CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021008/S-030

Trade Name: **SANDOSTATIN**

Generic Name: **Octreotide Acetate For Injectable Suspension**

Sponsor: **Novartis Pharmaceuticals Corporation**

Approval Date: July 17, 2014

Indications: Treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous injection for:

• Acromegaly

• Severe diarrhea/flushing episodes associated with metastatic carcinoid
tumors

• Profuse watery diarrhea associated with VIP-secreting tumors

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021008/S-030

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Omer A. Munir, R.Ph.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Munir:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sandostatin LAR Depot (octreotide acetate for injectable suspension), 10 mg, 20 mg, 30 mg.

We acknowledge receipt of your amendments dated September 24, October 9, 11, November 27, December 23, 2013, and February 10 and March 24, 2014. We also acknowledge your agreement with our revisions to the package insert via email to Jennifer Johnson of this Division on July 1, 2014.

This "Prior Approval" supplemental new drug application proposes the following changes: a new diluent for product reconstitution (pharmaceutically equivalent vehicle) and product presentation, including a simplified administration kit. Revisions have also been proposed to the package insert, healthcare practitioner instructions for use, and carton and container labels.

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, and with the revisions to the carton and container labels listed below:

Trade kit syringe labels submitted on December 23, 2013:

1) Under [redacted] (b) (4)

2) Under STORAGE: Change [redacted] (b) (4)
To:
"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light."

Trade kit revised carton labels submitted on March 24, 2014:

3) Under [redacted] (b) (4)

4) Under STORAGE: Change [redacted] (b) (4)

To:
"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light."

Trade kit revised vial labels submitted on March 24, 2014:

5) Under STORAGE: Change (b) (4)
To:
"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light."

Demonstration kit carton label submitted on February 10, 2014:

6) Under (b) (4)

Demonstration kit syringe label submitted on February 10, 2014:

7) Under (b) (4)

These requested revisions were conveyed to you via email on June 6, 2014, and you indicated via emails on June 6 and 13, 2014, your agreement to incorporate these revisions into the final printed labeling as a condition of approval for this supplement.

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), 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, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. These revisions are terms of the sNDA approval. 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 021008/S-030**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product 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, 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: Sandostatin LAR Depot (octreotide acetate for injectable suspension):

1. Package Insert
2. Healthcare Provider Instruction Booklet: Preparation and Administration (trade product kit)
3. Healthcare Provider Instruction Booklet: Instructions for Proper Suspension Technique (demonstration kit)
4. Carton labels (trade and demonstration kits)
5. Tray labels (trade and demonstration kits)
6. Vial labels (trade and demonstration kits)
7. Syringe labels (trade and demonstration kits)

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

/s/

JEAN-MARC P GUETTIER
07/17/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Sandostatin® LAR Depot (octreotide acetate for injectable suspension)
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------

Sandostatin LAR is a somatostatin analogue indicated for:
Treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous injection for:

- Acromegaly (1.1)
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors (1.2)
- Profuse watery diarrhea associated with VIP-secreting tumors (1.3)

----------DOSAGE AND ADMINISTRATION----------

Patients not currently receiving Sandostatin Injection subcutaneously:

- Acromegaly: 50 mcg three times daily Sandostatin Injection subcutaneously for 2 weeks followed by Sandostatin LAR 20 mg intragluteally every 4 weeks for 3 months (2.1)
- Carcinoid Tumors and VIPomas: Sandostatin Injection subcutaneously 100-600 mcg/day in 2-4 divided doses for 2 weeks followed by Sandostatin LAR 20 mg every 4 weeks for 2 months (2.2)

Patients currently receiving Sandostatin Injection subcutaneously:

- Acromegaly: 20 mg every 4 weeks for 3 months (2.1)
- Carcinoid Tumors and VIPomas: 20 mg every 4 weeks for 2 months (2.2)

Renal Impairment, patients on dialysis: 10 mg every 4 weeks (2.3)
Hepatic Impairment, patients with cirrhosis: 10 mg every 4 weeks (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For Injectable Suspension; Strengths 10 mg per 6 mL, 20 mg per 6 mL, or 30 mg per 6 mL vials(3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Gallbladder abnormalities may occur. Monitor periodically. (5.1)
- Glucose Metabolism: Hypoglycemia or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment may need adjustment. (5.2)
- Thyroid Function: Hypothyroidism may occur. Monitor thyroid levels periodically. (5.3)
- Cardiac Function: Bradycardia, arrhythmia, or conduction abnormalities may occur. Use with caution in at-risk patients. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions, occurring in ≥20% of patients are:

- Acromegaly: diarrhea, cholelithiasis, abdominal pain, flatulence (6.1)
- Carcinoid Syndrome: back pain, fatigue, headache, abdominal pain, nausea, dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

The following drugs require monitoring and possible dose adjustment when used with Sandostatin LAR: cyclosporine, insulin, oral hypoglycemic agents, beta-blockers, bromocriptine (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sandostatin LAR Depot 10 mg, 20 mg, and 30 mg is indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated.

1.1 Acromegaly

Long-term maintenance therapy in 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 GH and IGF-1 levels to normal [*see Clinical Studies (14)* and *Dosage and Administration (2)*].

1.2 Carcinoid Tumors

Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

1.3 Vasoactive Intestinal Peptide Tumors (VIPomas)

Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

1.4 Important Limitations of Use

In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

2 DOSAGE AND ADMINISTRATION

- Sandostatin LAR Depot should be administered by a trained healthcare provider. It is important to closely follow the mixing instructions included in the packaging. Sandostatin LAR Depot must be administered immediately after mixing.
- **Do not directly inject diluent without preparing suspension.**
- The recommended needle size for administration of Sandostatin LAR Depot is the 1½" 20 gauge safety injection needle (supplied in the drug product kit). For patients with a greater skin to muscle depth, a size 2" 20 gauge needle (not supplied) may be used.
- Sandostatin LAR Depot should be administered intramuscularly in the gluteal region at 4-week intervals. Administration of Sandostatin LAR Depot at intervals greater than 4 weeks is not recommended.
- Injection sites should be rotated in a systematic manner to avoid irritation. Deltoid injections should be avoided due to significant discomfort at the injection site when given in that area.
- **Sandostatin LAR Depot should never be administered intravenously or subcutaneously.**

The following dosage regimens are recommended.

2.1 Acromegaly

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously in an initial dose of 50 mcg three times daily which may be titrated. Most patients require doses of 100 mcg to 200 mcg three times daily for maximum effect but some patients require up to 500 mcg three times daily.

Patients should be maintained on Sandostatin Injection subcutaneous for at least 2 weeks to determine tolerance to octreotide. Patients who are considered to be "responders" to the drug, based on GH and IGF-1 levels and who tolerate the drug can then be switched to Sandostatin LAR Depot in the dosage scheme described below (Patients Currently Receiving Sandostatin Injection).

Patients Currently Receiving Sandostatin Injection

Patients currently receiving Sandostatin Injection can be switched directly to Sandostatin LAR Depot in a dose of 20 mg given IM intragluteally at 4-week intervals for 3 months. After 3 months, dosage may be adjusted as follows:

- GH ≤2.5 ng/mL, IGF-1 normal, and clinical symptoms controlled: maintain Sandostatin LAR Depot dosage at 20 mg every 4 weeks.
- GH >2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled, increase Sandostatin LAR Depot dosage to 30 mg every 4 weeks.
- GH ≤1 ng/mL, IGF-1 normal, and clinical symptoms controlled, reduce Sandostatin LAR Depot dosage to 10 mg every 4 weeks.
- If GH, IGF-1, or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks. Doses higher than 40 mg are not recommended.

In patients who have received pituitary irradiation, Sandostatin LAR Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity. If GH or IGF-1 levels increase and signs and symptoms recur, Sandostatin LAR Depot therapy may be resumed.

2.2 Carcinoid Tumors and VIPomas

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously. The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). Some patients may require doses up to 1500 mcg/day. The suggested daily dosage for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required.

Sandostatin Injection should be continued for at least 2 weeks. Thereafter, patients who are considered "responders" to octreotide acetate and who tolerate the drug may be switched to Sandostatin LAR Depot in the dosage regimen as described below (Patients Currently Receiving Sandostatin Injection).

Patients Currently Receiving Sandostatin Injection

Patients currently receiving Sandostatin Injection can be switched to Sandostatin LAR Depot in a dosage of 20 mg given IM intragluteally at 4-week intervals for 2 months. Because of the need for serum octreotide to reach therapeutically effective levels following initial injection of Sandostatin LAR Depot, carcinoid tumor and VIPoma patients should continue to receive Sandostatin Injection subcutaneously for at least 2 weeks in the same dosage they were taking before the switch. Failure to continue subcutaneous injections for this period may result in exacerbation of symptoms. (Some patients may require 3 or 4 weeks of such therapy.)

After 2 months, dosage may be adjusted as follows:

- If symptoms are adequately controlled, consider a dose reduction to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks. Many patients can, however, be satisfactorily maintained at a 10-mg dose every 4 weeks.
- If symptoms are not adequately controlled, increase Sandostatin LAR Depot to 30 mg every 4 weeks. Patients who achieve good control on a 20-mg dose may have their dose lowered to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks.
- Dosages higher than 30 mg are not recommended.

Despite good overall control of symptoms, patients with carcinoid tumors and VIPomas often experience periodic exacerbation of symptoms (regardless of whether they are being maintained on Sandostatin Injection or Sandostatin LAR Depot). During these periods they may be given Sandostatin Injection subcutaneously for a

few days at the dosage they were receiving prior to switching to Sandostatin LAR Depot. When symptoms are again controlled, the Sandostatin Injection subcutaneous can be discontinued.

2.3 Special Populations: Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg every 4 weeks. In other patients with renal impairment, the starting dose should be similar to a nonrenal patient (i.e., 20 mg every 4 weeks) [*see Clinical Pharmacology (12)*].

2.4 Special Populations: Hepatic Impairment – Cirrhotic Patients

In patients with established cirrhosis of the liver, the starting dose should be 10 mg every 4 weeks [*see Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Sandostatin LAR Depot is available in single-use kits for injectable suspension containing a 6-mL vial of 10 mg, 20 mg, or 30 mg strength, a syringe containing 2 mL of diluent, one vial adapter, and one sterile 1½" 20 gauge safety injection needle. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Sandostatin may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Patients should be monitored periodically [*see Adverse Reactions (6)*].

5.2 Hyperglycemia and Hypoglycemia

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon, and growth hormone, which may result in hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when Sandostatin LAR treatment is initiated, or when the dose is altered. Antidiabetic treatment should be adjusted accordingly [*see Adverse Reactions (6)*].

5.3 Thyroid Function Abnormalities

Octreotide suppresses the secretion of thyroid-stimulating hormone (TSH), which may result in hypothyroidism. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic octreotide therapy [*see Adverse Reactions (6)*].

5.4 Cardiac Function Abnormalities

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other ECG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and nonspecific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. Dose adjustments in drugs such as beta-blockers that have bradycardic effects may be necessary. In one acromegalic patient with severe congestive heart failure (CHF), initiation of Sandostatin Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge [*see Adverse Reactions (6)*].

5.5 Nutrition

Octreotide may alter absorption of dietary fats.

Depressed vitamin B_{12} levels and abnormal Schilling tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B_{12} levels is recommended during therapy with Sandostatin LAR Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the GI tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

5.6 Monitoring: Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy [*see Dosage and Administration (2.1, 2.2)*].

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide) baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy

5.7 Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine [*see Drug Interactions (7.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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 trial of another drug and may not reflect the rates observed in practice.

Acromegaly

The safety of Sandostatin LAR in the treatment of acromegaly has been evaluated in three phase 3 studies in 261 patients, including 209 exposed for 48 weeks and 96 exposed for greater than 108 weeks. Sandostatin LAR was studied primarily in a double-blind, cross-over manner. Patients on subcutaneous Sandostatin Injection were switched to the LAR formulation followed by an open-label extension. The population age range was 14-81 years old and 53% were female. Approximately 35% of these acromegaly patients had not been treated with surgery and/or radiation. Most patients received a starting dose of 20 mg every 4 weeks intramuscularly. Dose was up or down titrated based on efficacy and tolerability to a final dose between 10-60 mg every 4 weeks. Table 1 below reflects adverse events from these studies regardless of presumed causality to study drug.

Table 1. Adverse Events Occurring in ≥10% of Acromegalic Patients in the Phase 3 Studies

WHO Preferred Term	**Phase 3 Studies (Pooled) Number (%) of Subjects with AE's 10 mg/20 mg/30 mg (n=261) n (%)**
Diarrhea	93 (35.6)
Abdominal Pain	75 (28.7)

Flatulence	66 (25.3)
Influenza-Like Symptoms	52 (19.9)
Constipation	46 (17.6)
Headache	40 (15.3)
Anemia	40 (15.3)
Injection Site Pain	36 (13.8)
Cholelithiasis	35 (13.4)
Hypertension	33 (12.6)
Dizziness	30 (11.5)
Fatigue	29 (11.1)

The safety of Sandostatin LAR in the treatment of acromegaly was also evaluated in a postmarketing randomized phase 4 study. One-hundred four (104) patients were randomized to either pituitary surgery or 20 mg of Sandostatin LAR. All the patients were treatment naïve ('de novo'). Crossover was allowed according to treatment response and a total of 76 patients were exposed to Sandostatin LAR. Approximately half of the patients initially randomized to Sandostatin LAR were exposed to Sandostatin LAR up to 1 year. The population age range was between 20-76 years old, 45% were female, 93% were Caucasian, and 1% black. The majority of these patients were exposed to 30 mg every 4 weeks. Table 2 below reflects the adverse events occurring in this study regardless of presumed causality to study drug.

Table 2. Adverse Events Occurring in ≥10% of Acromegalic Patients in Phase 4 Study

WHO Preferred Term	**Phase 4 Study SAS LAR N=76 n (%)**	**Phase 4 Study Surgery N=64 n (%)**
Diarrhea	36 (47.4)	2 (3.1)
Cholelithiasis	29 (38.2)	3 (4.7)
Abdominal Pain	19 (25.0)	2 (3.1)
Nausea	12 (15.8)	5 (7.8)
Alopecia	10 (13.2)	5 (7.8)
Injection Site Pain	9 (11.8)	0
Abdominal Pain Upper	8 (10.5)	0
Headache	8 (10.5)	6 (9.4)
Epistaxis	0	7 (10.9)

Gallbladder Abnormalities

Single doses of Sandostatin Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex, or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge, and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin Injection therapy and died. Despite the high incidence of

new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In acromegaly patients treated with either Sandostatin Injection or Sandostatin LAR Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients [*see Warnings and Precautions (5.2)*].

Hypothyroidism

In acromegaly patients receiving Sandostatin Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin Injection. In acromegalic patients treated with Sandostatin LAR Depot, hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR Depot required initiation of thyroid hormone replacement therapy [*see Warnings and Precautions (5.3)*].

Cardiac

In acromegalic patients, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin Injection therapy. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [*see Warnings and Precautions (5.4)*].

Gastrointestinal

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 3.

Table 3. Number (%) of Acromegalic Patients with Common GI Adverse Events

Adverse Event	**Sandostatin Injection S.C. Three Times Daily n=114**		**Sandostatin LAR Depot Every 28 Days n=261**	
	n	%	n	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Nausea	34	(29.8)	27	(10.3)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Vomiting	5	(4.4)	17	(6.5)

Only 2.6% of the patients on Sandostatin Injection in US clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR Depot discontinued therapy for a GI event.

In patients receiving Sandostatin LAR Depot, the incidence of diarrhea was dose related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances, gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Pain at the Injection Site

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose related, being reported by 2%, 9%, and 11% of acromegalic patients receiving doses of 10 mg, 20 mg, and 30 mg, respectively, of Sandostatin LAR Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

Antibodies to Octreotide

Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR Depot.

Carcinoid and VIPomas

The safety of Sandostatin LAR in the treatment of carcinoid tumors and VIPomas has been evaluated in one phase 3 study. Study 1 randomized 93 patients with carcinoid syndrome to Sandostatin LAR 10 mg, 20 mg, or 30 mg in a blind fashion or to open-label Sandostatin Injection subcutaneously. The population age range was between 25-78 years old and 44% were female, 95% were Caucasian and 3% black. All the patients had symptom control on their previous Sandostatin subcutaneous treatment. 80 patients finished the initial 24 weeks of Sandostatin exposure in Study 1. In Study 1, comparable numbers of patients were randomized to each dose. Table 4 below reflects the adverse events occurring in ≥15% of patients regardless of presumed causality to study drug.

Table 4. Adverse Events Occurring in ≥15% of Carcinoid Tumor and VIPoma Patients in Study 1

	Number (%) of Subjects with AE's (n=93)			
WHO Preferred Term	**Sc N=26**	**10 mg N=22**	**20 mg N=20**	**30 mg N=25**
Abdominal Pain	8 (30.8)	8 (35.4)	2 (10.0)	5 (20.0)
Arthropathy	5 (19.2)	2 (9.1)	3 (15.0)	2 (8.0)
Back Pain	7 (26.9)	6 (27.3)	2 (10.0)	2 (8.0)
Dizziness	4 (15.4)	4 (18.2)	4 (20.0)	5 (20.0)
Fatigue	3 (11.5)	7 (31.8)	2 (10.0)	2 (8.0)
Flatulence	3 (11.5)	2 (9.1)	2 (10.0)	4 (16.0)
Generalized Pain	4 (15.4)	2 (9.1)	3 (15.0)	1 (4.0)
Headache	5 (19.2)	4 (18.2)	6 (30.0)	4(16.0)
Musculoskeletal Pain	4 (15.4)	0	1 (5.0)	0
Myalgia	0	4 (18.2)	1 (5.0)	1 (4.0)
Nausea	8 (30.8)	9 (40.9)	6 (30.0)	6 (24.0)
Pruritus	0	4 (18.2)	0	0
Rash	1 (3.8)	0	3 (15.0)	0
Sinusitis	4 (15.4)	0	1 (5.0)	3 (12.0)
URTI	6 (23.1)	4 (18.2)	2 (10.0)	3 (12.0)

Vomiting	3 (11.5)	0	0	4 (16.0)

Gallbladder Abnormalities

In clinical trials, 62% of malignant carcinoid patients who received Sandostatin LAR Depot for up to 18 months developed new biliary abnormalities including jaundice, gallstones, sludge, and dilatation. New gallstones occurred in a total of 24% of patients.

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR Depot [*see Warnings and Precautions (5.2)*].

Hypothyroidism

In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported [*see Warnings and Precautions (5.3)*].

Cardiac

Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR Depot. In carcinoid syndrome patients, sinus bradycardia developed in 19%, conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [*see Warnings and Precautions (5.4)*].

Other Clinical Studies Adverse Events

Other clinically significant adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR Depot were malignant hyperpyrexia, cerebral vascular disorder, rectal bleeding, ascites, pulmonary embolism, pneumonia, and pleural effusion.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the postapproval use of Sandostatin. Because these reactions 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.

Myocardial infarction has been observed in the postmarketing setting, mainly in patients with cardiovascular risk factors. Hypoadrenalism has been reported in some reports in patients 18 months of age and under.

Additional events reported in the postmarketing setting include anaphylactoid reactions, including anaphylactic shock, cardiac arrest, renal failure, renal insufficiency, convulsions, atrial fibrillation, aneurysm, hepatitis, increased liver enzymes, gastrointestinal hemorrhage, pancreatitis, pancytopenia, thrombocytopenia, arterial thrombosis of the arm, retinal vein thrombosis, intracranial hemorrhage, hemiparesis, paresis, deafness, visual field defect, aphasia, scotoma, status asthmaticus, pulmonary hypertension, diabetes mellitus, intestinal obstruction, peptic/gastric ulcer, appendicitis, creatinine increased, CK increased, arthritis, joint effusion, pituitary apoplexy, breast carcinoma, suicide attempt, paranoia, migraines, urticaria, facial edema, generalized edema, hematuria, orthostatic hypotension, Raynaud’s syndrome, glaucoma, pulmonary nodule, pneumothorax aggravated, cellulitis, Bell’s palsy, diabetes insipidus, gynecomastia, galactorrhea, gallbladder polyp, fatty liver, abdomen enlarged, libido decrease, and petechiae.

