson, Jennifer](#)
Cc: [Maslov, Yelena](#); [Thomas, Terrolyn](#); [Nguyen, Quynh Nhu](#)
Subject: 2014-475-1 Somatuline (lanreotide) Labels and Labeling Review (NDA 22074/S-004)
Date: Friday, June 06, 2014 2:10:47 PM
Attachments: [1. IFU Somatuline Depot - Revised per FDA 2014-05-12.pdf](#)
[2. Syringe Labels for 60, 90, and 120 mg.pdf](#)
[3. Pouch Front Somatuline 60 mg.pdf](#)
[3. Pouch Front Somatuline 90 mg.pdf](#)
[3. Pouch Front Somatuline 120 mg.pdf](#)
[3. Pouch Labels for 60, 90, and 120 mg.pdf](#)
[4. Carton Somatuline 60 mg.pdf](#)
[4. Carton Somatuline 90 mg.pdf](#)
[4. Carton Somatuline 120 mg.pdf](#)

Hello Jennifer,

DMEPA reviewed the revised labels and labeling submitted by Ipsen Biopharmaceuticals, Inc on June 3, 2014. We noted that the labels and labeling can be improved by increasing white space and/or prominence of statements to increase readability and reduce the risk of important information being overlooked by end users.

Based on this review, DMEPA recommends that the following be implemented prior to the approval of this NDA:

A. Pouch labeling - Front

- a. Relocate the route of administration statement (“For deep subcutaneous injection”) to be listed after the proprietary name, established name, and dosage form, on a separate line to reduce the risk of this important information from being overlooked. Additionally, please increase the prominence of the route of administration statement by using bold text.

Suggested order of information to be listed may include:

Somatuline Depot (lanreotide) Injection
For deep subcutaneous injection
IMPORTANT Somatuline Depot should be administered by a healthcare professional. Call 1-888-980-2889 and request training that includes delivering a practice injection.
REMEMBER Read both sides of the yellow instructions for use and prescribing information for complete instructions.
STORAGE Refrigerate at 2°C – 8°C (36°F – 46°F) in its original package.
Protect from light.
Keep device out of reach of children

- b. To increase the readability of important statements, increase the amount of white space between statements and/or increase the prominence of information.

B. Pouch labeling – Back

- a. On the pouch label (to be placed on the back side of the pouch), relocate the following statement “For single use only. Discard unused portion.” to be listed on a separate line from the established name of the product to reduce the risk of this important information from being overlooked.

C. Carton labeling

- a. Relocate the statement of strength to be listed on a separate line from the established name and dosage form of the product to reduce the risk of this important information from being overlooked.
- b. Relocate the route of administration statement (“For deep subcutaneous injection”) to be listed after the proprietary name, established name, and dosage form, on a separate line to reduce the risk of this important information from being overlooked. Additionally, please increase the prominence of the route of administration statement by using bold text.

Suggested order of information to be listed may include:

Somatuline Depot
(lanreotide) Injection
60 mg/0.2 mL
For deep subcutaneous injection
For single use only. Discard unused portion.
Somatuline Depot should be administered by a healthcare professional.
Leave at room temperature for 30 minutes before administration.

- c. To increase the readability of important statements, increase the amount of white space between statements and/or increase the prominence of information.

If you have further questions or need clarification, please contact Terrolyn Thomas, OSE Project Manager, at 240-402-3981.

Please archive this email to DARRTS to serve as the DMEPA review/memo.

Many thanks in advance!

Best,
Mishale

Mishale Mistry, PharmD, MPH | *Safety Evaluator*
Division of Medication Error Prevention and Analysis (DMEPA)
FDA/CDER/Office of Surveillance and Epidemiology
10903 New Hampshire Avenue
Building 22, Room #4471
Silver Spring, MD 20993
Mishale.Mistry@fda.hhs.gov | Office: (240) 402-4577

From: Johnson, Jennifer
Sent: Tuesday, June 03, 2014 4:28 PM
To: Mistry, Mishale
Cc: Nguyen, Quynh Nhu; Maslov, Yelena
Subject: Somatuline Depot (NDA 22074/S-004) - *Revised IFU + carton/container labels from applicant*

Hi Mishale and Quynh,

Regarding Somatuline Depot (lanreotide) Injection, NDA 22074/S-004, the applicant sent to me revised IFU and carton/container labels incorporating your requests/recommendations for revisions (per your human factors/labeling reviews dated 4/21/14 and 4/28/14 in DARRTS).

The revised packaging is attached – a few notes from Ipsen:

One extra change was made to the Instructions for Use (IFU) to carry over, for consistency, a comment you made on the cartons.

The original IFU, page 1 had read on the top, left-hand portion, "2. [REDACTED] (b) (4) [REDACTED] (b) (4) "

That line now reads, "2. Somatuline Depot should be administered by a healthcare professional." All other revisions were made exactly as directed.