7 DRUG INTERACTIONS

7.1 Cyclosporine

Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

7.2 Insulin and Oral Hypoglycemic Drugs

Octreotide inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when Sandostatin LAR treatment is initiated or when the dose is altered and antidiabetic treatment should be adjusted accordingly.

7.3 Bromocriptine

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.

7.4 Other Concomitant Drug Therapy

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

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.

7.5 Drug Metabolism Interactions

Limited published data 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 octreotide 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16x the highest recommended human dose and have revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [*see Nonclinical Toxicology (13.2)*].

8.3 Nursing Mothers

It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when Sandostatin LAR Depot is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of Sandostatin LAR Depot in the pediatric population have not been demonstrated.

No formal controlled clinical trials have been performed to evaluate the safety and effectiveness of Sandostatin LAR Depot in pediatric patients under 6 years of age. In postmarketing reports, serious adverse events, including hypoxia, necrotizing enterocolitis, and death, have been reported with Sandostatin use in children, most notably in children under 2 years of age. The relationship of these events to octreotide has not been established as the majority of these pediatric patients had serious underlying comorbid conditions.

The efficacy and safety of Sandostatin LAR Depot was examined in a single randomized, double-blind, placebo-controlled, 6-month pharmacokinetics study in 60 pediatric patients age 6–17 years with hypothalamic obesity resulting from cranial insult. The mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR Depot administered by IM injection every four weeks was approximately 3 ng/mL. Steady-state concentrations were achieved after 3 injections of a 40 mg dose. Mean BMI increased 0.1 kg/m^2 in Sandostatin LAR Depot-treated subjects compared to 0.0 kg/m^2 in saline control-treated subjects. Efficacy was not demonstrated. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. No unexpected adverse events were observed. However, with Sandostatin LAR Depot 40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was dosed at 10 to 30 mg once a month.

8.5 Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects age 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of Sandostatin. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in nonrenal patients [*see Clinical Pharmacology (12)*].

8.7 Hepatic Impairment-Cirrhotic Patients

In patients with established liver cirrhosis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. Once at a higher dose, patient should be maintained or dose adjusted based on response and tolerability as in any noncirrhotic patients [*see Clinical Pharmacology (12)*].

10 OVERDOSAGE

No frank overdose has occurred in any patient to date. Sandostatin Injection given in intravenous bolus doses of 1 mg (1000 mcg) to healthy volunteers did not result in serious ill effects, nor did doses of 30 mg (30,000 mcg) given intravenously over 20 minutes and of 120 mg (120,000 mcg) given intravenously over 8 hours to research patients. Doses of 2.5 mg (2500 mcg) of Sandostatin Injection subcutaneously have, however, caused hypoglycemia, flushing, dizziness, and nausea.

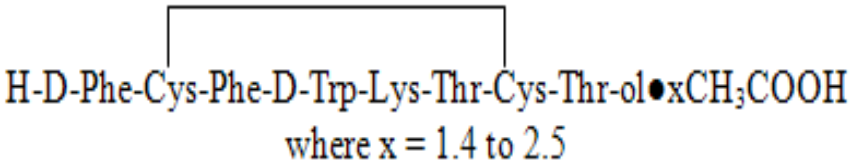
Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®**.

Mortality occurred in mice and rats given 72 mg/kg and 18 mg/kg intravenously, respectively, of octreotide.

11 DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxy-methyl) propyl]-, cyclic (2→7)-disulfide; [R-(R*,R*)].

The molecular weight of octreotide is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:



Sandostatin LAR Depot is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

Sandostatin LAR Depot is available as: sterile 6-mL vials in 3 strengths delivering 10 mg, 20 mg, or 30 mg octreotide-free peptide. Each vial of Sandostatin LAR Depot delivers:

Name of Ingredient	10 mg	20 mg	30 mg
octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D,L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg
mannitol	41.0 mg	81.9 mg	122.9 mg

*Equivalent to 10/20/30 mg octreotide base.

Each syringe of diluent contains:	
carboxymethylcellulose sodium	14.0 mg
mannitol	12.0 mg
poloxamer 188	4.0 mg
water for injection	2.0 mL

12 CLINICAL PHARMACOLOGY

Sandostatin LAR Depot is a long-acting dosage form consisting of microspheres of the biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer, containing octreotide. It maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form Sandostatin Injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis. Sandostatin LAR Depot is designed to be injected intramuscularly (intragluteally) once every 4 weeks.

12.1 Mechanism of Action

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

12.2 Pharmacodynamics

Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials, the incidence of gallstone or biliary sludge formation was markedly increased [*see Warnings and Precautions (5.1)*].

Octreotide may cause clinically significant suppression of thyroid-stimulating hormone (TSH).

12.3 Pharmacokinetics

Sandostatin Injection

According to data obtained with the immediate-release formulation, Sandostatin Injection solution, after subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100-mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area-under-the-curve (AUC) values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg 3 times daily (600 mcg/day). Clearance was reduced by about 66% suggesting nonlinear kinetics of the drug at daily doses of 600 mcg/day compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

In healthy volunteers, the distribution of octreotide from plasma was rapid ($t\alpha_{1/2}$=0.2 h), the volume of distribution (Vdss) was estimated to be 13.6 L and the total body clearance was 10 L/h.

In blood, the distribution of octreotide into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 hours, compared with the 1-3 minutes with the natural hormone, somatostatin. The duration of action of subcutaneously administered Sandostatin Injection solution is variable but extends up to 12 hours depending upon the type of tumor, necessitating multiple daily dosing with this immediate-release dosage form. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100-mcg dose) was reached in 0.7 hours after subcutaneous dosing. The Vdss was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

The half-life in renal-impaired patients was slightly longer than normal subjects (2.4-3.1 h versus 1.9 h). The clearance in renal-impaired patients was 7.3-8.8 L/h as compared to 8.3 L/h in healthy subjects. In patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in healthy subjects (from approximately 10 L/h to 4.5 L/h).

Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide half-life increasing to 3.7 h and total body clearance decreasing to 5.9 L/h, whereas patients with fatty liver disease showed half-life increasing to 3.4 h and total body clearance of 8.4 L/h. In normal subjects, octreotide half-life is 1.9 h and the clearance is 8.3 L/h which is comparable with the clearance in fatty-liver patients.

Sandostatin LAR Depot

The magnitude and duration of octreotide serum concentrations after an intramuscular injection of the long-acting depot formulation Sandostatin LAR Depot reflect the release of drug from the microsphere polymer matrix. Drug release is governed by the slow biodegration of the microspheres in the muscle, but once present

in the systemic circulation, octreotide distributes and is eliminated according to its known pharmacokinetic properties which are as follows.

After a single IM injection of the long-acting depot dosage form Sandostatin LAR Depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour after administration progressively declining over the following 3-5 days to a nadir of <0.01 ng/mL/mg, then slowly increasing and reaching a plateau about 2-3 weeks postinjection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak concentrations of about 0.07 ng/mL/mg. After about 6 weeks postinjection, octreotide concentration slowly decreased, to <0.01 ng/mL/mg by Weeks 12 to 13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release Sandostatin LAR Depot compared to immediate-release Sandostatin Injection solution given subcutaneously was 60%-63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR Depot were dose proportional. The transient Day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks postinjection. These plateau concentrations were maintained for nearly 2 weeks.

Following multiple doses of Sandostatin LAR Depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg Sandostatin LAR Depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR Depot. With the long-acting depot formulation Sandostatin LAR Depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44%-68%, compared to the 163%-209% variation encountered with the daily subcutaneous three times daily regimen of Sandostatin Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR Depot administered by IM injection every 4 weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after 2 injections of 20 mg and 30 mg and after 3 injections of 10 mg.

Sandostatin LAR Depot has not been studied in patients with renal impairment.

Sandostatin LAR Depot has not been studied in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin. No mutagenic potential of the polymeric carrier in Sandostatin LAR Depot, D,L-lactic and glycolic acids copolymer, was observed in the Ames mutagenicity test.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85-99 weeks at doses up to 2000 mcg/kg/day (8x the human exposure based on body surface area). In a 116-week subcutaneous study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10x the human exposure based on body surface area) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas in the

1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7x the human exposure based on body surface area.

13.2 Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at doses up to 16x the highest recommended human dose based on body surface area and have revealed no evidence of harm to the fetus due to octreotide.

14 CLINICAL STUDIES

14.1 Acromegaly

The clinical trials of Sandostatin LAR Depot were performed in patients who had been receiving Sandostatin Injection for a period of weeks to as long as 10 years. The acromegaly studies with Sandostatin LAR Depot described below were performed in patients who achieved GH levels of <10 ng/mL (and, in most cases <5 ng/mL) while on subcutaneous Sandostatin Injection. However, some patients enrolled were partial responders to subcutaneous Sandostatin Injection, i.e., GH levels were reduced by >50% on subcutaneous Sandostatin Injection compared to the untreated state, although not suppressed to <5 ng/mL.

Sandostatin LAR Depot was evaluated in three clinical trials in acromegalic patients.

In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level <5 ng/mL on Sandostatin Injection given in doses of 100 mcg or 200 mcg three times daily. Most patients were switched to 20 mg or 30 mg doses of Sandostatin LAR Depot given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with Sandostatin LAR Depot as they had been on Sandostatin Injection and this level of control remained for the entire duration of the trials.

A third trial was a 12-month study that enrolled 151 patients who had a GH level <10 ng/mL after treatment with Sandostatin Injection (most had levels <5 ng/mL). The starting dose of Sandostatin LAR Depot was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg, or 30 mg every 4 weeks, depending upon the degree of GH suppression [*see Dosage and Administration (2)*]. Growth hormone and IGF-1 were at least as well controlled on Sandostatin LAR Depot as they had been on Sandostatin Injection.

Table 5 summarizes the data on hormonal control (GH and IGF-1) for those patients in the first two clinical trials who received all 27 to 28 injections of Sandostatin LAR Depot.

Table 5. Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During[1] Treatment with Sandostatin LAR Depot

Mean Hormone Level	Sandostatin Injection S.C.		Sandostatin LAR Depot	
	n	%	n	%
GH <5.0 ng/mL	69/88	78	73/88	83
<2.5 ng/mL	44/88	50	41/88	47
<1.0 ng/mL	6/88	7	10/88	11
IGF-1 normalized	36/88	41	45/88	51
GH <5.0 ng/mL + IGF-1 normalized	36/88	41	45/88	51
<2.5 ng/mL + IGF-1 normalized	30/88	34	37/88	42
<1.0 ng/mL + IGF-1 normalized	5/88	6	10/88	11

[1]Average of monthly levels of GH and IGF-1 over the course of the trials.

For the 88 patients in Table 5, a mean GH level of <2.5 ng/mL was observed in 47% receiving Sandostatin LAR Depot. Over the course of the trials, 42% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels.

Table 6 summarizes the data on hormonal control (GH and IGF-1) for those patients in the third clinical trial who received all 12 injections of Sandostatin LAR Depot.

Table 6. Hormonal Response in Acromegalic Patients Receiving 12 Injections During[1] Treatment with Sandostatin LAR Depot

Mean Hormone Level	Sandostatin Injection S.C.		Sandostatin LAR Depot	
	n	%	n	%
GH <5.0 ng/mL	116/122	95	118/122	97
<2.5 ng/mL	84/122	69	80/122	66
<1.0 ng/mL	25/122	21	28/122	23
IGF-1 normalized	82/122	67	82/122	67
GH <5.0 ng/mL + IGF-1 normalized	80/122	66	82/122	67
<2.5 ng/mL + IGF-1 normalized	65/122	53	70/122	57
<1.0 ng/mL + IGF-1 normalized	23/122	19	27/122	22

[1]Average of monthly levels of GH and IGF-1 over the course of the trial

For the 122 patients in Table 6, who received all 12 injections in the third trial, a mean GH level of <2.5 ng/mL was observed in 66% receiving Sandostatin LAR Depot. Over the course of the trial, 57% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels. In comparing the hormonal response in these trials, note that a higher percentage of patients in the third trial suppressed their mean GH to <5 ng/mL on subcutaneous Sandostatin Injection, 95%, compared to 78% across the two previous trials.

In all three trials, GH, IGF-1, and clinical symptoms were similarly controlled on Sandostatin LAR Depot as they had been on Sandostatin Injection.

Of the 25 patients who completed the trials and were partial responders to Sandostatin Injection (GH >5.0 ng/mL but reduced by >50% relative to untreated levels), 1 patient (4%) responded to Sandostatin LAR Depot with a reduction of GH to <2.5 ng/mL and 8 patients (32%) responded with a reduction of GH to <5.0 ng/mL.

Two open-label clinical studies investigated a 48-week treatment with Sandostatin LAR Depot in 143 untreated (de novo) acromegalic patients. The median reduction in tumor volume was 20.6% in Study 1 (49 patients) at 24 weeks and 24.5% in Study 2 (94 patients) at 24 weeks and 36.2% at 48 weeks.

14.2 Carcinoid Syndrome

A 6-month clinical trial of malignant carcinoid syndrome was performed in 93 patients who had previously been shown to be responsive to Sandostatin Injection. Sixty-seven (67) patients were randomized at baseline to receive double-blind doses of 10 mg, 20 mg, or 30 mg Sandostatin LAR Depot every 28 days and 26 patients continued, unblinded, on their previous Sandostatin Injection regimen (100-300 mcg three times daily).

In any given month after steady-state levels of octreotide were reached, approximately 35%-40% of the patients who received Sandostatin LAR Depot required supplemental subcutaneous Sandostatin Injection therapy usually for a few days, to control exacerbation of carcinoid symptoms. In any given month, the percentage of patients randomized to subcutaneous Sandostatin Injection who required supplemental treatment with an increased dose of Sandostatin Injection was similar to the percentage of patients randomized to Sandostatin LAR Depot. Over the 6-month treatment period, approximately 50%-70% of patients who completed the trial on Sandostatin LAR Depot required subcutaneous Sandostatin Injection supplemental

therapy to control exacerbation of carcinoid symptoms although steady-state serum Sandostatin LAR Depot levels had been reached.

Table 7 presents the average number of daily stools and flushing episodes in malignant carcinoid patients.

Table 7. Average Number of Daily Stools and Flushing Episodes in Patients with Malignant Carcinoid Syndrome

Treatment		Daily Stools (Average Number)		Daily Flushing Episodes (Average Number)	
	n	Baseline	Last Visit	Baseline	Last Visit
Sandostatin Injection S.C.	26	3.7	2.6	3.0	0.5
Sandostatin LAR Depot					
10 mg	22	4.6	2.8	3.0	0.9
20 mg	20	4.0	2.1	5.9	0.6
30 mg	24	4.9	2.8	6.1	1.0

Overall, mean daily stool frequency was as well controlled on Sandostatin LAR Depot as on Sandostatin Injection (approximately 2-2.5 stools/day).

Mean daily flushing episodes were similar at all doses of Sandostatin LAR Depot and on Sandostatin Injection (approximately 0.5-1 episode/day).

In a subset of patients with variable severity of disease, median 24 hour urinary 5-HIAA (5-hydroxyindole acetic acid) levels were reduced by 38%-50% in the groups randomized to Sandostatin LAR Depot.

The reductions are within the range reported in the published literature for patients treated with octreotide (about 10%-50%).

Seventy-eight (78) patients with malignant carcinoid syndrome who had participated in this 6-month trial, subsequently participated in a 12-month extension study in which they received 12 injections of Sandostatin LAR Depot at 4-week intervals. For those who remained in the extension trial, diarrhea and flushing were as well controlled as during the 6-month trial. Because malignant carcinoid disease is progressive, as expected, a number of deaths (8 patients: 10%) occurred due to disease progression or complications from the underlying disease. An additional 22% of patients prematurely discontinued Sandostatin LAR Depot due to disease progression or worsening of carcinoid symptoms.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sandostatin LAR Depot is available in single-use kits containing a 6-mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2 mL of diluent, one vial adapter, and one sterile 1½” 20 gauge safety injection needle. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Drug Product Kits
10 mg kit ..... NDC 0078-0646-81
20 mg kit ..... NDC 0078-0647-81
30 mg kit ..... NDC 0078-0648-81
Demonstration kit..... NDC 0078-9648-81

For prolonged storage, Sandostatin LAR Depot should be stored at refrigerated temperatures between 2°C to 8°C (36°F to 46°F) and protected from light until the time of use. Sandostatin LAR Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

17 PATIENT COUNSELING INFORMATION

Patients with carcinoid tumors and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms.

Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

**Trademark of PDR Network.
Sandostatin® LAR Depot vials are manufactured by:
Sandoz GmbH, Schaftenau, Austria
(Subsidiary of Novartis Pharma AG, Basle, Switzerland)
The diluent syringes are manufactured by:
Abbott Biologicals B.V.
Olst, The Netherlands
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2013-XX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021008/S-030

MEDICAL REVIEW(S)

Medical Officer Memorandum for Labeling Supplement

NDA#:	21008/S-030
Submission Date:	08/27/13, 09/24/13, and 10/11/13
Brand Name:	Sandostatin LAR Depot
Generic Name:	Octreotide acetate powder
Formulation:	Injectable Suspension Depot for IM (Intragluteal) once monthly
Strength:	10, 20, and 30 mg/vial (three strengths)
Applicant:	Novartis
Type of submission:	Labeling supplement (LS-030)
Reviewer:	Naomi Lowy, M.D.

Introduction

This memorandum provides clinical justification for the approval of this supplement. The Biopharmaceutics Review stated that bioequivalence (BE), from the Agency definition, was not demonstrated for the new formulation.

Background

Sandostatin LAR Depot for Injection was approved on November 25, 1998 for three strengths (10, 20, and 30 mg/vial) to be given as an intramuscular injection following reconstitution. Is it indicated for the treatment of patients who have responded to and tolerated Sandostatin Injection subcutaneous injection (SC) for:

- Acromegaly
- Sever diarrhea/flushing episodes associated with metastatic carcinoid tumors
- Profuse watery diarrhea associated with VIP-secreting tumors

On August 27, 2013, Novartis submitted supplement LS-030 and introduced a dew vehicle for reconstitution of the currently approved product, Sandostatin LAR Depot. Data from a bioequivalence study (CSMS995L2106) were submitted to support this new vehicle. Novartis states that this new vehicle offers improved convenience for the preparation of the suspension because of improved (b) (4)

The Biopharmaceutics review made the following conclusions:

- Based on the Agency's BE Acceptance Criteria, the study results showed that all three primary PK parameters of interest were within the CIs of 80%-125% except the CI 90% upper boundary for $AUC_{D0-\infty}$ slightly exceeding the 125% limit (125.369%). The table below summarizes the results for the three BE parameters (excerpted from Dr. Tien-Mien Chen's Review):

Dependent	Test (New Vehicle) /Ref (Current Vehicle)		
	Ratio %Ref	CI 90 Lower	CI 90 Upper
$Ln(C_{max})$	105.6679	94.52896	118.1193
$Ln(AUC_{D0-98})$	112.6768	102.1981	124.2298
$Ln(AUC_{D0-\infty})$	113.7722	103.2481	125.369 (Failed)

Dr. Chen offers possible reasons why the final parameter failed:

A. Sandostatin when reconstituted with the new vehicle (Test) delivered a slightly higher mean dose (29.93 ± 1.10 mg) than that (29.09 ± 0.81 mg) with the currently approved vehicle; therefore the results are seemingly consistent with the different doses delivered. However, no dose adjustment was made.

B. This is a parallel study design, therefore, the factor of inter-subjects' variation was not canceled out as those in a crossover study design. Different inter-subjects' variations between parallel treatment group may cause wilder 90% CI.

He also states that the $AUC_{D0-\infty}$ is considered a less clinically meaningful parameter and less of a critical BE concern.

Conclusions/Comments:
The slight deviation of the third parameter in demonstrating BE is not clinically meaningful and should not limit the approval of this supplement for the acromegaly indication. Aside from the biopharmaceutical rationale of why the deviation may have occurred (including issues with the study design), from a clinical perspective this drug is generally prescribed by endocrinologists who closely follow clinical symptoms and IGF-1 levels to monitor for safety and efficacy. Were this new formulation to deliver a slightly higher mean dose, this may translate into slightly lower IGF-1 levels and possibly increased adverse events. However, given that the deviation is so slight, most likely no adverse clinical consequences would result.

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/s/

NAOMI N LOWY
03/11/2014

DRAGOS G ROMAN
03/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021008/S-030

CHEMISTRY REVIEW(S)

Review of Chemistry, Manufacturing and Controls

Chemist's Review No. 1	**1. Organization** OND Division DMEP	**2. NDA and Supplement Numbers** 21008

3. Name and Address of the Applicant	**4. Supplement Number: S030** **Letter Date**: 8/27/2013 **Stamped Date**: 8/27/2013 **Type:** PA **Due Date:** 02/27/2014* (extended for 2 month due to a major amendment filed) **Assignment Received Date:** 9/9/2013
Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, New Jersey 07936-1080	

5. Established Name	**6.Proprietary Name**	**7. Amendments, Report, Date**
Octreotide	Sandostatin® LAR Depot	12/23/2013

8. Supplement Provides for:

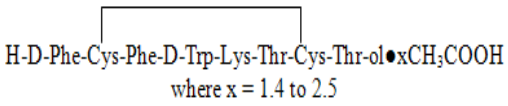
to introduce a new pharmaceutically equivalent vehicle and presentation for Sandostatin LAR Depot

9. Indication(s) for Use:	**10. How Dispensed**	**11a. Related Documents**
Somatostatin analogue, for the treatment of acromegaly	Rx	

12. Dosage Form	**13. Strengths**	**11b. Submission Media**
For injection	10 mg, 20 mg, and 30 mg	Electronic

14. Chemical Name and Structure

The molecular weight of octreotide is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:



L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1- (hydroxy-methyl) propyl]-, cyclic (2-7)-disulfide; [R-(R*,R*)]

15. Comments

-This supplement provides changes in composition and volume of vehicle solution; the injection accessories; container closure system and specifications for in-process control and finished product.

-The applicant has evaluated uniformity of delivered dose with new vehicle, the results show the delivered dose for Sandostatin LAR powder for suspension for injection by the current and new vehicle meet specified limits (minimum of (b) (4) maximum of (b) (4) and average of (b) (4) of labeled dose). The delivered dose values obtained for both current and new vehicle are similar.

-The applicant has conducted bioequivalence study to demonstrate the bioequivalence for Sandostatin LAR 30 mg with current vehicle and with new vehicle. The results have been evaluated by ONDQA/Biopharm reviewer Dr. Tien Mien Chen. Dr. Tien Mien Chen has concluded in his review that from the Biopharmaceutics perspective, a BE conclusion could not be made. The Medical Division should make a final decision/justification if the new vehicle could be approved for use with Sandostatin LAR for SC injection. No Biopharmaceutics comments are to be sent to the Applicant at this time (Review in DARRTs on 2/26/2014).

-The applicant has provided stability data that supports the changes made to the container closure system

and in the vehicle.
-Changes made to the specifications and test methods for the Sandostatin LAR bulk powder for suspension for injection (intermediate and finished product) are acceptable.
-The applicant has provided comparative batch data that shows the Sandostatin LAR bulk powder for suspension for injection made with proposed changes passed specifications and are with similar quality.
-Changes made in the device have been evaluated by Gail G. Gantt from CDRH. Gail G. Gantt has concluded that the applicant has adequately addressed the deficiencies identified from an earlier review.
-Draft carton label, syringe label, tray label, vial label, and container and health care practitioner instructions for use are acceptable from CMC perspective and DMPEPA's perspective.
- Product Quality Microbiology found the microbiology related information to be adequate for approval.

16. Conclusion and Recommendation
Recommended for Approval from CMC perspective, pending a satisfactory review by Clinical Group.

17. Name	18. Reviewer's Signature	19. Date Completed
Ping Jiang-Baucom	See appended electronic signature sheet	02/27/2014

Chemist's Review

Background & Proposed Change(s)

Sandostatin LAR 10, 20, and 30 mg powder for suspension for injection is a long acting release formulation of the drug substance octreotide acetate used for repeated application at approximately monthly intervals. This supplement provides the following changes:

- Change in composition and volume of vehicle solution
- Change in the administration/injection accessories, i.e. replacement of the former two injection needles by a vial adapter and a safety injection needle
- Change in the container closure system of the Sandostatin LAR® powder for suspension for injection (glass vial and rubber stopper)
- Change in the specifications and test methods for the Sandostatin LAR® bulk powder for suspension for injection (intermediate)
- Change in the specifications and test methods for the Sandostatin LAR® powder for suspension for injection in vials (finished product)

No changes have been made to the composition, manufacturing process and excipients of the Sandostatin LAR® powder for suspension for injection, or to the drug substance

Supplement Review

1. Environmental Assessment Information

The applicant certifies that this submission for Sandostatin LAR qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(a) as the concentration of the active moiety, octreotide acetate will not be increased.

2. Change in Composition and Volume of Vehicle Solution

According to the applicant the changes made to the composition is to improve quality of the suspension and to improve ability of injection. Compared to the current vehicle, the proposed new vehicle contains an increased concentration of carmellose sodium. In addition, a surfactant (Poloxamer 188) has been

added. The vehicle volume is also reduced from 2.5 ml to 2 ml. The applicant states, as the new vehicle permits shaking and inverting the vial, a vial adapter has been introduced as well as the needle diameter of the injection needle reduced from 19G (1.1mm) to 20G (0.9mm). The current vehicle composition and proposed vehicle composition are shown below:

Table 2-1 Vehicle for Sandostatin LAR®: Comparative overview of current and proposed vehicle

Ingredient	Current vehicle		Proposed vehicle		Function
	mg/syringe	mg/ml	mg/syringe	mg/ml	
Carmellose sodium / Carboxymethylcellulose sodium	12.5	5	14	7	(b) (4)
Mannitol	15	6	12	6	
(b) (4)					
Poloxamer 188	-	-	4	2	
Water for injections	ad 2.5ml	ad 1ml	ad 2ml	ad 1ml	

1) Uniformity of delivered dose with new vehicle

The applicant conducted uniformity of delivered dose test for two batches of Sandostatin LAR, 10 mg and 30 mg powder for suspension for injection, using the new vehicle in 2 mL pre-fill syringe *vs.* currently approved vehicle in a 2.5mL pre-filled syringe. The results provided are reproduced below:

Table 2-1 Comparison of uniformity of delivered dose for Sandostatin LAR 10 mg powder for suspension for injection used in combination with the current and new vehicle

Vial	Current vehicle	New vehicle
	2.5 ml pre-filled syringe batch 515631 Sandostatin LAR® batch DB9783	2.0 ml pre-filled syringe batch Y224 1209 Sandostatin LAR® batch DE6193
1	106.5	101.2
2	97.7	100.7
3	103.4	104.4
4	102.9	101.2
5	98.2	100.5
6	97.9	99.2
7	105.2	101.2
8	103.5	100.9
9	100.5	100.4
10	99.4	102.2
Mean	101.5	101.2
Min	97.7	99.2
Max	106.5	104.4
RSD	3.15	1.35

Table 2-2 Comparison of uniformity of delivered dose for Sandostatin LAR 30 mg powder for suspension for injection used in combination with the current and new vehicle

Vial	Current vehicle 2.5 ml pre-filled syringe batch 514719 Sandostatin LAR® batch BY0258 [1]	New vehicle 2.0 ml pre-filled syringe batch Y178 1208 Sandostatin LAR® batch BY0263 [1]
1	100.8	105.1
2	100.0	102.9
3	100.1	104.0
4	100	99.2
5	99.9	102.6
6	100.3	100.9
7	101.6	102.2
8	99.7	100.7
9	100.0	101.1
10	99.9	105.4
Mean	100.2	102.4
Min	99.7	99.2
Max	101.6	105.4
RSD	0.56	1.96

[1] Both batches were filled with the same bulk microparticle batch.

Evaluation: Acceptable

The data provided shows the delivered dose for Sandostatin LAR powder for suspension for injection by the current and new vehicle meet specified limits (minimum of (b) (4)*, maximum of* (b) (4) *and average of* (b) (4) *of labeled dose). The delivered dose values obtained for both current and new vehicle are similar.*

2) Bioequivalence study/Delivered dose investigations

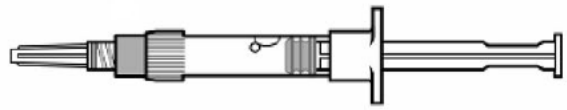
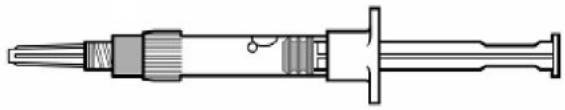
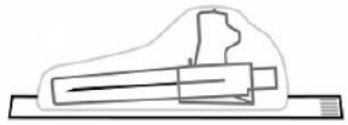
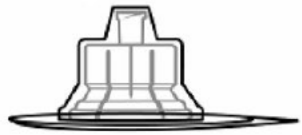
To demonstrate the bioequivalence for Sandostatin LAR 30 mg with current vehicle and with new vehicle, the applicant has conducted bioequivalence study and provided the results in reports CSMS995L2102 and CSMS995L2106. Results in these studies have been evaluated by Biopharm reviewer Dr. Tien Mien Chen. Dr. Tien Mien Chen has concluded in his review that from the Biopharmaceutics perspective, a BE conclusion could not be made. The Medical Division should make a final decision/justification if the new vehicle could be approved for use with Sandostatin LAR for SC injection. No Biopharmaceutics comments are to be sent to the Applicant at this time (Review in DARRTs on 2/26/2014).

3. Change in the administration/injection accessories, i.e. replacement of the former two injection needles by a vial adapter and a safety injection needle

The proposed new vehicle solution allows shaking and inversion of the vial, a vial adapter is introduced and the injection needle diameter is reduced from 1.1 mm to 0.9 mm. The current injection needle was replaced by a safety injection needle with integrated safety shelf to reduce risk of needle injury. Comparative presentations are shown below:

Table 2-2 Sandostatin LAR®: Comparative overview of current and proposed presentation

Current presentation of Sandostatin LAR®	Proposed new presentation of Sandostatin LAR®
One vial of Sandostatin LAR® 10mg, 20mg or 30 mg powder for suspension for injection	One vial of Sandostatin LAR® 10mg, 20mg or 30 mg powder for suspension for injection

Current presentation of Sandostatin LAR®	Proposed new presentation of Sandostatin LAR®
	
One prefilled syringe of Vehicle for Sandostatin LAR® 2.5 ml solution	One prefilled syringe of Vehicle for Sandostatin LAR® 2ml solution
	
Two injection needles (19G, 1.1 mm)	One safety injection needle (20G, 0.9 mm)
	
	One vial adapter
	

Gail G. Gantt performed CDRH Consult Review and has concluded the applicant has addressed all deficiencies identified by their previous review dated 5/2/2011. There are no additional device specific deficiencies. CDRH consult review has been filed in DARRTs as a memo by project manager Jennifer Johnson on 12/12/2013.

4. Change in the container closure system of the Sandostatin LAR

In the proposed new presentation a different glass vial/rubber stopper is being used for the Sandostatin LAR powder for suspension for injection in order to be compatible with the vial adapter.

According to the applicant, the new glass vial is of the same quality (b) (4) It has the same nominal size and differs only very slightly in few dimensions and tolerances. The new rubber stopper is a (b) (4). It replaces the currently used (b) (4) Both current and proposed rubber stopper comply with the Ph. Eur. and USP requirements for parenteral rubber closure.

Table 2-3 Sandostatin LAR® powder for suspension for injection: Comparative overview of current and proposed container closure system

Current container closure system of Sandostatin LAR® powder for suspension for injection	Proposed container closure system of Sandostatin LAR® powder for suspension for injection
Glass vial	Glass vial
(b) (4) glass vial, 6 ml (5 ml (see Table 2-6))	(b) (4) glass vial, 6 ml
Rubber stopper	Rubber stopper
	(b) (4)

Stability data in the new vial and rubber stopper has been provided in 3.2.P.8. The applicant has provided stability data on six batches (3 for each strength) of drug product for up to 36 months for 10mg and 30mg/vial dosage strengths. The stability data shows the product was stable for up to 36 months when stored under the 5 °C/ambient storage condition, over 6 months under the 25 °C /60% RH storage condition. The applicant states the current shelf life of 36 months is based on current stability data up to 36 months. Stability data supports the proposed changes.

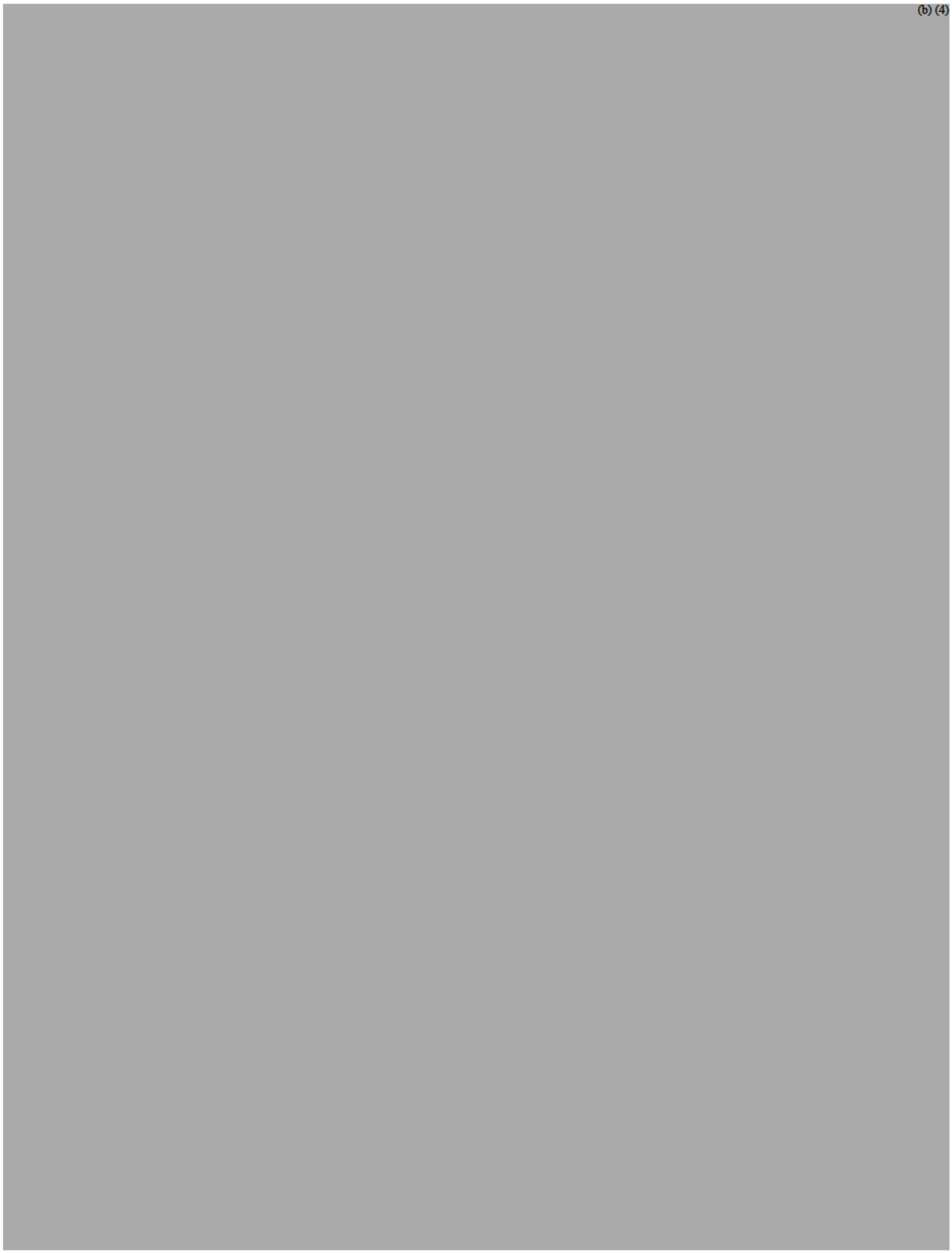
5. Change in the specifications and test methods for the Sandostatin LAR bulk powder for suspension for injection (intermediate)

(b) (4)

Comments:

Proposed changes are to include some of the tests stated in the finished product specifications with a foot note of (b) (4) are now formally included in the bulk microspheres specification. These tests have already be approved and used at the finished product testing therefore they are acceptable for in-process control purpose.

6. Change in the specifications and test methods for the Sandostatin LAR bulk powder for suspension for injection (finished product)



Comments: The proposed changes are summarized as following:

- Addition of new test methods for added quality control for the drug product
- Editorial change
- Updated existing methods with more state of the art method while keeping the same principle
- Methods are updated to reflect the use of new vehicle/vial adapter
- Change in the test method for the residual solvents, updated to a more state of the art method while keeping the same basic principle
- Tightening existing specifications
- Method change due to use of new vehicle/vial adapter

These changes should be acceptable since the changes should not affect the quality of the product.

7. Batch data

The applicant has provided the following batch data:

- Four batches used in Bioequivalence study that including two batches manufactured with the currently approved vehicle and two batches manufactured with the proposed vehicle.
- Six batches from registration stability batch: three batches for strength 10 mg, three batches for 30mg strength.

The data provided shows all batches of Sandostatin LAR Powder for suspension for injection at both 10 mg and 30 mg strengths meet currently approved specifications. The batches in the same strength show similar values in all the physical and chemical attributes examined.

8. Revised PI, carton/container and health care practitioner IFU (instructions for use)

Changes made to the CMC sections of the "Highlights of Prescribing Information" are acceptable from CMC perspective. The changes reflected the changes made to the needles provided, as well as the addition of a vial adapter component.

The applicant has provided the following labels:

10mg carton label
10mg syringe label
10mg tray label
10mg vial label
20mg carton label
20 mg syringe label
20 mg tray label
20 mg vial label
30mg carton label
30mg syringe label
30mg tray label
30mg vial label
Demonstration carton label
Demonstration syringe label
Demonstration tray label
Demonstration vial label

Provided labels for carton, syringe, tray and vial are adequate from CMC standpoint of view.

9. Consults results

OND project manager Jennifer Johnson has submitted the following consults on 9/3/2013:

- To OSE/DMEPA to evaluate the human study report, health care provider instructions for use, proposed package insert and carton/container labels submitted with this supplement.

- To the Office of Combination Products (CDRH): to review and comment on the Human Factors Study report and IFU.
- To the Office of Combination Products (CDRH): to review and comment on the new proposed device.

Reasol Agustin at the OSE/DMEPA has evaluated the results of the applicant's human factor validation study, as well as the proposed prescribing information, container label, carton labeling and instructions for use (IFU) and has concluded that the proposed changes are acceptable (review in DARRTs on 1/22/2014. The review has also recommended revisions to the vial label, carton labeling and IFU to be implemented prior to approval of this product.

Gail G. Gantt has performed CDRH Consult Review and has concluded that the applicant has addressed all deficiencies identified by their previous review dated 5/2/2011. CDRH consult review has been filed as a memo in DARRTs by project manager Jennifer Johnson on 12/12/2013.