Let me know if these labels are acceptable, or if you need anything further.

Thanks!
Jennifer
6-2194

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/s/

JENNIFER L JOHNSON

06/06/2014

DMEPA review (by Mishale Mistry, with TL concurrence from Yelena Maslov) of applicant's revised labels submitted via email on 5/15/14 and forwarded to DMEPA on 6/3/14.

From: Johnson, Jennifer
To: ["Mary Jane CHEAH"](#)
Cc: (b) (6) [Steven SCOTT](#)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 22074/S-004 (Somatuline Depot): FDA Requested Revisions to IFU and Carton/Container Labels
Date: Monday, May 12, 2014 7:28:00 PM

Dear Mary Jane,

We have completed our review of your Instructions for Use (IFU) and carton/container labels submitted to NDA 22074/S-004, Somatuline Depot (lanreotide) injection on January 16 and April 4, 2014, and have the following recommendations and revisions:

1. Instructions for Use

a) Remove Step (b) (4). It's important that the patient remains as still as possible during the injection" as this information is repeated from Step B6.

b) Consider revising the statement, (b) (4) in Step C9 to read:

"Remove the syringe from the injection site WHILE keeping your finger on the plunger rod" in order to clarify the intended meaning of the instruction.

2. Syringe label

a) Revise the spelling of the word "Manufacturer" on the proposed syringe label for the 120 mg/0.5 mL strength.

b) Include the following statement regarding package type, "Discard unused portion" as this is important information that may be overlooked by the user if the carton labeling is discarded. Suggested text may include: "For single use only – Discard unused portion" as stated on your carton labeling.

3. Pouch labeling

a) We recommend the labels and labeling should conform with the United States Pharmacopeia (USP) General Chapter <1> Injections. Revise statements of strength when listed anywhere on the labeling so that strengths are expressed in terms of total strength per total amount of milliliters. For example, revise "60 mg" to "60 mg/0.2 mL" or "60 mg per 0.2 mL".

b) Include storage information on the pouch labeling per Guidance: Container Labels and Carton Labeling, April 2013 as this is important information that may be overlooked by the user if the carton labeling is discarded.¹ Suggested text may include: "Storage: Refrigerate

at 2°C-8°C (36°F-46°F) in its original package. Protect from light.”

c) Include route of administration, “For deep subcutaneous injection”, as this is important information that may be overlooked by the user if the carton labeling is discarded.

d) Include the following statement regarding package type, “Discard unused portion” as this is important information that may be overlooked by the user if the carton labeling is discarded. Suggested text may include: “For single use only – Discard unused portion” as stated on your carton labeling.

e) Reorient the product barcode and NDC number in the same direction and field of vision as other text on the pouch labeling (i.e., readable without having to turn or rotate the pouch) in accordance with 21 CFR 201.15.

f) Revise the following statement [REDACTED] (b) (4) as this statement is contradictory to information in Section 2 Dosage and Administration of the Full Prescribing Information, where it states that Somatuline Depot should be administered by a healthcare professional. Suggested text may include: “Important: Somatuline Depot should be administered by a healthcare professional. Call 1-(800)-XXX-XXXX and request training that includes delivering a practice injection.”

4. Carton labeling

a) See comment 3(a) above.

b) Relocate the NDC number from the back panel to appear prominently in the top third of the principal display panel in accordance with 21 CFR 207.35(3)(iii).

c) Consider relocating the following sentence “Each syringe contains lanreotide acetate corresponding to 60 mg of lanreotide base per 0.2 mL solution, which is the equivalent of 60 mg lanreotide per syringe” from the principal display panel to the back panel as this information is repetitive of other information on the principal display panel and creates clutter.

d) In addition to the storage information listed on the back panel, add the following statement, “Protect from light”, per FDA Guidance: Container Labels and Carton Labeling, April 2013 as this is important information listed in Section 16 How Supplied/Storage and Handling of the Full Prescribing Information that may be overlooked by the user.¹

e) Remove the following statement [REDACTED] (b) (4) [REDACTED] as this statement is contradictory to information in Section 2 Dosage and Administration of the Full Prescribing Information, where it states that Somatuline Depot

should be administered by a healthcare professional.

f) Include the following statement, “Somatuline Depot should be administered by a healthcare professional”, as both the product and Instructions for Use were validated through a Human Factors Study with healthcare professionals as the end users.

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

We request that the IFU and carton/container labels be revised in accordance with the above recommendations prior to approval of S-004. The revised IFU and labels can be submitted to me via email (i.e., no formal submission to the sNDA is needed at this time).