ONDQA project manager Pyrianka Kumar submitted Micro consults on 10/1/2013. Dr. Vinayak B. Pawar has performed the Product Quality Microbiology Review and recommended this supplement for Approval (review in DARRTs on 10/15/2013).

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/s/

PING JIANG-BAUCOM
02/27/2014

RAMESH RAGHAVACHARI
02/27/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021008/S-030

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

October 15, 2013

NDA: 21-008/S030

Drug Product Name
Proprietary: Sandostin LAR Depot
Non-proprietary: octreotide acetate for injectable suspension

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
August 27, 2013	August 27, 2013	October 1, 2013	October 3, 2013

Submission History (for 2nd Reviews or higher) - N/A

Applicant/Sponsor
Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza, East Hanover, NJ 07936-1080.
Representative: Demetre Stamatis, Global Program Reg. Manager
Telephone: 862-778-7847

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR: A modified diluent (vehicle) for product reconstitution.

3. MANUFACTURING SITE: Abbott Biologicals B.V.
Veerweg 12, 8121AA Olst,
The Netherlands
FEI 3000268812

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Depot Injection; 10, 20 and 30 mg.
- Vehicle for Sandostatin LAR® 2ml solution.

5. METHOD(S) OF STERILIZATION: Vehicle in pre-filled syringe is (b) (4).

6. PHARMACOLOGICAL CATEGORY: Somatostatin

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: Novartis Pharmaceuticals Corporation submits a (PAS) supplemental NDA 21-008/S030, Sandostatin® LAR Depot (octreotide acetate for injectable suspension) for a modified diluent for product reconstitution. This electronic submission provides information in support of the modified diluent.

filename: **N021008S030R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The modified compounded solution is [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER

B. Endorsement Block _____
John W. Metcalfe, Ph.D., Sr. Review Microbiologist, OPS/CDER

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – N/A

P DRUG PRODUCT

The Drug Product: There are no changes to the drug product [Sandostatin LAR® powder] composition, manufacturing process, excipients or to the drug substance. However, there is a change in the container closure system (glass vial and the rubber stopper) of the Sandostatin® LAR powder for suspension. The glass vial is the same size and quality but differs slightly in few dimensions and tolerances not affecting the integrity. The rubber stopper is changed from (b) (4) but not the size. These changes are noted and are not expected to affect the sterility of the (b) (4) product as was evidenced in the process validation batch results and therefore does not require microbiology review. Finally, changes were made in the specifications and test methods for the Sandostatin® LAR 10mg, 20mg and 30 mg drug product. These changes did not pertain to microbiological specifications and test methods and therefore requires no review.

The Vehicle: The purpose of this submission is to introduce a modified pharmaceutically equivalent diluent (vehicle) used to suspend the Sandostatin® LAR drug product for injection. Besides the addition of Poloxamer 188 as a (b) (4), the vehicle volume was changed from 2.5 mL to 2.0 mL with change in administration/injection accessories such as vial adapter and a safety injection needle. These changes in the vehicle are the primary reason for this submission and will be the thrust of this review.

Vehicle for Sandostatin LAR® 2ml solution

P.1 Description of the Composition of the Drug Product

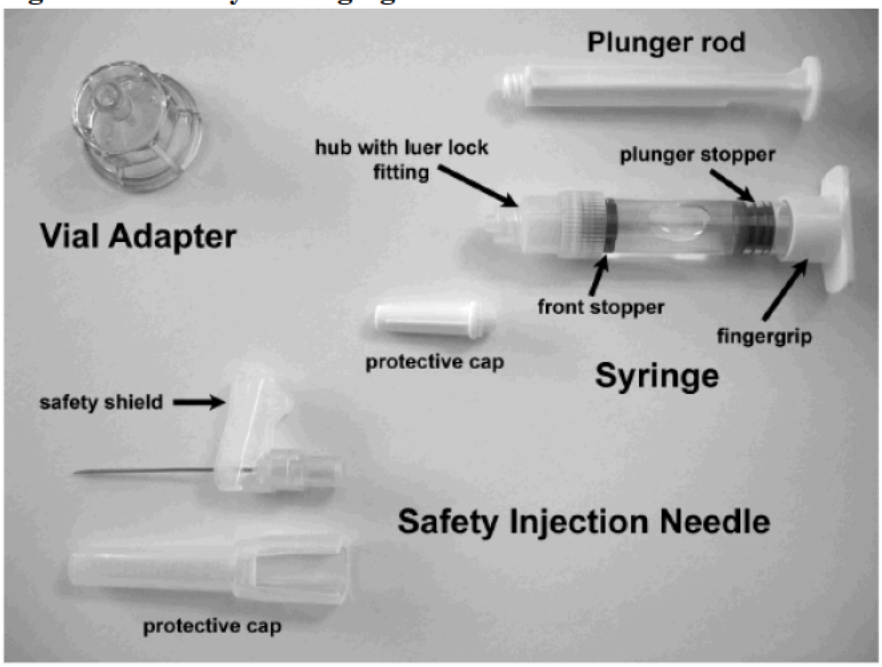
- Description of drug product – No change.
- Drug product Vehicle Composition – Composition of the modified diluent is provided in Table 1(copied from Table 2-1, Section 3.2.P.1).
- Description of Vehicle container closure system –
  The primary container closure system of the vehicle for Sandostatin LAR® 2ml solution consists of a 3 ml colorless glass syringe (type I glass) which is closed with a grey front and a grey plunger rubber stopper (b) (4) The syringe contains the following

additional administration accessories/features: a hub with a luer lock fitting (b) (4) a cap to protect the luer end of the hub (b) (4); a fingergrip (b) (4); and a plunger rod (b) (4) [See Figure 1, copied from Figure 1-1, Section 3.2.P.7).

Table 1. Syringe content of Vehicle for Sandostatin LAR® 2ml

Ingredient	Amount per syringe [mg] [1]	Function	Reference to standards
Carmellose sodium / Carboxymethylcellulose sodium	14	(b) (4)	
Mannitol	12		
(b) (4)			
Poloxamer 188	4		
Water for injections / Water for injection	ad 2 ml		
(b) (4)			

Figure 1. Primary Packaging and Administration Accessories



In addition, along with the vehicle prefilled syringe and Sandostatin LAR® drug product, the accessories package contains a vial adapter (b) (4) and a 20G x 1.5'' safety injection needle (stainless steel with safety shield/protective cap (b) (4)), each packed in a protective thermoformed and sealed plastic blister.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Vehicle Container-Closure and Package integrity –
To confirm container closure integrity, a microbiological challenge test with the primary packaging materials for Vehicle for Sandostatin LAR® 2ml solution was performed. Primary packaging material (syringe) for Vehicle for Sandostatin LAR® 2ml solution was filled with (b) (4) The sponsor states that this is a standard approved procedure to cover the stress from processing as well as the (b) (4) It is summarized below for information purposes.

(b) (4)

Forty units are tested at time 0 months storage and for the stability tests all remaining samples are stored in a horizontal position for 6 months, 1, 2, 3, 4 and 5 years (up to the maximum shelf life) at 25 ± 2°C and at 5°C ± 3°C. At each testing point one test with 40 units each is performed as described in the following for the initial and the stability time points. The cumulative results from the Process Validation Batches are provided in Table 2 (copied from Table 6-15, Section 3.2.P.3).

Table 2. Container Closure Integrity Test Results.

Storage time and temperature for the 40 units tested	No. of contaminated units:	Storage time and temperature for the 40 units tested	No. of contaminated units:
Storage time at 25°C		**Storage time at 5°C**	
0	0	0	0
6 months	0	6 months	0
12 months	-	12 months	-
24 months	0	24 months	0
36 months	0	36 months	0
48 months	0	48 months	0
60 months	To follow	60 months	To follow

- Not performed

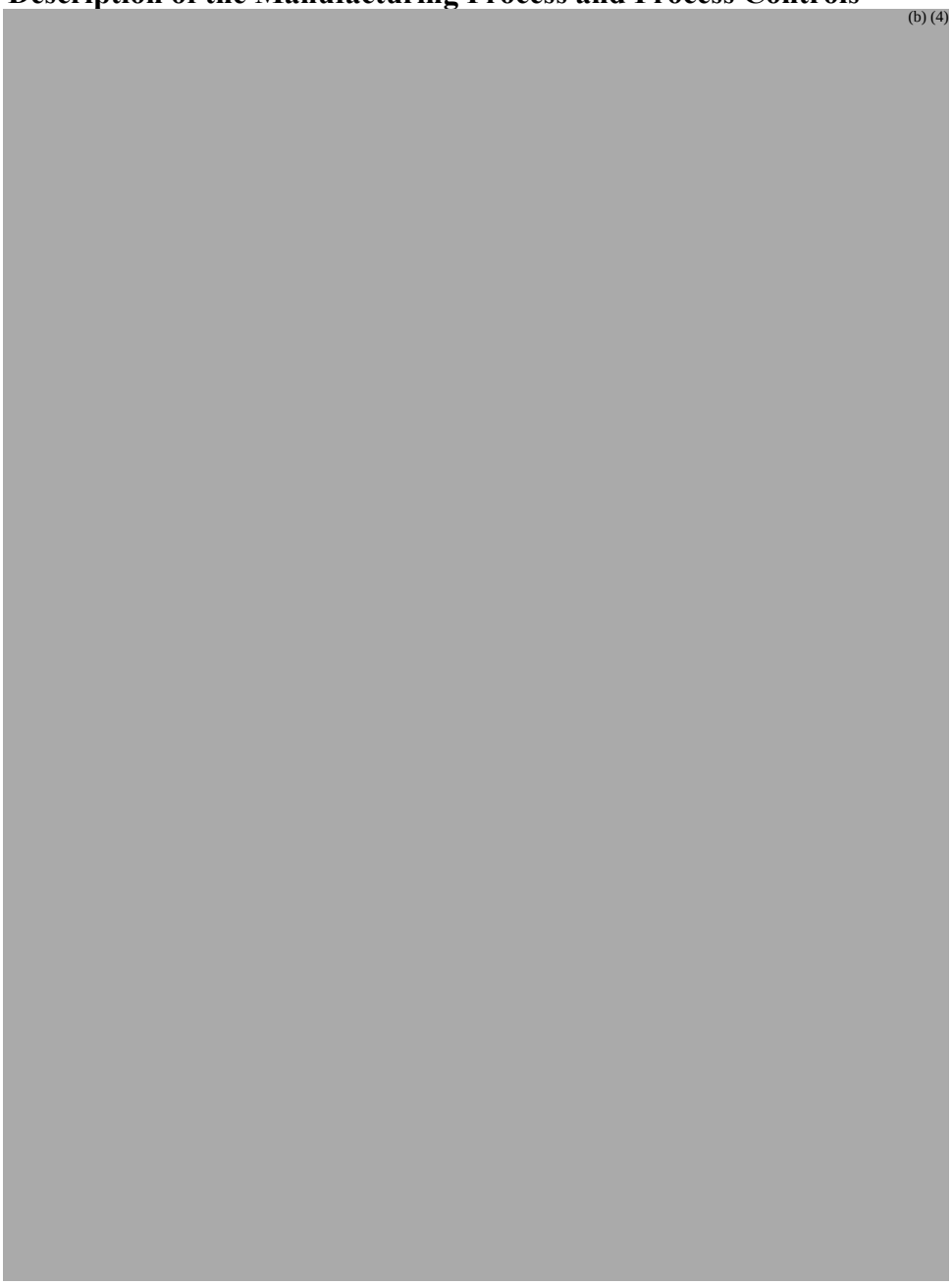
- Preservative Effectiveness – N/A
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

ADEQUATE

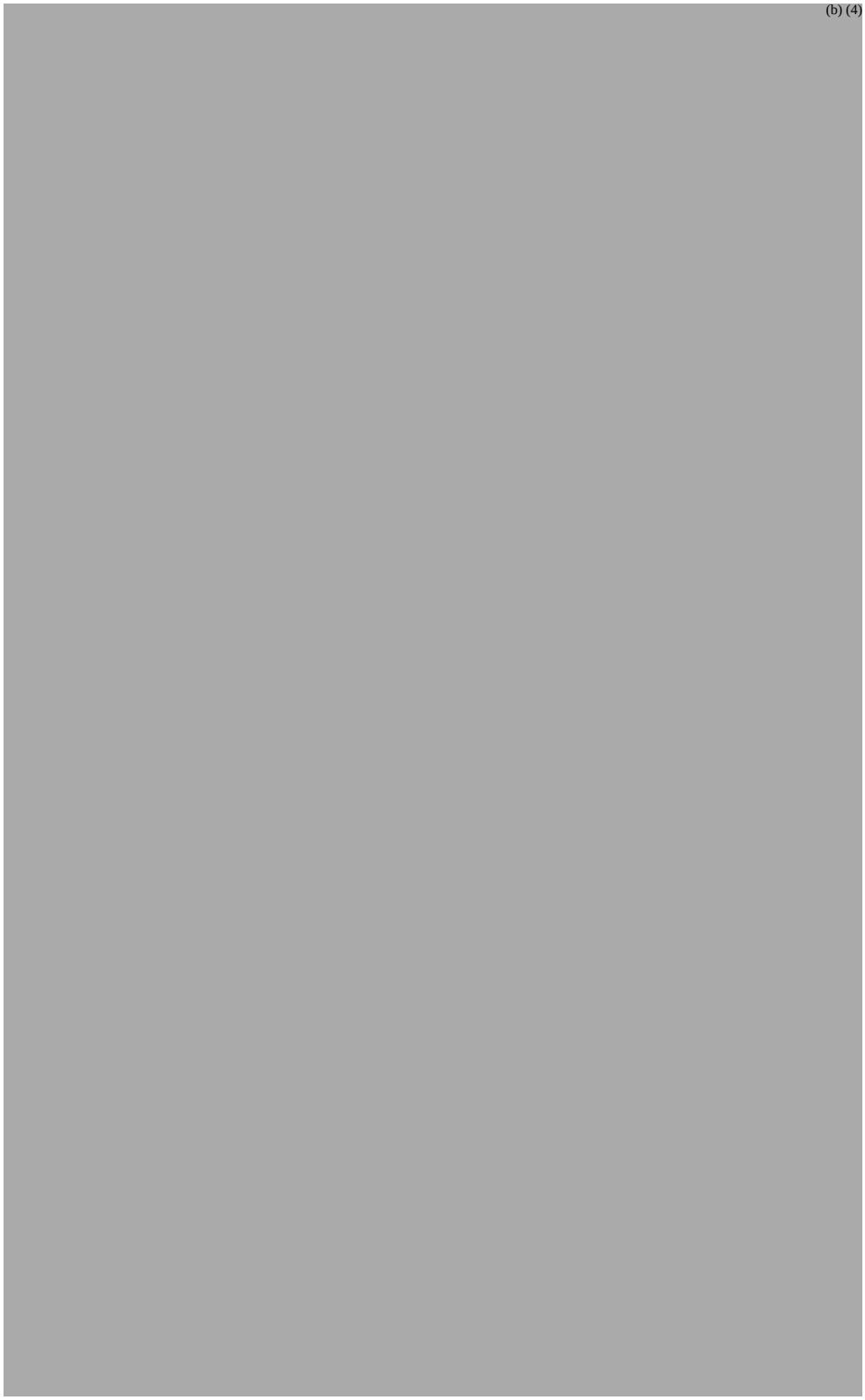
REVIEWER COMMENT – The applicant meets the regulatory expectations for validating the integrity of the primary packaging (syringe) system.

P.3 Manufacture
P.3.1 Manufacturers
P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)



(b) (4)



ADEQUATE

REVIEWER COMMENT – The previously approved manufacturing process described above provides adequate sterility assurance in that (b) (4) through an approved process.

P.3.5 Process Validation and/or Evaluation

(b) (4)

(b) (4)

(b) (4)

ADEQUATE

REVIEWER COMMENT – Through the process validation studies the applicant has demonstrated that the manufacturing process for the (b) (4) vehicle in a syringe meets the regulatory expectations.

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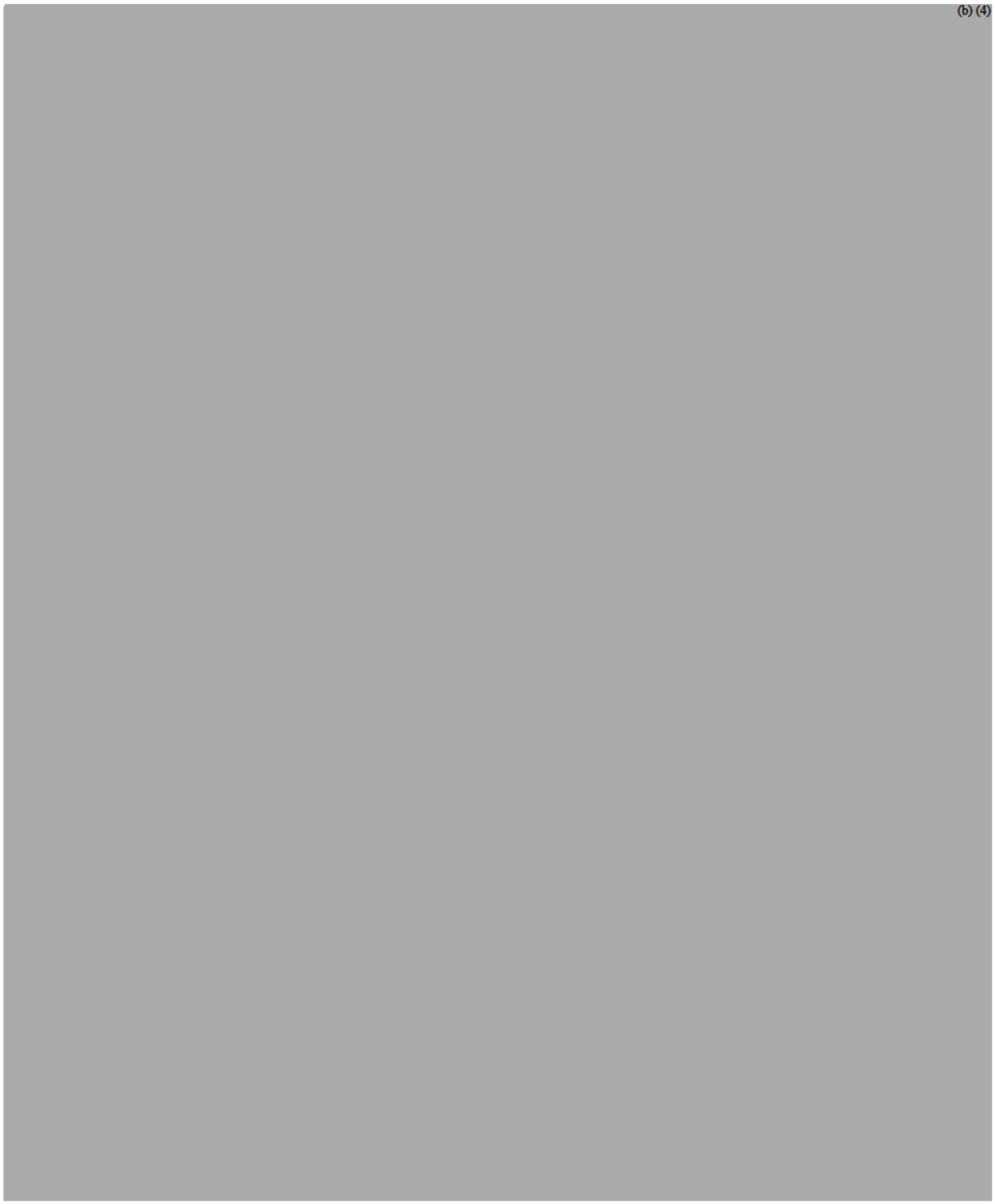
(b) (4)



P.5 Control of Drug Product
P.5.1 Specifications
P.5.2 Analytical Procedures

(b) (4)

ADEQUATE

REVIEWER COMMENT – The analytical test data meets the regulatory expectations with regard to the approved Bacterial Endotoxins and Sterility test methods.