Revisions to the package insert will be sent via a separate email soon.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

05/12/2014

Recommended revisions to IFU and carton/container labels per DMEPA review dated 4/21/14

From: Johnson, Jennifer
To: ["Mary Jane CHEAH"](#)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 22074/S-004 (Somatuline Depot): Request for Revised Labels and Samples
Date: Tuesday, April 01, 2014 2:29:00 PM

Dear Mary Jane,

For CMC supplement NDA 22074/S-004 (Somatuline Depot) currently under review, we are requesting the following items:

1. We note that the syringe and sachet (b) (4) back pouch) labels submitted on January 16, 2014 are draft text only and in French. Please submit color mock-ups (pdf format) of your proposed labels in all strengths in English as a formal amendment (via the Central Document Room) to S-004.
2. Please provide samples (3) of your proposed device to me directly at the following address within one week:

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Food & Drug Administration
10903 New Hampshire Avenue
Building 22, Room 3114
Silver Spring, MD 20993

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

04/01/2014

Requests from DMEPA reviewer Mishale Mistry (concurrence from team leader Yelena Maslov) on 3/31/14

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division: Div of Anesthesiology, Gen Hospital, Infection Control & Dental Devices, Anesthe

Mail Code: HF

Consulting Reviewer Name: QuynhNhu Nguyen

Building/Room #: WO66 Room 2531

Phone #: 301-796-6273

Fax #: N/A

Email Address: quynht.nguyen@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: Center for Drug Evaluation & Research

Division: Metabolism and Endocrinology Products

Mail Code: HFD-510

Requesting Reviewer Name: Jennifer Johnson, RPM

Building/Room #: WO22 Rm 3114

Phone #: 301-796-2194

Fax #: 301-796-9712

Email Address: jennifer.johnson@fda.hhs.gov

RPM/CSO Name and Mail Code: Jennifer Johnson

Requesting Reviewer's Concurring

Supervisor's Name: Mehreen Hai/Julie Marchick

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 19, 2012

Requested Completion Date: September 5, 2012

Submission/Application Number: NDA 22074/S-004
(Not Barcode Number)

Submission Type: Quality Amendment (Revised HFS protocol and IFU)
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: July 5, 2012 (received document room July 12, 2012)

Official Submission Due Date: non-PDUFA; see above requested date

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Please review the sponsor's revised draft human factors study (HFS) study protocol, entitled "Simulated-Use Validation Testing of Somatuline Depot", for this product. The sponsor has also included a revised Instructions for Use (IFU), package insert (PI) and carton labels for our review. This is a paper submission, but a pdf version of the submission may also be located in the DMEP eRoom (link to be sent via separate email).

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Recall that CMC S-004 provided for a newly integrated sharps injury prevention feature (i.e., modified device) and that we issued a Complete Response letter (CDRH and DMEPA deficiencies) to the applicant on February 3, 2012, in response to the sponsor's resubmission on October 3, 2011. Refer also to the CDRH review dated February 3, 2012, in DARRTS (under author Jennifer Johnson). The sponsor is requesting our feedback on this revised protocol, IFU and labeling/labels prior to its plans to begin its user validation study in September 2012.

Please note that a separate consult request is being sent to OSE/DMEPA as well. Feel free to contact me with any questions or concerns.

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/s/

JENNIFER L JOHNSON
02/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Terrolyn Thomas, Safety RPM, WO22 Rm 4417, 240-402-3981 Mail: OSE (DMEPA)		FROM: Jennifer Johnson, RPM, Division of Metabolism and Endocrinology Products, WO22 Rm 3114, 301-796-2194		
DATE February 26, 2014	IND NO. N/A	NDA NO. 22074/S-004	TYPE OF DOCUMENT CMC supplement (with labeling) resubmission (#3)	DATE OF DOCUMENT January 16, 2014
NAME OF DRUG Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Somatostatin analog	DESIRED COMPLETION DATE April 18, 2014
NAME OF FIRM: Ipsen Pharma (U.S. Agent: Ipsen Biopharmaceuticals, Inc.)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DMEPA review is being requested for this CMC supplement with labeling (OND managed), which was resubmitted on January 16, 2014 (4 th review cycle), in response to the Complete Response letter which issued on May 25, 2013. Recall that the first resubmission was dated October 3, 2011, in response to the Complete Response letter which issued on May 4, 2011. The CMC reviewer recommended approval but a CR letter was issued because of DMEPA/CDRH concerns regarding the proposed device. The resubmission is in electronic/paper formats – the 1-volume paper submission has been scanned and uploaded into the DMEP eRoom, and the electronic components (including a revised package insert with a revised Instructions for Use, and carton/container labeling) are available in the EDR via the following link: http://cdsesub4inonectd/nda022074/5451962 The scanned paper submission dated January 16, 2014, is in the DMEP eRoom via the following link: http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_41c11 The relevant documents for S-004 are in the eRoom at the following link: http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_20cb3 Refer to the DMEPA reviews dated November 18, 2010, April 13 and September 11, 2012, and May 23, 2013; and to the CDRH reviews dated February 22, 2011, February 3 and September 10, 2012, and April 26, 2013, for an overview of the device and labeling deficiencies and recommendations provided to the sponsor in the CR letters. The division action goal date is Friday, May 16, 2014. Let me know if I can provide further assistance. Many thanks, Jennifer				
SIGNATURE OF REQUESTER Jennifer Johnson		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS/EMAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