P.7 Container Closure System - See Review Section P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

Three production scale batches of Vehicle for Sandostatin LAR® 2ml solution (Y224 1209, Y225 1209, Y226 1209) manufactured at Abbott Biologicals B.V., Olst, Netherlands have been placed on stability per approved stability program. The Sterility and Bacterial endotoxins results have been provided in Review Section P.5.2.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

There are no changes to the specifications and testing schedule for post-approval stability program.

P.8.3 Stability Data – See Review Section P.8.1.

ADEQUATE

REVIEWER COMMENT – The stability data are consistent with the regulatory expectations with regard to the approved stability program.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.

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

/s/

VINAYAK B PAWAR
10/15/2013

JOHN W METCALFE
10/15/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021008/S-030

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	21008/S-030
Submission Date:	08/27/13, 09/24/13, and 10/11/13
Brand Name:	Sandostatin LAR Depot
Generic Name:	Octreotide acetate powder
Formulation:	Injectable Suspension Depot for IM (Intragluteal) q. one month
Strength:	10, 20, and 30 mg/vial (three strengths)
Applicant:	Novartis
Type of submission:	Labeling supplement (LS-030)
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Novartis' NDA 21008 for Sandostatin LAR Depot (octreotide acetate powder) for Inj. Suspension accompanied with a diluent for reconstitution was approved on 11/25/98 for three strengths (10, 20, and 30 mg/6-mL vial). After reconstitution, Sandostatin LAR Depot in suspension is to be given by intramuscular (IM) injection monthly. It is indicated for the treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous (SC) injection for:

- Acromegaly
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors
- Profuse watery diarrhea associated with VIP-secreting tumors

Post its approval, the Applicant proposed to change the vehicle (diluent) for reconstitution and conducted a bioequivalence (BE) study No **CSMS995L2102** for comparison between the new and current diluents. In a meeting held between the Agency and Novartis on 05/10/11, the results of the above BE study for the changes in diluent was not accepted by FDA for the reported pharmacokinetic (PK) parameters were dose-adjusted due to difference in doses delivered. Please see 05/10/11 MM (meeting minutes) for details.

Based on the FDA's recommendation, Novartis conducted another BE study No. **CSMS995L2106** in order to show bioequivalence between the newly proposed vehicle and the currently marketed vehicle for reconstitution. The Applicant reported that a technical root-cause analysis successfully identified reconstitution at low temperature as the critical step of the reconstitution procedure which led to the lower administered dose in the previous BE study No **CSMS995L2102**.

Current Submission

On 08/27/13, Novartis submitted supplement LS-030 and introduced a new diluent (vehicle) for reconstitution of the currently approved product, Sandostatin LAR Depot. A

new BE study No. **CSMS995L2106** was also submitted to support the newly proposed vehicle.

The test formulation reconstituted with the new vehicle was investigated in the above BE study as the test article. This test formulation is composed of the same microparticles currently used in Sandostatin LAR but reconstituted with a new vehicle (changes to compositions and volume). This new vehicle was expected to offer improved convenience for the preparation of the suspension because of improved (b) (4). In addition, the volume of the vehicle was reduced from 2.5 (current) to 2.0 mL (proposed). The new vehicle permits moderate shaking and turning upside down of the vial, which allows the introduction of a transfer device and a SEN (safety injection needle) for administration of the product. A comparison of the Current vs. the Proposed Vehicles is described in Table 8 in a later section of this review.

On 09/24/13, the Applicant provided for review the Bioanalytical Method Validation reports as well as the bioanalytical data report for the measurement of Octreotide in human plasma samples obtained from the BE study.

Upon Biopharmaceutics/ONDQA's request, the Applicant submitted on 10/11/13 for review:

1. A biowaiver request for the two lower strengths (10 and 20 mg/vial) reconstituted with the newly proposed vehicle which had not been clinically tested in the above BE study or any clinical studies,
2. Comparative *in vitro* drug release profiles/data relating the 10mg/vial and 20mg/vial to the 30mg/vial strength.
3. SAS xpt files for BE study No. **CSMS995L2106** to allow Agency to reassess the BE data and to validate the Applicant's BE conclusions.

Per CDRH/FDA's request, a study report No. **P1208-R-005** was also submitted for review, the Human Factors Engineering Summary Report for the Somatostatin Delivery System.

Biopharmaceutics Review

The Applicant reported no changes being made to the above currently approved compositions/formulation of the Sandostatin LAR Depot (octreotide acetate powder) for Inj. Suspension. The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed changes in the volume and composition of the diluting vehicle, the new BE study **CSMS995L2106** results, the biowaiver request for the two lower strengths, and the *in vitro* comparative release profile/data to support the labeling changes.

Reviewer's Comments:

1. The biowaiver request with justification for the two lower strengths, 10 and 20 mg/vial which were not tested clinically or employed in the BE study were also reviewed and found acceptable.

2. The assay and validation reports for the submitted BE study were reviewed and found acceptable

3. The Applicant concluded BE results (Table 3 in the later section of this review). The BE data were reassessed by this reviewer. The Agency's results shown below, however, were slightly different from the Applicant's BE results.

   Based on the Agency's BE Acceptance Criteria, the Agency's study results showed that all three primary PK parameters of interests are within CIs of 80%-125% except the CI 90% upper boundary for $AUC_{D0-\infty}$ being slightly exceeded the 125% limit (125.369%) as shown below.

Dependent	Test (New Vehicle) /Ref (Current Vehicle)		
	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
Ln(C_{max})	105.6679	94.52896	118.1193
Ln(AUC_{D0-98})	112.6768	102.1981	124.2298
Ln($AUC_{D0-\infty}$)	113.7722	103.2481	125.369 (Failed)

   The reasons of slightly missing the Agency's BE Acceptance Criteria may be due to:

   a. Sandostatin when reconstituted with the new vehicle (Test) delivered a slightly higher mean dose (29.93 ± 1.10 mg) than that (29.09 ± 0.81 mg) with the currently approved vehicle (Ref), i.e., the results are seemingly consistent with the different doses delivered. However, no dose adjustment was made.

   b. This is a parallel study design; therefore, the factor of inter-subjects' variation was not canceled out as those in a crossover study design. Different inter-subjects' variations between parallel treatment group may cause wilder 90% CI.

   Nevertheless, since this is a monthly IM injection, the slight deviation of the upper CI limit of $AUC_{D0-\infty}$ after a single-dose IM injection is considered less clinically meaningful. On the other hand, the $C_{max,ss}$ (peak plasma levels at steady state), $C_{ave,ss}$ (average plasma levels at the steady state), and $C_{trough,ss}$ (trough plasma levels at the steady state) are considered to be more relevant for safety and efficacy of Sandostatin after IM inj.

4. Thus, the Medical Division should make a final decision if the new vehicle could be approved for use with Sandostatin LAR Depot for IM injection.

5. No Biopharmaceutics comments are made to the proposed labeling changes.

RECOMMENDATION

From the Biopharmaceutics perspective, a BE conclusion could not be made. The Medical Division should make a final decision/justification if the new vehicle could be approved for use with Sandostatin LAR for IM injection.

No Biopharmaceutics comments are to be sent to the Applicant at this time.

_____ _____02/14/14_____
Tien-Mien Chen, Ph.D. Date
ONDQA Biopharmaceutics Reviewer

_____ _____02/26/14_____
Tapash Ghosh, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

CC: DARRTS/NDA No.21008/LS-030/RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Novartis' NDA 21008 for Sandostatin LAR Depot (octreotide acetate powder) for Inj. Suspension accompanied with a diluent for reconstitution was approved on 11/25/98 for three strengths (10, 20, and 30 mg/6-mL vial). After reconstitution, Sandostatin LAR Depot in suspension is to be given by intramuscular (IM) injection monthly. It is indicated for the treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous (SC) injection for:

- Acromegaly
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors
- Profuse watery diarrhea associated with VIP-secreting tumors

Post its approval, the Applicant proposed to change the vehicle (diluent) for reconstitution and conducted a bioequivalence (BE) study No **CSMS995L2102** for comparison between the new and current diluents. These changes to the vehicle are reportedly intended to improve convenience for health care providers administering the product and for patients requiring long-term parenteral somatostatin analog therapy.

In a meeting held between the Agency and Novartis on 05/10/11, the results of the above BE study for the changes in diluent was not accepted by FDA for the reported PK parameters were dose-adjusted due to difference in doses delivered. Please see 05/10/11 MM (meeting minutes) for details.

Based on the FDA's recommendation, Novartis conducted another BE study No. **CSMS995L2106** (protocol submitted 10/11/11, IND 37,768, Clinical Information Amendment, Serial No. 352), in order to show bioequivalence between the newly proposed vehicle and the currently marketed vehicle for reconstitution. The Applicant reported that a technical root-cause analysis successfully identified reconstitution at low temperature as the critical step of the reconstitution procedure which led to the lower administered dose in the previous BE study No **CSMS995L2102**.

CURRENT SUBMISSION

On 08/27/13, Novartis submitted supplement LS-030 and introduced a new diluent (vehicle) for reconstitution of the currently approved product, Sandostatin LAR Depot. A new BE study No. **CSMS995L2106** was also submitted to support the newly proposed vehicle.

Under this LS-030, the following changes were proposed:

- Change in composition and volume of vehicle solution (a new vehicle),
- Change in the administration/injection accessories, i.e. replacement of the former two injection needles by a vial adapter and a SEN, as well as the needle diameter of the injection needle reduced from 19G (1.1 mm) to 20G (0.9 mm).
- Change in the container closure system of the Sandostatin LAR powder for suspension for injection (glass vial and rubber stopper),

- Change in the specifications and test methods for the Sandostatin LAR bulk powder for suspension for injection (intermediate), and
- Change in the specifications and test methods for the Sandostatin LAR powder for suspension for injection in vials (finished product).

The test "formulation" reconstituted with the new vehicle was investigated in the above BE study as the test article. This test formulation is composed of the same microparticles currently used in Sandostatin LAR but reconstituted with a new vehicle. This new vehicle was expected to offer improved convenience for the preparation of the suspension because of improved (b) (4). In addition, the volume of the vehicle was reduced from 2.5 (current) to 2.0 mL (proposed). The new vehicle permits moderate shaking and turning upside down of the vial, which allows the introduction of a transfer device and a SEN for administration of the product. A comparison of the Current vs. the Proposed Vehicles is described in Table 8 in a later section of this review.

No changes are made to the composition, manufacturing process and excipients of the drug product (DP), Sandostatin LAR powder for suspension for injection, or to the drug substance (DS). Overall, the new vehicle and its new presentation with vial adapter and SEN reportedly enhance the convenience and safety for the reconstitution and administration of the product for health care professionals and patients.

On 09/24/13, the Applicant provided for review the Bioanalytical Method Validation reports as well as the bioanalytical data report for the measurement of Octreotide in human plasma samples obtained from the BE study.

In order to support the biowaiver request for the two lower strengths (10 and 20 mg/vial) reconstituted with the newly proposed vehicle which had not been clinically tested in the above BE study or any clinical studies, the Applicant submitted on 10/11/13 (upon the Biopharmaceutics/ONDQA's request),

1. A biowaiver request
2. Comparative *in vitro* drug release profiles/data relating the 10mg/vial and 20mg/vial to the 30mg/vial strength (including biolot).
3. SAS xpt files for BE study No. **CSMS995L2106** to allow Agency to reassess the BE data and to validate the Applicant's BE conclusions.

The CMC changes are under review by the chemist/ONDQA. The BE study report, the biowaiver request, and *in vitro* comparative release data are under review by the Biopharmaceutics/ONDQA.

Per CDRH/FDA's request, a study report No. **P1208-R-005** was also submitted, Human Factors Engineering Summary Report for the Somatostatin Delivery System. The study results are under review by CDRH/FDA.

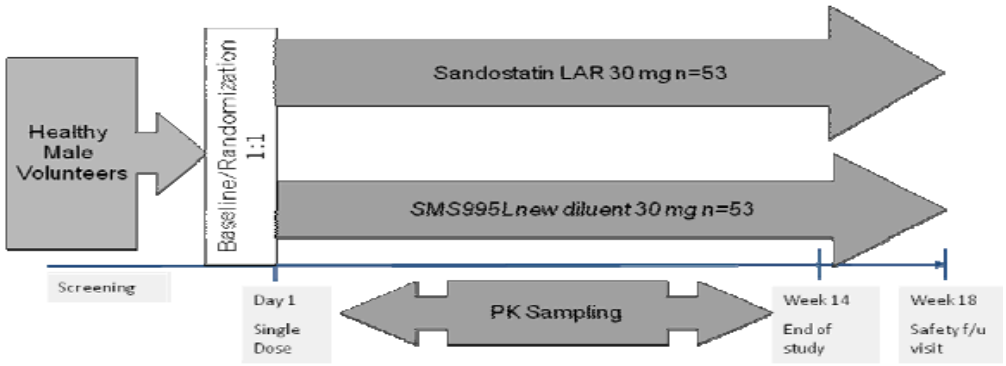
BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the BE study results, the biowaiver request, and the *in vitro* comparative release profile/data to support the labeling changes.

BE Study Report No. CSMS995L2106

"A phase I, open-label, randomized, parallel, single center study to assess the bioequivalence of a single-dose IM injection of Octreotide (Sandostatin LAR 30 mg with new vehicle vs. Sandostatin LAR 30 mg with current vehicle) in healthy male volunteers"

This was a single dose, open-label, randomized, single center study using 2 parallel treatment arms to assess the BE of a single injection of either Sandostatin LAR 30 mg reconstituted with new vehicle or Sandostatin LAR 30 mg reconstituted with current vehicle in healthy male volunteers. The study design was depicted below (Scheme).



Source: Figure 4-1 of the protocol, Appendix 16.1.1

The study medication formulation and batch numbers are listed below:

Table 1. The Articles Employed in the BE Study

Study drug and strength	Batch number	Expiry date
SMS995L 30 mg powder	Y111 1011	Sep 2014
Vehicle for SMS995L	Y224 1209	Dec 2012
Safety needles for SMS995L	PV0037	Dec 2013
Vial adapter for SMS995L	2328	Apr 2014
Kit containing - Sandostatin LAR 30 mg - Vehicle for Sandostatin LAR and - Needles	Y110 1011	Sep 2014

Note: In the previously failed BE study No. **CSMS995L2102**, the mean delivered dose was 16% lower in the Test arm then that in the Ref arm. The Applicant reported that 1). A technical root-cause analysis successfully identified reconstitution at low temperature as the critical step of the reconstitution procedure which led to the lower administered dose and 2). The instructions for use have subsequently been updated to more clearly describe the requirement of reconstitution at room temperature. Please see study synopsis in Appendix 1 for details.

Venous blood samples (2.6 mL each) were planned to be drawn following a single IM dose to the male healthy subjects enrolled in both treatment arms at pre-dose (-1 min), 0.5, 1, 2, 3, 4, 6, and 8 hours post dose on Day 1, and on Days 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23,

25, 27, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, and 99. The results of the BE study are reviewed and the PK parameters of interests are summarized below. Please see the study synopsis in Appendix 1 for details.

Table 2. Summary of Adjusted Geometric Mean PK Parameters by Treatment Comparisons

PK Parameter (unit)	(Test) SMS995L 30 mg N=49	(Ref) Sandostatin LAR 30 mg N=50
Primary parameters		
Cmax (ng/mL)	2.60 (35.96)	2.40 (36.36)
AUC0-d98 (h*ng/mL)	1863.58 (30.24)	1663.56 (32.96)
AUC0-inf (h*ng/mL)	1900.22 (29.80)	1699.29 (32.02)

The Applicant reported the mean doses injected, i.e., 29.93 ± 1.10 mg (Test) and 29.09 ± 0.81 mg (Ref). The difference in the mean dose injected, however, is not much (<3%). No dose-adjustment was made to the above primary PK parameters of interest. The results of BE assessment are shown below in Table 4 (Mean PK parameters) and Figure 1 (Mean PK profiles).

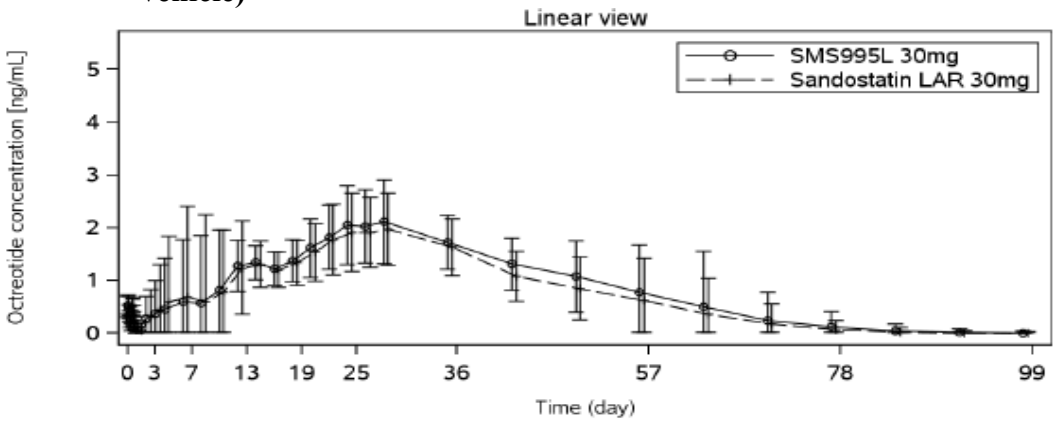
Table 3. Results of BE Assessments (Point Estimate with 90% CI) between Treatments

PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean**	Comparison(s) Test / Reference	Treatment Comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
Cmax (ng/mL)	SMS995L	49	2.60				
	Sandostatin LAR	50	2.40	SMS995L / Sandostatin LAR	1.08	0.96	1.22
AUC0-d98 (h*ng/mL)	SMS995L	49	1863.58				
	Sandostatin LAR	50	1663.56	SMS995L / Sandostatin LAR	1.12	1.01	1.24
AUC0-inf (h*ng/mL)	SMS995L	49	1900.22				
	Sandostatin LAR	50	1699.29	SMS995L / Sandostatin LAR	1.12	1.01	1.24

- n* = number of subjects with non-missing values
- **The log-transformed PK parameters were analyzed using an ANOVA model including the term of treatment as the independent variable. "Adjusted" refers to a statistical adjustment in the ANOVA.

Source: Table 14.2-1.1

Figure 1. Arithmetic Mean (SD) Concentration-Time Profile (Day 0 to 98) for Octreotide following Single Dose of 30 mg Test (Octreotide with new vehicle) and Reference (Sandostatin LAR with new Currently approved vehicle)



Analytical Method and Its Validation:
The FDA currently approved assay method for octreotide (SMS995) in human plasma was used and its description and validation results are summarized below.

Test compound	SMS995
Matrix	Human plasma
Sample preparation	Not applicable
Method	Competitive radioimmunoassay
Detection	γ counter (^{125}I)
Validation	The validation of the method was performed following th processes described in the report (BxSD R0751134).
Calibration curves	4-Parameter Logistic (4PL) fit. The acceptance criteria for the mean accuracy were met: Deviation ≤15.0% from nominal concentration within the working range for at least ¾ (with a minimum of 6) of the non-zero calibration samples. CV≤15.0% on the concentration on triplicate determination for each standard.
LLOQ	50.0 pg/mL human EDTA plasma from run 1 to 3 100 pg/mL human EDTA plasma from run 4 to 8 (see section 2.5.2 "Reagents")
ULOQ	2200 pg/mL human EDTA plasma

Standard Curve (C): Range from 39.1 pg/mL to 2500 pg/mL (n=7) diluted from the solution 100 ng/mL (samples being analyzed in triplicate).