JENNIFER L JOHNSON
02/26/2014

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, April 24, 2013 5:07 PM
To: 'Scott, Steven R'
Cc: (b) (6)
Subject: NDA 22074/S-004 (Somatuline Depot Injection): Information Request

Dear Steve and (b) (6)

We are currently reviewing your Complete Response resubmission of S-004 to NDA 22074, Somatuline Depot (lanreotide) Injection, and have the following request for additional information:

We note that two participants in group D failed to successfully perform Task #9: Twist and Pull to remove plunger protector.

You have noted in your HFS summary that "*removing the plunger protector is essential for proper operation but failure to do so has no measurable impact. Two problems that might result from a failure to remove the plunger protector: an injection performed with the plunger protector in place may not deliver all the medication and after an injection, the needle will not retract.*"

Although you mention that failure to do this task has no measurable impact, we are concerned that failure to remove the plunger protector will result in patients not receiving the full dose, resulting in underdose and needle not retracting resulting in accidental needle stick as you have stated in your assessment. Therefore, we have the following questions:

1. Is the plunger protector currently a part of the marketed product?
2. If yes, has the above risk been identified in your existing product and what actions have you taken to mitigate the risk?
3. If this is a new risk identified with the proposed product, how do you intend to mitigate this risk?

Additionally, could you please send to me samples of the proposed syringe with the sharps protection system, and a sample of the currently marketed syringe for comparison purposes? These samples can be sent to me directly at the following address:

Jennifer Johnson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 3114
10903 New Hampshire Avenue
Silver Spring, MD 20903 (if shipping via USPS)
*If shipping via any other carrier (e.g., UPS, DHL, FedEx), use zip code 20993

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

04/26/2013

Information request sent on behalf of DMEPA on 4/24/13

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Ermias Zerislassie, Safety RPM, WO22 Rm 4486, 301-796-0097 Mail: OSE (DMEPA)		FROM: Jennifer Johnson, RPM, Division of Metabolism and Endocrinology Products, WO22 Rm 3114, 301-796-2194		
DATE February 12, 2013	IND NO. N/A	NDA NO. 22074/S-004	TYPE OF DOCUMENT CMC supplement (with labeling) resubmission (#2)	DATE OF DOCUMENT January 25, 2013
NAME OF DRUG Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Somatostatin analog	DESIRED COMPLETION DATE May 17, 2013
NAME OF FIRM: Ipsen Pharma (U.S. Agent: Ipsen Biopharmaceuticals, Inc.)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DMEPA review is being requested for this CMC supplement with labeling (OND managed), which was resubmitted on January 24, 2013, in response to the Complete Response letter which issued on February 3, 2012. (The applicant submitted the resubmission on December 21, 2012, but as the submission did not include the required content of labeling in electronic format, an "Acknowledge Incomplete Response" letter issued, followed by an "Acknowledge Complete Response" letter once the January 24 th labeling amendment submission was received.) Recall that the first resubmission was dated October 3, 2011, in response to the Complete Response letter which issued on May 4, 2011. The CMC reviewer recommended approval but a CR letter was issued because of DMEPA/CDRH concerns regarding the proposed device. The resubmission is in electronic/paper formats – the 1-volume paper submission has been scanned and uploaded into the DMEP eRoom, and the electronic components (including a revised package insert with a new Instructions for Use subsection in Section 2, Dosage and Administration, and carton/container labeling) are available in the EDR via the following link: http://cdsesub4/nonectd/nda022074/5222548 The submission dated December 21, 2012, is in the DMEP eRoom via the following link: http://erom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_33bf9				
Refer to the DMEPA reviews dated November 18, 2010, April 13 and September 11, 2012; and to the CDRH reviews dated February 22, 2011 and February 3, 2012, for an overview of the device and labeling deficiencies and recommendations provided to the sponsor in the CR letters. The division action goal date is <u>Friday, May 24, 2013</u> . Let me know if I can provide further assistance. Many thanks, Jennifer				
SIGNATURE OF REQUESTER Jennifer Johnson		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS/EMAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

JENNIFER L JOHNSON
02/12/2013



NDA 022074/S-004

ACKNOWLEDGE INCOMPLETE RESPONSE

Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma
Attention: Archana Reddy, MPH, MS
Director, Regulatory Affairs
106 Allen Road
Basking Ridge, NJ 07920

Dear Ms. Reddy:

We acknowledge receipt on December 21, 2012, of your December 26, 2012, submission to your supplemental new drug application (sNDA) for Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg.