Quality Control (D): Range from 50 pg/mL to 2200 pg/mL (n=4)

1. HIGH (2200 pg/mL): 22 µL C2 + 978 µL matrix
2. MEDIUM (1000 pg/mL): 10 µL C2 + 990 µL matrix
   intermediary solution D2: 100 µL MEDIUM + 100 µL matrix
3. LOW (100 pg/mL): 100 µL D2 + 400 µL matrix
4. LLOQ (50 pg/mL): 100 µL LOW + 100 µL matrix

(QC samples being analyzed in duplicate).

Validation Results:

Table 4. Seven Standard Curves Prepared: (Inter-day Variation for Accuracy and Precision)

		Nominal SMS995 concentration (pg/mL)						
		39.1	78.1	156	313	625	1250	2500
Run ID	Date	Back-calculated SMS995 concentration (pg/mL)						
Mean		38.5	78.0	159	310	630	1250	2510
S.D.		1.7	1.2	3.7	3.8	6.4	9.3	13.1
CV%		4	1	2	1	1	1	1
Bias%		-1	0	2	-1	1	0	0
n		8	8	8	8	8	8	8

Run 6: rejected run
Run ID 0 according to ATL-07-0096.
Run ID 1 to 8 according to ATL-12-0813.

Table 5. Seven Quality Control Prepared: (Inter-day Variation for Accuracy and Precision)

		Nominal SMS995 concentration (pg/mL)			
		50.0	100	1000	2200
Run ID	Date	Measured SMS995 concentration (pg/mL)			
Mean		59.0	105	1030	2210
S.D.		7.0	12.3	43.1	115.5
CV%		12	12	4	5
Bias%		18	5	3	1
n		7	16	16	16

Run 6: rejected run
Run ID 0 according to ATL-07-0096.
Run ID 1 to 8 according to ATL-12-0813.
Bolded value: out of acceptance criteria, included in statistics
NC: not calculated
/: No sample

Please see Assay method and validation report submitted on 09/24/13 for details.

Reviewer's Comments on the BE Study:

1. The above assay method and its validation results were reviewed and found acceptable.
2. The BE data were assessed using the Agency's BE acceptance criteria based on the 2-1-sided test with 90% CIs (confidence intervals) for log-transformed mean C_{max}, $AUC_{0\text{-}98day}$, and $AUC_{D0\text{-}\infty}$. The BE data were reassessed by this reviewer. The Agency's results (shown below in Table 6), however, were slightly different from those obtained by the Applicant (Table 3 in the earlier section of this review) which showed BE results.

Table 6. BE Data Reassessment by the Agency

	Test/Ref		
Dependent	**Ratio_%Ref_**	**CI_90_Lower**	**CI_90_Upper**
Ln(C_{max})	105.6679	94.52896	118.1193
Ln($AUC_{D0\text{-}98}$)	112.6768	102.1981	124.2298
Ln($AUC_{D0\text{-}\infty}$)	113.7722	103.2481	125.369 (Failed)

All three primary PK parameters of interests are all within CIs of 80%-125% except the CI 90 upper boundary for $AUC_{D0\text{-}\infty}$ slightly exceeded the 125% limit (125.369%). Therefore, a BE conclusion could not be made. The reasons could be

a. Sandostatin when reconstituted with the new vehicle (Test) delivered a slightly higher dose (29.93 ± 1.10 mg) than that (29.09 ± 0.81 mg) reconstituted with the currently approved vehicle (Ref), i.e., the results are consistent with the dose delivered. However, no dose adjustment was made.

b. This is a parallel study design, therefore, the factor of inter-subjects' variation was not canceled out as those in a crossover study design.

FORMULATION COMPARISONS

The compositions/formulations of the currently approved Sandostatin LAR powder for suspension for injection (three strengths) are shown below.

Table 7. The Compositions and Formulation of the Currently Approved Sandostatin LAR, 10, 20, and 30 mg/Vial

Ingredient	Amount per 10 mg vial (mg)	Amount per 20 mg vial (mg)	Amount per 30 mg vial (mg)	Function	Reference to standards
Drug substance					(b) (4)
Octreotide acetate	11.2[1]	22.4 [2]	33.6 [3]		
Excipients					
Poly(DL-lactide-co-glycolide	188.8	377.6	566.4		
Mannitol, sterilized	41.0	81.9	122.9		
					(b) (4)

The Applicant reported no changes being made to the above currently approved compositions/formulation of the DP. The compositions of the currently approved and the proposed new vehicles for reconstitution are shown below.

Table 8. Comparisons of the Current vs. the Proposed Vehicles

Ingredient	Current vehicle		Proposed vehicle		Function
	mg/syringe	mg/ml	mg/syringe	mg/ml	
Carmellose sodium / Carboxymethylcellulose sodium	12.5	5	14	7	(b) (4)
Mannitol	15	6	12	6	
					(b) (4)
Poloxamer 188	-	-	4	2	
Water for injections	ad 2.5ml	ad 1ml	ad 2ml	ad 1ml	

The vehicle is used to suspend Sandostatin LAR Depot powder for suspension for injection prior to injection. The proposed vehicle for Sandostatin LAR Depot 2ml is a colorless to slightly yellow or brown solution filled into 3ml syringes closed at both ends with grey rubber stoppers.

In addition, along with the vehicle prefilled syringe and Sandostatin LAR Depot drug product, provided also are

- A vial adapter (b) (4) and
- A 20G x 1.5'' safety injection needle (stainless steel with safety shield/protective cap (polypropylene)), each packed in a protective thermoformed and sealed plastic blister.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The following FDA currently approved dissolution method was employed as shown below.

Dissolution conditions	
Speed of rotation	6 rpm
Test medium	Acetate buffer (0.06 M, pH 4)
Volume of test medium	5 ml
Temperature	37 ± 0.5°C
Number of samples	1
Time-points for sampling	1 h, 4 h and 24 h

Dissolution conditions	
Speed of rotation	50 rpm
Test medium	Buffer (pH 10)
Volume of test medium	30 ml
Temperature	37 ± 0.5°C
Number of samples	6
Time-points for sampling	1 h, 4 h and 24 h
Filtered sample volume	200 µl

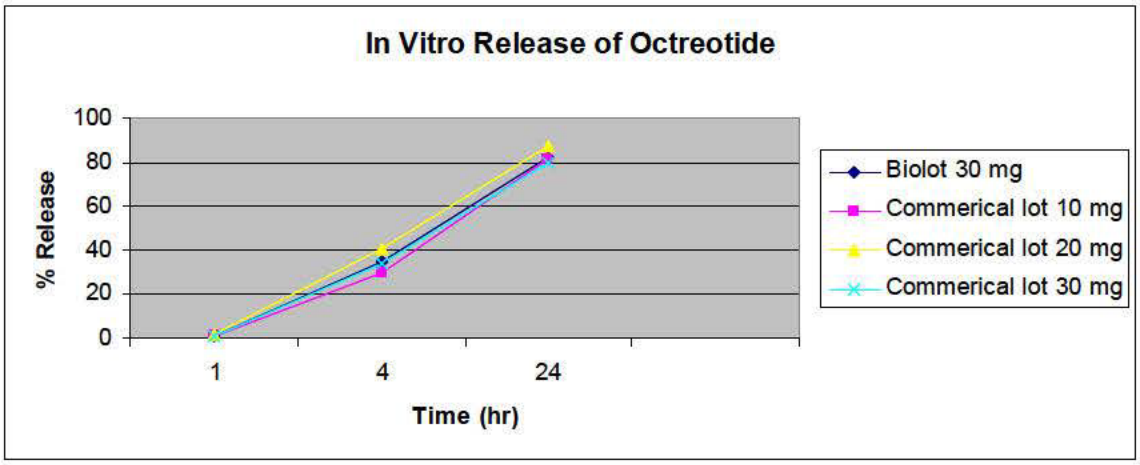
Results of comparative dissolution testing for all three strengths are summarized below:

Table 9. Mean Comparative *In Vitro* Release Data of The Two Lower Strengths, (10mg and 20 mg/Vial) Compared with The Highest Strength (30 mg/Vial; including the Biolot No. Y111/1011)

Strength	Batch number	Manuf. date	Dissolution results					
			Dissolution pH 4, 6 rpm (mean %)			Dissolution pH 10, 50 rpm (mean %)		
			1h	4h	24h	1h	4h	24h
Requirements			≤ 1.5%	≤ 4.0%	≤ 5.0%	≤ 10%	10-50%	58-90%
10 mg	CU7416 /S0003	25.08.2012	0.4	0.8	2.4	1	30	81
10 mg	DE6193 /S0004	14.02.2013	0.4	0.7	1.6	1	34	80
10 mg	DP3601 /S0007	17.07.2013	0.3	0.7	1.9	2	41	83
20 mg	DP3559 /S0010	15.07.2013	0.3	0.5	1.4	2	41	87
20 mg	DC7032 /S0007	21.01.2013	0.2	0.5	1.3	2	36	76
20 mg	CN5844 /S0005	21.05.2012	0.4	0.6	1.3	2	40	80
30 mg	DH0561 /S0016	25.03.2013	0.3	0.7	2.1	1	34	80
30 mg	DP1000 /S0023	13.07.2013	0.3	0.6	1.7	3	40	82
30 mg	DB9795 /S0012	11.01.2013	0.2	0.5	1.3	2	37	78
30 mg	Y111 /1011	12.09.2011	0.1	0.3	0.6	1	35	82

A representative figure of the comparative *in vitro* release profiles of Octreotide is shown below.

Figure 2. Comparative In Vitro Release Profiles of Octreotide of Three Commercial Strengths Compared with the Biolot 30 mg



BIOWAIVER:
Please see 10/11/13 Applicant's response for details for the biowaiver request for the two lower strengths (10 and 20 mg/vial) and its justification plus requested *in vitro* comparative release results.

Reviewer's Comment on Biowaiver Request:
The Applicant's 10/11/13 response for submitting the Biowaiver request and its justification plus comparative *in vitro* release data for the two lower strengths (10mg and 20 mg/vial) compared with the biolot (Y111 1011) and also the commercial lots of the highest strength (30 mg/vial) were reviewed. The results showed that all the lots released octreotide *in vitro* meet the FDA currently approved release criteria [redacted] (b) (4)

Overall Comments:

1. The BE data were reassessed by this reviewer. Based on the Agency's BE Acceptance Criteria, the results showed that all three primary PK parameters of interests are within CIs of 80%-125% except the CI 90% upper boundary for $AUC_{0-\infty}$ being slightly exceeded the 125% limit (125.369%). The reasons for slightly missing the Agency's BE Acceptance Criteria could be due to

   a. Sandostatin when reconstituted with the new vehicle (Test) delivered a slightly higher mean dose (29.93 ± 1.10 [redacted] (b) (4) than that (29.09 ± 0.81 mg) with the currently approved vehicle (Ref), i.e., the results are consistent with the dose delivered. However, no dose adjustment was made.

   b. This is a parallel study design, therefore, the factor of inter-subjects' variation was not canceled out as those in a crossover study design. The inter-subjects' variations may cause wilder 90% CI.

   Since this is a monthly IM injection, the $C_{max,ss}$ (peak plasma levels at steady state), $C_{ave,ss}$ (average plasma levels at the steady state), and $C_{trough,ss}$ (trough plasma levels at the steady state) may be considered more relevant to the safety and efficacy of Sandostatin after IM inj. The $AUC_{D0-\infty}$ after a single-dose IM injection is, however, considered less clinical meaningful and/or less of a critical BE concern.

2. The biowaiver request for the two lower strengths 10 and 20 mg/vials were reviewed and found acceptable.

3. Thus, the Medical Division should make a final decision if the new vehicle could be approved for use with Sandostatin LAR Depot for IM injection.

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APPEARS THIS WAY ON ORIGINAL

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

/s/

TIEN MIEN CHEN
02/26/2014

TAPASH K GHOSH
02/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021008/S-030

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products (DMEP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 021008/S-030

Name of Drug: Sandostatin LAR Depot (octreotide acetate) for injectable suspension; 10 mg, 20 mg and 30 mg

Applicant: Novartis Pharmaceuticals Corporation

Material Referenced:
Previously approved supplements:

- Approval letter and labeling for S-006 and S-010 dated April 19, 2004 (Final printed labeling submission dated April 12, 2004).
- Approval letter and labeling for S-028 dated May 19, 2014.

S-030:

- CDRH device consult review dated May 2, 2011.
- Pre-sNDA guidance meeting minutes dated June 9, 2011.
- RPM email to applicant on October 4, 2013 (biopharmaceutics information requests).
- Microbiology review dated October 15, 2013.
- CMC supplement review extension letter dated November 8, 2013.
- RPM email to applicant on November 8, 2013 (requesting color mock-ups for proposed carton and container labels and stand-alone pdf version of healthcare provider instructions for use – Word version had been requested via email on September 20, 2013 and responses submission received on October 9, 2013).
- RPM email to applicant on November 14, 2013 (clarification requests regarding Human Factors Study SMS995L).
- CDRH device consult review memo dated December 12, 2013.
- DMEPA human factors and labeling review dated January 22, 2014.
- CDRH human factors consult review dated January 30, 2014.
- ONDQA biopharmaceutics review dated February 26, 2014.
- CMC review dated February 27, 2014.
- Clinical review memo dated March 11, 2014.
- RPM email to applicant on March 7, 2014: CDRH and DMEPA labeling and human factors/healthcare provider instructions for use (IFU) revision requests.
- RPM email to applicant on June 6, 2014: FDA-revised package insert and labeling comments/revision requests regarding the carton and container labels.
- Comprehensive email chain between RPM and applicant (between May 14-July 2, 2014): discussion regarding final agreed-upon labels and labeling; final agreement by applicant on July 1, 2014 and communication of final agreed-upon labels/labeling on July 2, 2014 (DARRTS communication dated July 3, 2014).

Related IND 037768:

- Human Factors Study (HFS) draft protocol and proposed IFU submitted October 3, 2011 (SDN 401; follow-up to FDA request made at Pre-sNDA guidance meeting held on May 10, 2011; HFS study to validate IFU implemented in BE study to support sNDA submission).
- Bioequivalence (BE) Study SMS995L2106 protocol submitted October 9, 2011 (SDN 402; follow-up to FDA request for submission of repeat BE study protocol made at Pre-sNDA guidance meeting on May 10, 2011).
- CDRH HFS protocol review dated December 2, 2011.
- Clinical pharmacology review dated December 5, 2011.
- Response advice letter (BE study SMS995L2106 protocol comments) issued December 9, 2011.
- Response advice letter (HFS protocol comments) issued December 9, 2011.
- DMEPA review dated December 12, 2011 (HFS draft protocol and proposed IFU).
- Email to sponsor dated February 1, 2012 (HFS mitigation plan feedback following teleconference held on January 12, 2012 with clinical/DMEPA/CDRH reviewers).

Labeling Reviewed

Submission Dates:

July 1, 2014:	final agreed-upon package insert – Word format (via email)
March 23, 2014:	revised carton/vial labels (trade) and healthcare practitioner instructions for use (IFU) – pdf format
February 10, 2014:	demonstration kit labels (carton/syringe/tray/vial) – pdf format
December 23, 2013:	syringe/tray labels (trade) – pdf format

Receipt Dates:

July 1, 2014:	final agreed-upon package insert – Word format (via email)
March 23, 2014:	revised carton/vial labels (trade) and trade instruction booklet/healthcare practitioner IFU – pdf format
February 10, 2014:	demonstration kit labels (carton/syringe/tray/vial) and instruction booklet/healthcare provider IFU – pdf format
December 23, 2013:	syringe/tray labels (trade) – pdf format

Background and Summary Description:

NDA 021008 for Sandostatin LAR Depot was approved on November 25, 1998, for the treatment of acromegaly, malignant carcinoid tumors and VIPoma. Sandostatin LAR has been

available in vials that contain 10, 20 or 30 mg of octreotide acetate injectable suspension in single-use kits that include a syringe containing 2.5 mL diluent. Sandostatin LAR must be stored refrigerated.

On May 19, 2014, FDA approved prior approval labeling supplement S-028 (submitted on March 29, 2013) which provided for revisions to Sections 2, 3 and 16 of the package insert based on feedback from healthcare professionals regarding the administration of this product, including preference for a safety needle to reduce the incidence of accidental needle sticks and to further comply with the Needlestick Safety and Prevention Act. The revisions to these sections involved changes to the product kit components: the replacement of two sterile 1 ½ inch 19-gauge needles and two alcohol wipes with one sterile 1 ½ inch 19-gauge standard needle for transfer and drug product reconstitution and one sterile 1 ½ inch 19-gauge safety injection needle.

On August 27, 2013, Novartis submitted this prior approval CMC manufacturing supplement that provided for the following changes: a new diluent for product reconstitution (changes in composition and volume of the vehicle solution to support a pharmaceutically equivalent vehicle) and product presentation, including a simplified administration kit (changes to injection accessories, the container closure system and specifications for in-process control and the finished product). This supplement also included a revised package insert, as well as revised instruction booklets/healthcare practitioner instructions for use (IFU) and carton/container labels. Note: this supplement was discussed at a Pre-sNDA meeting held on May 10, 2011, and minutes of that meeting issued on June 9, 2011. During this meeting, bioequivalence (BE) Study CSMS995L2102 results were discussed and determined to not be acceptable to FDA, since the reported pharmacokinetic parameters were dose-adjusted due to a difference in doses delivered. FDA recommended that the applicant conduct another BE study.

Novartis followed FDA's recommendation and conducted another BE Study CSMS995L2106 in order to demonstrate bioequivalence between the currently approved vehicle and the new proposed vehicle, using the 30 mg strength. The data from that study was included in the sNDA submission. However, it was determined at the filing meeting on October 4, 2013, that necessary items for review were missing from the original sNDA submission, including SAS files or datasets in Excel format, comparative drug release profiles/data of the two lower strengths, and a biowaiver request for the two lower strengths. This information was requested via email on October 4, 2013, and Novartis submitted its response on October 11, 2013. This submission was designated as a major amendment and used to extend the review clock by two months; the review extension letter issued on November 8, 2013. Also on this date, color mock-ups of the applicant's proposed carton and container labels (not included in the original sNDA submission as required) were requested via email.

In addition to a repeat BE study, the applicant included a human factors validation study report

("Human Factors Engineering Summary Report for the SMS995L Delivery System") to support approval of S-030. During the Pre-sNDA meeting in May 2011, FDA recommended that Novartis conduct a human factors validation study to evaluate the new SMS995L delivery system (simplified administration kit). Additional communication between Novartis and FDA took place following the meeting, along with review of the draft human factors study protocols. Refer to these communications and reviews in the "Material Referenced" section above.

It was determined during review team discussion between the clinical and ONDQA Biopharmaceutics reviewers on February 24, 2014, that a bioequivalence conclusion could not be made from the Biopharmaceutics perspective [i.e., the study results did not conclude BE since **Ln($AUC_{D0-\infty}$)** missed the 90% confidence interval upper boundary by 0.369]. Therefore, a decision regarding approvability of this supplement (new vehicle) was deferred to DMEP clinical reviewers. DMEP clinical reviewers did not believe that failure of BE by 0.369 should bar approval of S-030 for the acromegaly indication (approved in DMEP). However, DMEP thought it would be wise to seek clinical concurrence from the other two divisions (Division of Gastroenterology and Inborn Errors Products, for the metastatic carcinoid tumors indication; and Division of Oncology Products 2, for the VIPomas indication). Clinical reviewers in both divisions agreed with the assessment made by DMEP clinical reviewers:

Agreement from DOP2 (Patricia Keegan) on February 24, 2014 (1:58 pm):
Yes, DOP2 agrees that this does not pose a significant safety issue.