We do not consider this a complete response to our action letter. Therefore, we will not start the review clock until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

Your submission does not include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm> Please refer to our Complete Response letter dated February 3, 2012, in which we describe this requirement.

If you have any questions, call Jennifer Johnson, Regulatory Health 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 H PARKS
01/28/2013

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division: Div of Anesthesiology, Gen Hospital, Infection Control & Dental Devices, Anesthe

Mail Code: HF

Consulting Reviewer Name: QuynhNhu Nguyen

Building/Room #: WO66 Room 2531

Phone #: 301-796-6273

Fax #: N/A

Email Address: quynht.nguyen@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: Center for Drug Evaluation & Research

Division: Metabolism and Endocrinology Products

Mail Code: HFD-510

Requesting Reviewer Name: Jennifer Johnson, RPM

Building/Room #: WO22 Rm 3114

Phone #: 301-796-2194

Fax #: 301-796-9712

Email Address: jennifer.johnson@fda.hhs.gov

RPM/CSO Name and Mail Code: Jennifer Johnson

Requesting Reviewer's Concurring

Supervisor's Name: Mehreen Hai/Julie Marchick

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 19, 2012

Requested Completion Date: September 5, 2012

Submission/Application Number: NDA 22074/S-004
(Not Barcode Number)

Submission Type: Quality Amendment (Revised HFS protocol and IFU)
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: July 5, 2012 (received document room July 12, 2012)

Official Submission Due Date: non-PDUFA; see above requested date

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Please review the sponsor's revised draft human factors study (HFS) study protocol, entitled "Simulated-Use Validation Testing of Somatuline Depot", for this product. The sponsor has also included a revised Instructions for Use (IFU), package insert (PI) and carton labels for our review. This is a paper submission, but a pdf version of the submission may also be located in the DMEP eRoom (link to be sent via separate email).

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Recall that CMC S-004 provided for a newly integrated sharps injury prevention feature (i.e., modified device) and that we issued a Complete Response letter (CDRH and DMEPA deficiencies) to the applicant on February 3, 2012, in response to the sponsor's resubmission on October 3, 2011. Refer also to the CDRH review dated February 3, 2012, in DARRTS (under author Jennifer Johnson). The sponsor is requesting our feedback on this revised protocol, IFU and labeling/labels prior to its plans to begin its user validation study in September 2012.

Please note that a separate consult request is being sent to OSE/DMEPA as well. Feel free to contact me with any questions or concerns.

Reference ID: A244960

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/s/

JENNIFER L JOHNSON
01/14/2013



NDA 022074/S-004

GENERAL ADVICE

Ipsen Biopharmaceuticals, Inc., U.S. Agent for Ipsen Pharma
Attention: Archana P. Reddy, MPh, MS
Director, Regulatory Affairs (Endocrinology)
106 Allen Road
Basking Ridge, NJ 07920

Dear Ms. Reddy:

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

We also refer to your July 2, 2012, submission, containing a revised user validation testing protocol and Instructions for Use (IFU) and request for FDA feedback prior to study implementation, in response to the Complete Response letter which issued on February 3, 2012. We further refer to your August 23, 2012, submission, containing revised pouch labeling, requested by Jennifer Johnson of this Division on August 20, 2012.

We have reviewed your submissions and have the following comments and recommendations.

HUMAN FACTORS STUDY

Overall, the protocol appears adequate in terms of methodology and type of data necessary to determine safe and effective use with some exceptions. Please address the following:

Instructions for Use Validation

1. It is not clear how you will validate the instructions for use. You should validate the instructions to ensure that the end users will be able to correctly understand and follow them and to assess the extent to which the instructions support safe and effective use of your system by the intended users. If any other elements of labeling (e.g., packaging, inserts) are critical to use, include them in your validation testing as well. You may conduct these assessments in a separate study (with different participants, prior to the device validation study) or include them in your validation testing (following the device validation portion). To assess user understanding of critical messages in the labeling that cannot be assessed through observation of participant behavior, you can ask explicit, detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e., don't make the correct responses obvious) and for this reason, we discourage use of forced-choice responses. The participants should also provide subjective feedback regarding any

wording in the labeling they found confusing, misleading or incomplete. Additionally, the clarity of the IFU/DHA should be evaluated with respect to findings on task failures/use errors observed in the study.