Agreement from DGIEP (Ruyi He) on February 24, 2014 (1:51 pm):

After discussion with Andrew, DGIEP agrees with the DMEP clinical position.

Thanks,
Ruyi

Original email sent to both DGIEP and DOP2:

From: Johnson, Jennifer
Sent: Monday, February 24, 2014 12:49 PM
To: Jones, Karen; Hughes, Monica L; Ishihara, Richard; Strongin, Brian K; He, Ruyi; Demko, Suzanne; Keegan, Patricia
Cc: Hai, Mehreen; Balakrishnan, Suchitra; Lowy, Naomi; Roman, Dragos; Guettier, Jean-Marc; Lucarelli, Pamela K; Chen, Tien Mien; Ghosh, Tapash
Subject: RE: TM/Sandostatin LAR S-030/Novartis - *Need clinical input from DGIEP and OHOP/DOP2*

Hello DGIEP and DOP2 colleagues,

This morning we had a meeting with our clinical and ONDQA biopharm reviewers for Sandostatin LAR Depot S-030, a prior approval CMC supplement which provides for a new diluent for product reconstitution (pharmaceutically equivalent vehicle and presentation). *The sponsor has included CMC data, clinical data from the BE study CSMS995L2106 (conducted with the 30 mg strength) and results of a human factors study, as well as revised labeling (PI, IFU, carton and container labels). A biowaiver request was also submitted for the lower 2 strengths (10 and 20 mg).*

It was determined by ONDQA biopharm that:

The study results did not conclude BE for the **Ln($AUC_{D0-\infty}$)** missed the 90% CI upper boundary by just 0.369.

	Test (New Vehicle) /Ref (Current Vehicle)		
Dependent	**Ratio_%Ref_**	**CI_90_Lower**	**CI_90_Upper**
Ln(C_{max})	105.6679	94.52896	118.1193
Ln(AUC_{D0-98})	112.6768	102.1981	124.2298
Ln($AUC_{D0-\infty}$)	113.7722	103.2481	125.369 (Failed)

They will defer to clinical as to whether this poses a clinical safety concern, and ultimately whether we should approve this supplement. If we approve it, the biowaiver for the 10 and 20 mg strengths will be granted.

Our clinical reviewers do not think that failure of BE by 0.369 should bar approval for the acromegaly indication in DMEP. However, since the metastatic carcinoid tumors (DGIEP) and VIPomas (DOP2) indications reside in your divisions, we are seeking clinical input before approving this supplement. ***Do you agree with the DMEP clinical position?***

Let me know if you have any questions.

Thanks,
Jennifer

Also refer to the DMEP clinical review dated March 11, 2014, recommending approval.

Review

Review of the Package Insert

The final agreed-upon package insert is being compared to the currently approved package insert (attached to approval letter for S-028 issued on May 19, 2014). Additions to the text are noted by underline and deletions by ~~strikethrough~~.

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Note: these changes are acceptable to Dragos Roman (Clinical Team Leader) and Ramesh Raghavachari (Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA) per email on May 28, 2014. Also refer to CMC review dated February 27, 2014. The clarifying addition of "For Injectable Suspension: Strengths" by FDA was agreed to by the applicant via email on June 6, 2014.

(b) (4)

Note: the change in revision date is acceptable.

FULL PRESCRIBING INFORMATION

(b) (4)

(b) (4)

Note: these changes are acceptable per Dragos Roman (Clinical Team Leader) and Ramesh Raghavachari (Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA) via email on May 28, 2014. The term "safety" was deleted by FDA for simplicity and promotional reasons. Kendra Jones of the Office of Prescription Drug Promotion (OPDP) agreed with this deletion via email on May 29, 2014. The revised PI was sent to and agreed to by the applicant via email on June 6, 2014. However, on June 23, 2014, the applicant sent via email a justification for keeping the term "safety" in the PI, as it is an accurate description of the needle now supplied in the drug kit. (The applicant included images showing the difference between the previously used non-safety needle and the safety needle approved with S-028, where the needle is described as "safety" in its packaging. The applicant further explained that the (b) (4) *needle is packaged as a safety needle per the manufacturer and argued that it is therefore not promotional in nature. One of the images showed the updated Sandostatin LAR package, where the new 20 gauge needle is also included by the same manufacturer and is labeled as a safety needle.) During follow-up internal discussions (verbal and via email) with Dragos Roman, Keith Marin (CDRH) and Kendra Jones on June 24, 2014, it was determined that the term "safety" was not considered promotional in this case. Therefore, the term "safety" was re-inserted into the sections of the PI from which it had been deleted, and the revised PI was sent via email to the applicant on June 26, 2014. (In that same email, the applicant was told that the request previously made via email on June 20, 2014, to remove "safety" from the carton/container labels and the IFU in the final printed labeling submission could now be disregarded.) The applicant agreed via email on July 1, 2014.*

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Note: these changes are acceptable to Dragos Roman (Clinical Team Leader) and Ramesh Raghavachari (Branch Chief, Branch IX, Division of New Drug Quality Assessment III,

ONDQA) per email on May 28, 2014. Refer to CMC review dated February 27, 2014. The clarifying addition of "for injectable suspension" and deletion of "safety" (because of its promotional tone; concurrence by Kendra Jones of OPDP via email on May 29, 2014) by FDA was included in the revised PI that was sent to and agreed to by the applicant via email on June 6, 2014.

However, on June 23, 2014, the applicant sent via email a justification for keeping the term "safety" in the PI, as it is an accurate description of the needle now supplied in the drug kit. (The applicant included images showing the difference between the previously used non-safety needle and the safety needle approved with S-028, where the needle is described as "safety" in its packaging. The applicant further explained that the (b) (4) *needle is packaged as a safety needle per the manufacturer and argued that it is therefore not promotional in nature. One of the images showed the updated Sandostatin LAR package, where the new 20 gauge needle is also included by the same manufacturer and is labeled as a safety needle.) During follow-up internal discussions (verbal and via email) with Dragos Roman, Keith Marin (CDRH) and Kendra Jones on June 24, 2014, it was determined that the term "safety" was not considered promotional in this case. Therefore, the term "safety" was re-inserted into the sections of the PI from which it had been deleted, and the revised PI was sent via email to the applicant on June 26, 2014. (In that same email, the applicant was told that the request previously made via email on June 20, 2014, to remove "safety" from the carton/container labels and the IFU in the final printed labeling submission could now be disregarded.) The applicant agreed via email on July 1, 2014.*

5 WARNINGS AND PRECAUTIONS

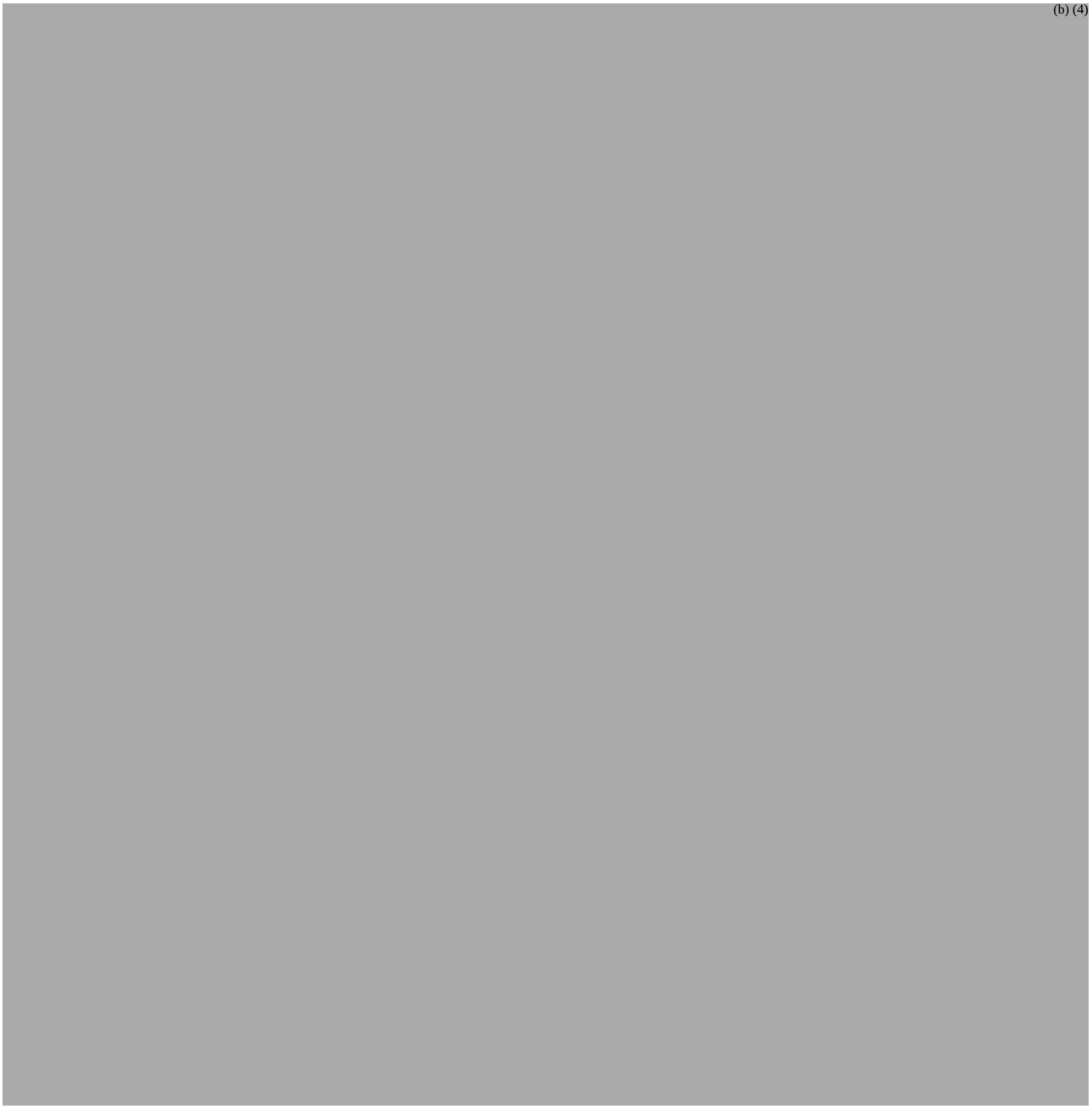
…

(b) (4)

Note: this minor clarifying editorial revision by the applicant is acceptable to Dragos Roman (Clinical Team Leader) via email on May 28, 2014.

6 ADVERSE REACTIONS

(b) (4)



…

Note: these minor editorial and clarifying changes proposed by the applicant are acceptable to Dragos Roman (Clinical Team Leader) per email on May 28, 2014.

11 DESCRIPTION

(b) (4)

Note: these changes are acceptable to Ramesh Raghavachari (Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA) via email on May 28, 2014. Also refer to CMC review dated February 27, 2014. The relocation of the molecular weight/amino acid sequence statement by FDA was agreed to by the applicant via email on June 6, 2014.

12 CLINICAL PHARMACOLOGY

…

12.1 Mechanism of Action

…

(b) (4)

Note: this minor editorial and clarifying change proposed by the applicant is acceptable to Dragos Roman (Clinical Team Leader) per email on May 28, 2014.

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

(b) (4)

Note: these changes are acceptable to Dragos Roman (Clinical Team Leader) and Ramesh Raghavachari (Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA) per email on May 28, 2014. Refer to CMC review dated February 27, 2014. The addition of updated NDC numbers, the replacement of "-" with "to" in the storage temperature range, and the deletion of "safety" (because of its promotional tone; concurrence by Kendra Jones of OPDP via email on May 29, 2014) by FDA was included in the revised PI that was sent to and agreed to by the applicant via email on June 6, 2014.

However, on June 23, 2014, the applicant sent via email a justification for keeping the term "safety" in the PI, as it is an accurate description of the needle now supplied in the drug kit. (The applicant included images showing the difference between the previously used non-safety needle and the safety needle approved with S-028, where the needle is described as "safety" in its packaging. The applicant further explained that the (b) (4) *needle is packaged as a safety needle per the manufacturer and argued that it is therefore not promotional in nature. One of the images showed the updated Sandostatin LAR package, where the new 20 gauge needle is also included by the same manufacturer and is labeled as a safety needle.) During follow-up internal discussions (verbal and via email) with Dragos Roman, Keith Marin (CDRH) and Kendra Jones on June 24, 2014, it was determined that the term "safety" was not considered promotional in this case. Therefore, the term "safety" was re-inserted into the sections of the PI from which it had been deleted, and the revised PI was sent via email to the applicant on June 26, 2014. (In that same email, the applicant was told that the request previously made via email on June 20, 2014, to remove "safety" from the carton/container labels and the IFU in the final printed labeling submission could now be disregarded.) The applicant agreed via email on July 1, 2014.*

Review of the Healthcare Practitioner Instructions for Use (IFU)
Trade Kit Instruction Booklet

The applicant's final agreed-upon healthcare provider IFU (submitted to S-030 on March 24, 2014, is being compared to the currently approved IFU (attached to the approval letter for S-006 and S-010, which issued on April 19, 2004). Where appropriate, additions to the text are noted by underline and deletions by ~~strikethrough~~.

The differences between the currently approved IFU and the applicant's proposed IFU are as follows:

(b) (4)

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Note: the changes to the IFU are acceptable per Yelena Maslov (DMEPA team leader) and QuynhNhu Nguyen (CDRH) via email on April 29, 2014. Also refer to DMEPA labeling and human factors review dated January 22, 2014, and to CDRH human factors review dated January 30, 2014. (Consolidated comments and revision requests from DMEPA and CDRH were sent to the applicant via email on March 7, 2014, and the applicant submitted a revised Instruction Booklet on March 24, 2014.)

Review of the Healthcare Practitioner Instructions for Use (IFU)
Demonstration Kit Instruction Booklet

The applicant's final agreed-upon demonstration kit healthcare provider IFU (submitted to S-030 on February 10, 2014, is being compared to the currently approved IFU (attached to the approval letter for S-006 and S-010, which issued on April 19, 2004). Where appropriate, additions to the text are noted by underline and deletions by ~~strikethrough~~.

(b) (4)

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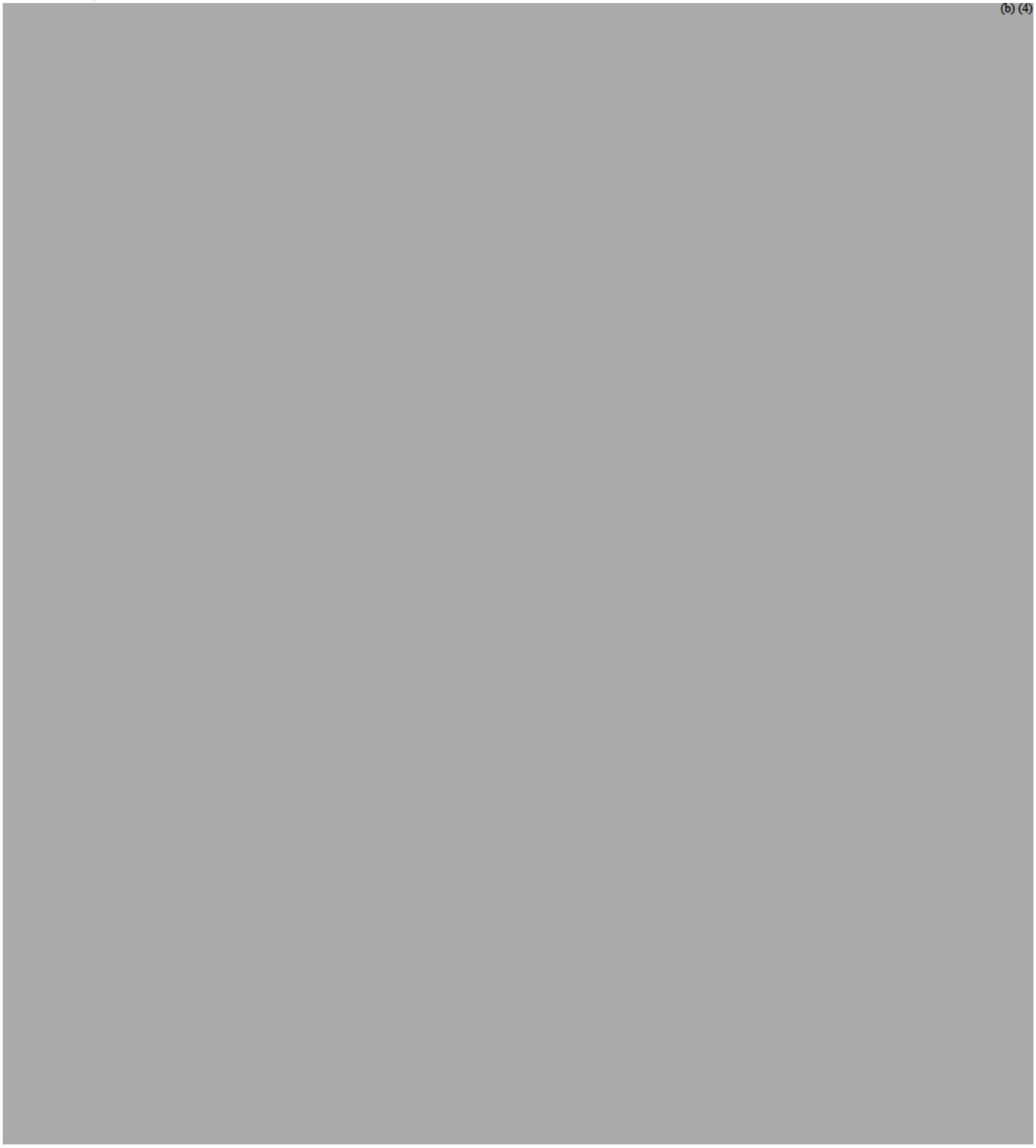
(b) (4)



Note: these revisions are acceptable per Yelena Maslov (DMEPA team leader) via email on April 30, 2014.

Review of the Carton and Container Labels

The applicant's final agreed-upon trade and demonstration kit carton and container labels (submitted to S-030 on December 23, 2013 and on February 10 and March 24, 2014, and agreement by the applicant via email on June 6 and 13, 2014, to FDA's requested post-approval revisions to be implemented in the final printed labeling submission) are being compared to the currently approved carton and container labels (approved with S-006 and S-010 on April 19, 2004).

Trade Kit

Syringe labels submitted December 23, 2013

The differences between the currently approved labels and the applicant's proposed labels are as follows:

(b) (4)

(b) (4)

Note: these revisions are acceptable. Refer to DMEPA review dated January 22, 2014, and to CMC review dated February 27, 2014. On May 7 and 14, 2014, RPM Jennifer Johnson sent emails to CMC reviewer Ping Jiang-Baucom (and Ramesh Raghavachari, Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA), following up on the reviewer comments regarding the carton/container labels included in the CMC review since revision requests had been sent to the applicant on behalf of DMEPA and CDRH after the CMC review had been completed. (The applicant had submitted revised carton/container labels and IFU for the trade kit on March 24, 2014.) The CMC reviewer replied via email on May 15, 2014, including the following requested revisions to the trade kit carton and vial labels to improve clarity and in order to be consistent with the final agreed-upon package insert:

(b) (4)

Although these changes were not requested to be made to the syringe (diluent) labels by the CMC reviewer, they were requested of the applicant via email on June 6, 2014, in order to be consistent with the changes requested for the carton and vial labels. The applicant agreed via emails on June 6 and 13, 2014, to commit to making the changes in the final printed labeling (FPL) submission following approval. (The CMC reviewer had agreed to this proposal via email on May 16, 2014.) This agreement should be documented in the approval letter.

Tray labels submitted December 23, 2013
The differences between the currently approved labels and the applicant's proposed labels are as follows:

(b) (4)

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(b) (4)

Note: these revisions are acceptable. Refer to DMEPA review dated January 22, 2014, and to CMC review dated February 27, 2014.