Study Population and Training

2. Your study population consists of 20 non-professional caregivers (NPCs) who are all trained then tested and 30 health-care providers (HCPs) divided into 3 arms: 1) Training + Testing, 2) IFU + Testing, and 3) No IFU + Testing. Although the study population (HCPs and NPCs) is representative of Somatuline Depot end users, the number of HCP users per arm is insufficient. Additionally, you did not account for the fact that not all NCP users may receive training. Although you stated that most will be trained prior to first use and it is unlikely that patients will use the product without training unless they have used the currently marketed product and do not request training, the labeling of the product does not reflect this aspect, and thus there may be circumstances where the product is received by the patient and/or caregiver before any training or education is provided. In this case, patients and/or caregivers may attempt to use the product without prior formal training. Therefore, we continue to recommend that not all participants in the NPC group receive formal training; participants should use the IFU as they desire while interacting with the device. Thus, the study should include at least 60 participants divided as follows:
 - a. Participants who receive verbal training that will be representative of the actual training (15 of HCPs and 15 of NPCs).
 - b. Participants who are provided with the kit containing the IFU, but not specifically instructed to refer to the IFU. Participants should use the IFU as they desire while interacting with the device and should not receive any training regarding use of the product (15 of HCPs and 15 of NPCs).

If you wish, you may exclude the arm where the kit is provided and the moderator prompts the participants to read the IFU prior to administration.

Study Design

3. The protocol states that each participant will complete 10 injections per session. Please address the following:
 - a. You indicated that the study design will consist of one-on-one sessions where the users will be asked to perform a total of 10 injections, and to provide response to comprehension questions and follow-up questions. It was not clear why the testing specified that each participant performs 10 injections. Please provide a rationale for the 10 injections, or alternatively, the number of injections that will be evaluated in the study should represent realistic use.
 - b. Although we have no objection to this approach, we recommend that results regarding the first injection are reported separately from the results reported for second through tenth injections. We are most interested in the data validations from the first injection, since this is most reflective of the expected use of patients when first exposed to the product. Also, the performance of injections two through ten may be influenced by learning that occurs with repeated sequential

use which is not reflective of actual use since your product is administered every 4 weeks.

4. The protocol states that the Moderator will ask the participant how he/she would position the patient for injection, then the moderator will orient the pad accordingly: either vertically (lying down) or horizontally (sitting or standing). Since your product should be administered by a health care professional or a caregiver, in order to simulate real-life scenario, we recommend using a dummy and the participant can orient the dummy into the position he/she would want to position a person for injection. Then the participant should inject the drug into a dummy (or pad on a dummy). Since the IFU specifically states that only two areas can be used for deep subcutaneous injection, this will ensure that participants are knowledgeable regarding the proper location for the injection.
5. The standardized scoring A= Assisted defined as “Successful completion of the task was only possible with the assistance from the Moderator.” This study approach appears unrealistic because in actual use, we expect that there will be no test moderator, and the users are expected to use the device on their own. Thus, we will consider instances where the moderator intervenes/coaches/prompts the study participants as failures.

Study Report

6. You stated that both observational data and subjective evaluations will be collected. It should be noted that the follow-up questions ask the participants whether or not they recall any use errors, close calls, or operational difficulties. It might be challenging for the participant to recall use-related issues. We recommend that the questions include first open-ended questions so that users can share their overall use experience openly, and then questions on whether they recall any actions that would have been considered as a user error/close call/operational difficulty, and then questions that are targeted at specific failures/user errors that you may observe.

Additional Comments

7. You reported that several formative evaluations were conducted on the proposed device. Observed use-related issues were addressed by employing subsequent risk control measures. You also included a user task analysis and along with a use FMEA in the protocol. While both analyses are comprehensive, the clinical impact/consequence was not included such that we are clear on which tasks should be prioritized in the testing. Please add to both analyses some discussions with respect to the clinical impact/consequence for all hazards/potential use errors, and clarify which tasks (critical and essential) will be prioritized in the study. Please note the following:
 - a. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Please ensure that you clearly identify and include all critical and essential tasks associated with safe and effective use of the device. Note that criteria for determining whether a task has been completed successfully should be defined in advance. We consider task failure as action/lack of action that could lead to clinical harm. Furthermore, use errors that can be corrected should be discussed in detail with respect to how users were able to recognize the potential

failures and what steps they took to correct themselves and how the design of the device and its labeling influenced the patient's behavior for self-correction.

- b. Depending on your response on the clinical impact/consequences, we might need clarification on your rationale on the severity rating of the hazards identified in your use FMEA. Please ensure that the severity rating for all hazards corresponds appropriately to the clinical impact/consequences.
8. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

For more information on human factors, you might want to visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of human factors consultants that can assist in conducting a human factors study.

INSTRUCTIONS FOR USE (IFU)

9. In Section B8, remove the (b) (4) because they may be interpreted as the proper location for the injection. The (b) (4) usually represents the spot of injection; therefore, we recommend only marking the areas that should be injected.

If you have questions, 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 H PARKS
09/17/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division: Div of Anesthesiology, Gen Hospital, Infection Control & Dental Devices, Anesthe

Mail Code: HF

Consulting Reviewer Name: QuynhNhu Nguyen

Building/Room #: WO66 Room 2531

Phone #: 301-796-6273

Fax #: N/A

Email Address: quynht.nguyen@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: Center for Drug Evaluation & Research

Division: Metabolism and Endocrinology Products

Mail Code: HFD-510

Requesting Reviewer Name: Jennifer Johnson, RPM

Building/Room #: WO22 Rm 3114

Phone #: 301-796-2194

Fax #: 301-796-9712

Email Address: jennifer.johnson@fda.hhs.gov

RPM/CSO Name and Mail Code: Jennifer Johnson

Requesting Reviewer's Concurring

Supervisor's Name: Mehreen Hai/Julie Marchick

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 19, 2012

Requested Completion Date: September 5, 2012

Submission/Application Number: NDA 22074/S-004
(Not Barcode Number)

Submission Type: Quality Amendment (Revised HFS protocol and IFU)
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: July 5, 2012 (received document room July 12, 2012)

Official Submission Due Date: non-PDUFA; see above requested date

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Please review the sponsor's revised draft human factors study (HFS) study protocol, entitled "Simulated-Use Validation Testing of Somatuline Depot", for this product. The sponsor has also included a revised Instructions for Use (IFU), package insert (PI) and carton labels for our review. This is a paper submission, but a pdf version of the submission may also be located in the DMEP eRoom (link to be sent via separate email).

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Recall that CMC S-004 provided for a newly integrated sharps injury prevention feature (i.e., modified device) and that we issued a Complete Response letter (CDRH and DMEPA deficiencies) to the applicant on February 3, 2012, in response to the sponsor's resubmission on October 3, 2011. Refer also to the CDRH review dated February 3, 2012, in DARRTS (under author Jennifer Johnson). The sponsor is requesting our feedback on this revised protocol, IFU and labeling/labels prior to its plans to begin its user validation study in September 2012.

Please note that a separate consult request is being sent to OSE/DMEPA as well. Feel free to contact me with any questions or concerns.

Reference ID: A161720

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/s/

JENNIFER L JOHNSON
07/19/2012

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/s/

JENNIFER L JOHNSON
07/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Ermias Zerislassie, Safety RPM, WO22 Rm 4486, 301-796-0097 Mail: OSE (DMEPA)		FROM: Jennifer Johnson, RPM, Division of Metabolism and Endocrinology Products, WO22 Rm 3114, 301-796-2194		
DATE July 19, 2012	IND NO. N/A	NDA NO. NDA 22074/S-004	TYPE OF DOCUMENT Quality information (Revised Human Factors Study Protocol and Instructions for Use)	DATE OF DOCUMENT July 2, 2012 (received paper submission in document room on July 12, 2012); SDN 191
NAME OF DRUG Somatuline Depot (lanreotide) Injection, 60 mg, 90 mg, 120 mg		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Somatostatin analog	DESIRED COMPLETION DATE September 5, 2012
NAME OF FIRM: Ipsen Pharma (U.S. Agent: Ipsen Biopharmaceuticals Inc.)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<p>COMMENTS/SPECIAL INSTRUCTIONS: Please review the sponsor's revised draft human factors study (HFS) study protocol, entitled "Simulated-Use Validation Testing of Somatuline Depot", for this product. The sponsor has also included a revised Instructions for Use (IFU), package insert (PI) and carton labels for our review. Recall that CMC S-004 provided for a newly integrated sharps injury prevention feature (i.e., modified device) and that we issued a Complete Response letter to the applicant on February 3, 2012, in response to the sponsor's resubmission on October 3, 2011. The sponsor is requesting our feedback on this revised protocol, IFU and labeling/labels prior to its plans to begin its user validation study in September 2012. This is a paper submission, but a pdf version of the submission may also be located in the DMEP eRoom (link to be sent via separate email).</p> <p>Please note that a separate consult request is being sent to CDRH as well. Feel free to contact me with any questions or concerns. Many thanks, Jennifer</p>				
SIGNATURE OF REQUESTER Jennifer Johnson		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL/DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

JENNIFER L JOHNSON
07/19/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, January 23, 2012 5:19 PM
To: 'Shawn McLaughlin'
Subject: NDA 22074/S-004 (Somatuline Depot): FDA Patient Labeling Revisions

Attachments: lanreotide (Somatuline Depot) Injection 22074 S-004 DMPP PPI Review marked.doc;
lanreotide (Somatuline Depot) Injection 22074 S-004 DMPP PPI Review clean.doc

Dear Shawn,

We have reviewed the patient labeling submitted with the NDA 22074/S-004 resubmission received on October 4, 2011, and have the following comments and revisions (see attached clean and marked-up copies).



lanreotide
Somatuline Depot) .Somatuline Depot) .



When you respond, you do not have to submit officially. You can make your revisions and comments to the clean copy.

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

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JENNIFER L JOHNSON
01/24/2012

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: Center for Devices and Radiological Health
Division: Div of Anesthesiology, Gen Hospital,
Infection Control & Dental Devices, Anesthesiology &
Respiratory Devices Branch/General Hospital Devices
Branch

Mail Code: HF_-

Consulting Reviewer Name: Jacqueline Ryan and
QuynhNhu Nguyen

Building/Room #: WO66 Room 1257 (JR)/WO66 Room
2531 (QN)

Phone #: 301-796-9599 (JR)/301-796-6273 (QN)

Fax #: N/A

Email Address: jacqueline.ryan@fda.hhs.gov and
quynht.nguyen@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Metabolic and Endocrine Products

Mail Code: HFD-510

Requesting Reviewer Name: Reasol Agustin, Division
of Medication Error Prevention and Analysis (DMEPA)

Building/Room #: WO 51 Room 2204

Phone#: 301-796-2932

Fax #:

Email Address: reasol.agustin@fda.hhs.gov

RPM/CSO Name and Mail Code: Jennifer Johnson,
HFD-510

Requesting Reviewer's Concurring Supervisor's Name:
Carlos Mena-Grillasca (DMEPA)

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: January 20, 2012 (original email
October 7, 2011)

Submission/Application Number: NDA 22074/S-004

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: October 4, 2011

Name of Product: Somatuline Depot (lanreotide)
Injection, 60 mg, 90 mg, 120 mg

Requested Completion Date: **PDUFA goal date
February 4, 2012**

Submission Type: NDA

Official Submission Due Date: February 4, 2012

Name of Firm: Ipsen Pharma (U.S. Agent: Biomeasure
Incorporated)

Intended Use: long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy (orphan indication)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): The original CMC supplement provided for changes to the drug product container closure system to add a sharps protection system to the syringe. (Refer to the Complete Response letter which issued on May 4, 2011, and contained mainly CDRH and DMEPA deficiencies.) Please review the device performance information (Jackie Ryan) and the human factors information (QuynhNhu Nguyen). Refer to CMC review dated August 17, 2010, to DMEPA review dated November 18, 2010 and to CDRH review dated February 22, 2011 (DARRTS date; actual review completed January 27, 2011, by Jackie Ryan). I have scanned the resubmission and uploaded it to the DMEP eRoom. Also, here is the direct EDR link to the electronic components, including an injection demonstration video: \\CDSESUB4\NONECTD\NDA022074\4941684. Feel free to contact me with any questions. Many thanks, Jennifer Johnson, RPM (WO22 Rm 3114, 301-796-2194, jennifer.johnson@fda.hhs.gov)

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

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/s/

JENNIFER L JOHNSON
01/20/2012

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/s/

JENNIFER L JOHNSON
10/20/2011

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: Center for Devices and Radiological Health
Division: Anesthesiology, General Hospital Infection Control, and Dental Devices, General Hospital Devices Branch
Mail Code: HF_-
Consulting Reviewer Name: Nikhil Thakur

Building/Room #: WO66 Room 2562

Phone #: 301-796-5536

Fax #: 301-847-8137

Email Address: nikhil.thakur@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER
Division: Division of Metabolic and Endocrine Products

Mail Code: HFD-510

Requesting Reviewer Name: Jibril Abdus-Samad,
Division of Medication Error Prevention and Analysis (DMEPA)

Building/Room #: WO 22 Room 4423

Phone#: 301-796-2196

Fax #:

Email Address: jibril.abdus-samad@fda.hhs.gov

RPM/CSO Name and Mail Code: Jennifer Johnson,
HFD-510

Requesting Reviewer's Concurring Supervisor's Name:
Todd Bridges, Denise Toyer, Carol Holquist (DMEPA)

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: December 9, 2010

Submission/Application Number: NDA 22074/S-004

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: May 3, 2010

Name of Product: Somatuline Depot (lanreotide)
Injection, 60 mg, 90 mg, 120 mg

Requested Completion Date: **January 11, 2010**

Submission Type: NDA

Official Submission Due Date: September 3, 2010

Name of Firm: Ipsen Pharma (U.S. Agent: Biomeasure Incorporated)

Intended Use: long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy (orphan indication)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): This CMC supplement provides for changes to the drug product container closure system to add a sharps protection system to the syringe. Please evaluate the proposed syringe and sharps protection system since this device has not been approved for use with this drug product. Refer to CMC review dated August 17, 2010, and to DMEPA review dated November 18, 2010. Feel free to contact me with any questions. Many thanks, Jennifer Johnson, RPM (WO22 Rm 3114, 301-796-2194, jennifer.johnson@fda.hhs.gov)

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

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JENNIFER L JOHNSON
12/09/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22074	SUPPL-4	BEAUFOUR IPSEN PHARMA	SOMATULINE DEPOT, 60,90,120 MG

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/s/

JENNIFER L JOHNSON
07/16/2010