(b) (4)

(b) (4)

Note: these revisions are acceptable per DMEPA team leader Yelena Maslov and CDRH human factors reviewer QuynhNhu Nguyen via email on April 29, 2014. Refer to DMEPA review dated January 22, 2014, and to CMC review dated February 27, 2014. On May 7 and 14, 2014, RPM Jennifer Johnson sent emails to CMC reviewer Ping Jiang-Baucom (and Ramesh Raghavachari, Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA), following up on the reviewer comments regarding the carton/container labels included in the CMC review since revision requests had been sent to the applicant on behalf of DMEPA and CDRH after the CMC review had been completed. (The applicant had submitted revised carton/container labels and IFU for the trade kit on March 24, 2014.) The CMC reviewer replied via email on May 15, 2014, including the following requested revision to the trade kit vial labels to improve clarity and in order to be consistent with the final agreed-upon package insert:

Under STORAGE: Change (b) (4) *to*

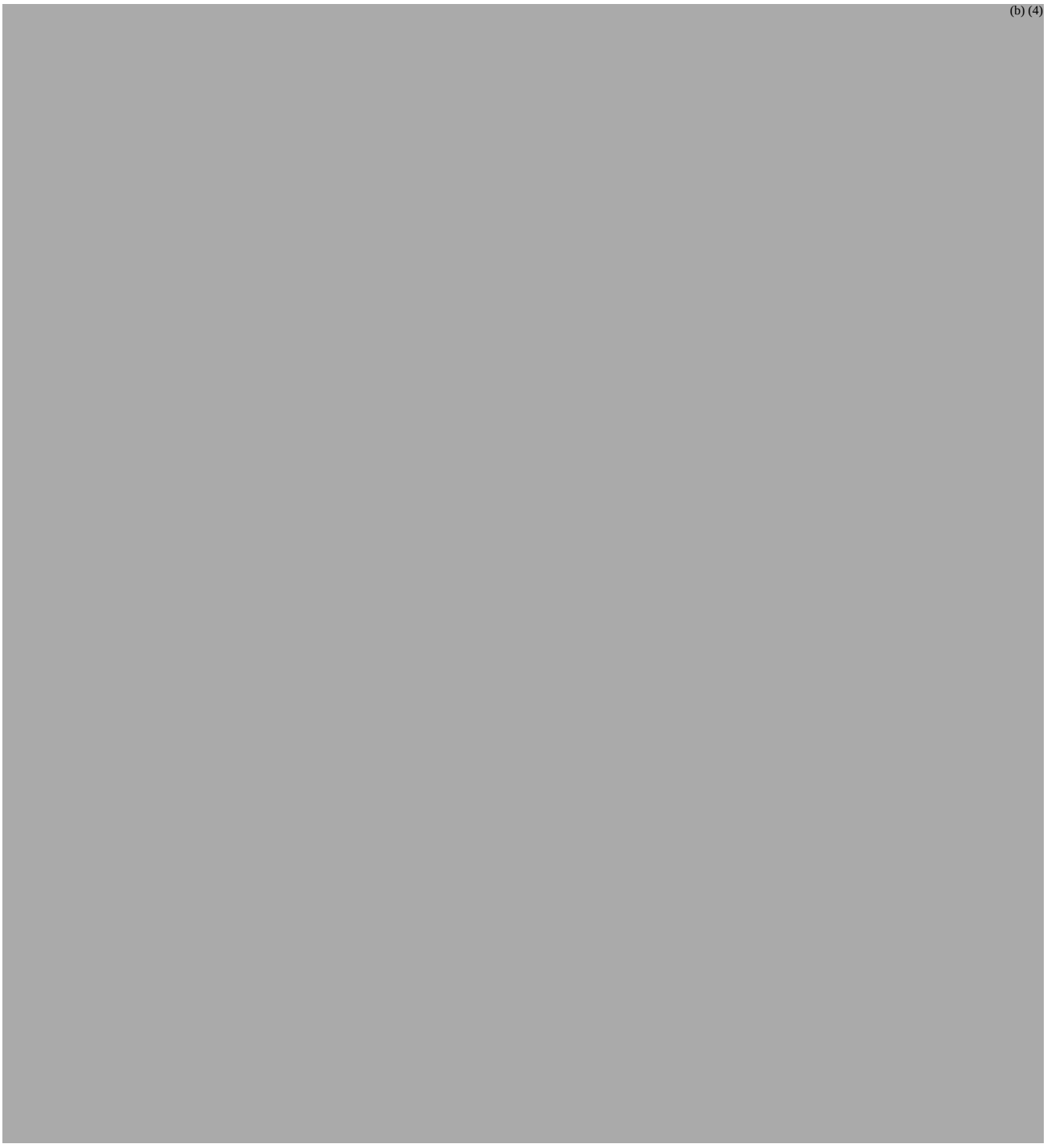
"Refrigerate at 2°C to 8°C (36°F-46°F). Protect from light".

These changes were requested of the applicant via email on June 6, 2014, and the applicant agreed via emails on June 6 and 13, 2014, to commit to making the changes in the final printed labeling (FPL) submission following approval. (The CMC reviewer had agreed to this proposal via email on May 16, 2014.) This agreement should be documented in the approval letter.

Carton labels submitted March 24, 2014
The differences between the currently approved label and the applicant's proposed label are as follows:

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



Note: these revisions are acceptable per DMEPA team leader Yelena Maslov and CDRH human factors reviewer QuynhNhu Nguyen via email on April 29, 2014. Refer to DMEPA review dated

January 22, 2014, and to CMC review dated February 27, 2014. On May 7 and 14, 2014, RPM Jennifer Johnson sent emails to CMC reviewer Ping Jiang-Baucom (and Ramesh Raghavachari, Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA), following up on the reviewer comments regarding the carton/container labels included in the CMC review since revision requests had been sent to the applicant on behalf of DMEPA and CDRH after the CMC review had been completed. (The applicant had submitted revised carton/container labels and IFU for the trade kit on March 24, 2014.) The CMC reviewer replied via email on May 15, 2014, including the following requested revisions to the trade kit carton labels to improve clarity and in order to be consistent with the final agreed-upon package insert:
1) Under "Each diluent syringe contains", (b) (4) *, and*
2) Under STORAGE: Change (b) (4) *" to "Refrigerate at 2°C to 8°C (36°F-46°F). Protect from light".*

These changes were requested of the applicant via email on June 6, 2014, and the applicant agreed via emails on June 6 and 13, 2014, to commit to making the changes in the final printed labeling (FPL) submission following approval. (The CMC reviewer had agreed to this proposal via email on May 16, 2014.) This agreement should be documented in the approval letter.

(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Note: these revisions to the demonstration kit labels are acceptable per DMEPA team leader Yelena Maslov via email on April 30, 2014. Also refer to CMC review dated February 27, 2014. On May 7 and 14, 2014, RPM Jennifer Johnson sent emails to CMC reviewer Ping Jiang-Baucom (and Ramesh Raghavachari, Branch Chief, Branch IX, Division of New Drug Quality Assessment III, ONDQA), following up on the reviewer comments regarding the carton/container labels included in the CMC review since revision requests had been sent to the applicant on behalf of DMEPA and CDRH after the CMC review had been completed. (The applicant had submitted revised carton/container labels and IFU for the trade kit on March 24, 2014.)

The CMC reviewer replied via email on May 15, 2014, including the following requested revision to be made to the demonstration kit carton and syringe labels in order to be more consistent with the changes requested to the trade kit labels and the final agreed-upon package insert: under "Each diluent syringe contains", (b) (4)

These changes were requested via email to the applicant on June 6, 2014, and the applicant agreed via email on June 6, 2014, but requested to make the changes to the final printed labeling (FPL) submission post-approval. (The CMC reviewer had agreed to this proposal via email on May 19, 2014.) This agreement will also be documented in the approval letter for this supplement.

Recommendations

An approval letter should be issued for this supplement.

Jennifer Johnson	July 11, 2014
Regulatory Project Manager	Date
Pamela Lucarelli	July 15, 2014
Chief, Project Management Staff	Date

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/s/

JENNIFER L JOHNSON
07/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

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

CDRH Human Factors Consult Review

DATE: January 21, 2013
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 21008 S30**
Applicant: Novartis
Device Constituent: Vial and Prefilled Syringe
Drug Constituent: Sandostatin LAR Depot
Intended Treatment: for patients with acromegaly, metastatic carcinoid tumors, and vasoactive intestinal peptide tumors
CDRH CTS Tracking No. 1300447

_____
QuynhNhu Nguyen, Combination Products Human Factors Specialist

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

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 21008 S30
Applicant: Novartis
Device Constituent: Vial and Prefilled Syringe
Drug Constituent: Sandostatin LAR Depot
Intended Treatment: for patients with acromegaly, metastatic carcinoid tumors, and vasoactive intestinal peptide tumors
CDRH CTS Tracking No. 1300447

CDRH Human Factors Involvement History

- 9/3 2013: CDRH HF was requested to perform review and comment on the Human Factors Study report and IFU located in Module 5, section 5.3.5.4. Direct link to EDR submission: \\CDSESUB1\evsprod\NDA021008\0035
- 1/21/2014: CDRH HF provided comments on the human factors report.

Overview and Recommendation

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, requested CRH Human Factors consultative review of a human factors engineering summary report for SMS995L delivery system. The delivery system consists of a vial and syringe to administer Sandostatin LAR Depot (octreotide acetate).

This Prior Approval CMC supplement provides for a new diluent for product reconstitution (pharmaceutically equivalent vehicle and presentation). Submission includes CMC data, bioequivalence data from Study CSMS995L2106, human factors study results and revised PI, carton/container labels and health care practitioner IFU. Along with the new drug vehicle, the sponsor proposes a simplified administration kit with one safety engineered needle and a vial adapter (instead of 2 needles), a lower injection volume (2 mL instead of 2.5 mL) and a smaller needle diameter (0.9 mm instead of 1.1 mm).

The Human Factors validation study for the SMS995L delivery system was conducted in the US with a total of 30 health care professionals (HCPs) representative of the end user population. Participants' ability to use a SMS995L delivery system to simulate the preparation of SMS995L and administer an injection into an injection pad was assessed. Study results showed that multiple participants failed to perform critical tasks where participants needing to wait for specific amount of time to completing a particular task. For example, 5 participants failed to state intent to wait at least 30 minutes for the delivery system to reach room temperature (Task 1), or 7 participants (23%) failed to let the vial stand for a minimum of 2 minutes until the powder was wetted (Task 11), or 3 participants (10%) failed to shake the vial for 30 seconds (Task 13).

The Sponsor referred to a study report, Report PHAD001436B, where the Sponsor argued that failure to perform the above tasks do not significantly affect the uniformity of the delivered dose. Of the three failures above, failing to shake the vial for 30 seconds would result in an underdose of 65%-85% of the nominal dose. Note that this consultant does not have access to this report and since it is not part of human factors testing, the consultant will defer the acceptability of this study results to the relevant reviewer. Nevertheless, the consultant notes that these are knowledge-based tasks and believes that the Instructions for Use (IFU) can be improved to call out the user's attention to the

waiting time for those tasks. The finalized IFU currently includes an attention box in red as follows before it provides individual user steps:

However, the same information was not called out in the same manner in the individual tasks. For example, the attention in step 1 is shown below:

It was also noted that the use of terminology was not used consistently in the IFU. In the red box, the Sponsor indicates that there are three critical steps. In the individual task, the Sponsor uses the term (b) (4) The consultant recommends that consistent terminology used in the IFU, and the attention section in the individual task should be further emphasized to call the user's attention to the wait time associated with each task.

In addition, there were other task failures where 2 participants (7%) failed to clean the rubber stopper of the vial with an alcohol swab (Task 4), and 5 participants (17%) failed to dispose of the syringe in a sharps container (Task 25). The Sponsor indicated that if the stopper is not disinfected, the likelihood that the drug product would be contaminated is very low. Furthermore, as the device is for single-use, it is extremely unlikely that omission of the sterilization task would lead to a clinically significant adverse event such as a fatal infection. The Sponsor clarified that sharps disposal is part of standard clinical practice and is often regulated by the hospital or office standard procedures. The consultants reviewed the IFU and the IFU did not appear to include these two steps. The consultant recommends that the IFU includes these steps.

The consultant would also like the Sponsor to clarify if the finalized IFU was used in the validation study.

Please transmit the following comments to the Sponsor:
The Human Factors validation study results showed that multiple participants failed to perform critical tasks where participants needing to wait for specific amount of time to completing a particular task. For example, 5 participants failed to state intent to wait at least 30 minutes for the delivery system to reach room temperature (Task 1), or 7 participants (23%) failed to let the vial stand for a minimum of 2 minutes until the powder was wetted (Task 11), or 3 participants (10%) failed to shake the vial for 30 seconds (Task 13).

Your finalized IFU includes an attention box in red as follows before it provides individual user steps:

However, the same information did not seem to be emphasized in the same manner in the individual task description. For example, the attention in step 1 is shown below:

We also note that the use of terminology was not used consistently in the IFU. In the red box, you indicate that there are three critical steps. In the individual task, you use the term (b) (4)

Please clarify if you used the finalized IFU in the validation study. If that is the case, for the above described task failures, we recommend that the IFU includes consistent terminology throughout. Furthermore, we recommend that the attention section in the individual step should be further emphasized to call the user's attention to the wait time associated with each task.

In addition, we note two other task failures where 2 participants (7%) failed to clean the rubber stopper of the vial with an alcohol swab (Task 4), and 5 participants (17%) failed to dispose of the syringe in a sharps container (Task 25). However, your current IFU did not appear to include these steps. We recommend that the IFU includes these steps.

Due to the nature of the changes that we are recommending, we ask that you provide evidence of improved IFU.

Appendix 1: CDRH Human Factors Review

Novartis performed use-related risk analyses on the SMS995L delivery system via a User Failure Mode and Effects Analysis (User FMEA). Novartis reported that two preliminary formative user studies were conducted on the delivery system components, including the vial adapter, the safety injection needle, the active drug product, the vehicle for suspension, and the Instructions for Use (IFU). A third formative user study was conducted on the finalized delivery system components along with the IFU and commercially-representative packaging and labeling. The Human Factors validation study for the SMS995L delivery system was conducted in the US with a total of 30 health care professionals (HCPs) representative of the end user population. Participants' ability to use a SMS995L delivery system to simulate the preparation of SMS995L and administer an injection into an injection pad was assessed.

The study tasks were categorized as critical, necessary, and desirable.

Designation	Criterion type	Criterion definition
C	Critical	Steps that are required for safe and effective use of the product.
N	Necessary	Steps that are required in order to complete the use process, but do not constitute a safety hazard if omitted or not performed correctly.
D	Desirable	Steps that are part of good clinical practice but are not directly related to the design or use of the specific product being investigated

The focus of this review as on study results where multiple participants experienced failure or reported difficulties
Critical Tasks:
A total of 12 participants (40%) experienced 15 failures across 3 different critical tasks:

- 5 participants (17%) failed to state intent to wait at least 30 minutes for the delivery system to reach room temperature (Task 1)
  Study analysis showed that two of the failures were attributed to study artifacts. The sponsor indicated that according to dedicated UDD testing, failing to acclimatize the delivery system (but performing the other 2 UDD-critical tasks) does not significantly affect the uniformity of the delivered dose (>85%; Report PHAD001436B). Failing to acclimatize the delivery system and failing to shake the vial for 30 seconds would result in an underdose of 65%-85% of the nominal dose (Report PHAD001436B). This level of underdose administered to a patient systematically is considered a low severity hazard involving reduced efficacy of the drug according to the User FMEA (P1208-RA-003).
- 7 participants (23%) failed to let the vial stand for a minimum of 2 minutes until the powder was wetted (Task 11)
  Study analysis showed that five of the failures were attributed to study artifacts. The sponsor indicated that according to dedicated UDD testing, failing to let the vial stand for two minutes does not significantly affect the uniformity of the delivered dose (>85%; Report PHAD001436B).
- 3 participants (10%) failed to shake the vial for 30 seconds (Task 13)
  Study analysis showed that of the participants experiencing failures on this step, two felt that the drug product was fully reconstituted. According to dedicated UDD testing, failing to shake the vial for a minimum of 30 seconds (but performing the other 2 UDD-critical tasks)

does not significantly affect the uniformity of the delivered dose (>85%; Report PHAD001436B).

Necessary tasks

None of the participants experienced failures on any of the 11 necessary tasks. 4 participants (13%) had difficulties lifting the packaging off the vial adapter (Task 7). Study analysis showed that participants initially did not realize to remove the vial adapter packaging but were able to do so during the course of the study.

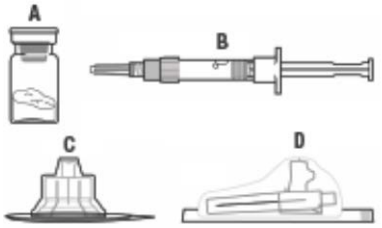
Desirable tasks

A total of 7 participants (23%) experienced 8 failures across 3 different desirable tasks. None of the participants experienced difficulties on any of the desirable tasks.

- 2 participants (7%) failed to clean the rubber stopper of the vial with an alcohol swab (Task 4). The Sponsor indicated that if the stopper is not disinfected, the likelihood that the drug product would be contaminated is very low. Furthermore, as the device is for single-use, it is extremely unlikely that omission of the sterilization task would lead to a clinically significant adverse event such as a fatal infection
- 5 participants (17%) failed to dispose of the syringe in a sharps container (Task 25). The Sponsor clarified that sharps disposal is part of standard clinical practice and is often regulated by the hospital or office standard procedures.

Appendix 2: Device Related Information

The following proprietary information was obtained from the submission. The following figure provides the components of the delivery system



A One vial containing Sandostatin LAR powder
B One prefilled syringe containing the diluent solution for reconstitution
C One vial adapter for drug product reconstitution
D One safety injection needle (20G x 1.5")

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/s/

JENNIFER L JOHNSON

01/30/2014

CDRH review of Human Factors Study and Instructions for Use completed by Quynh Nguyen and Ron Kaye of CDRH on 1/27/14

HUMAN FACTOR, 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*****

Application Type and Number:	NDA 021008/S-030
Date of Submission:	August 27, 2013
Established Name and Strength:	Sandostatin LAR Depot (octreotide acetate for injectable suspension) 10 mg, 20 mg and 30 mg Single-use kits
Product Type:	Single ingredient
Marketing Category:	Prescription
Applicant Name:	Novartis
OSE RCM #:	2013-2011 and 2013-2012
Date of This Review:	January 21, 2014
Primary Reviewer:	Reasol Agustin, PharmD
Team Leader:	Yelena Maslov, PharmD

1. REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested DMEPA to evaluate the results of the Applicant's Human Factor Validation Study, as well as the proposed Prescribing Information, container label, carton labeling, and Instructions for Use (IFU) to ensure the intended population is able to use the proposed product, Sandostatin LAR Depot, safely and effectively.

2. CONCLUSION

The Human Factors Usability Study had the following failures related to the reconstitution procedure due to physical properties of the active ingredients and the diluent:

1. Five participant participants failed to state the intent to wait a minimum of 30 minutes before reconstituting (Task #1). Failure to wait can result in an incomplete reconstitution and up to 15% reduction in delivered dose.

2. Seven participants failed to let the vial stand for a minimum of 2 minutes, until powder is wetted (Task #11). Failure to wait at least 2 minutes can result in incomplete reconstitution, leading to up to 7% reduction in delivered dose.
3. Three participants failed to keep the plunger pressed and shook the vial moderately in a horizontal direction for about 30 seconds (minimum of 30 seconds total shaking time) (Task #13). Failure to shake the vial for a minimum of 30 seconds can result in an incomplete reconstitution and needle clogging.

Despite these failures, we find the proposed changes to the product's design acceptable (i.e., use of the vial adapter for transfer of diluent to the product vial and safety needle) for the following reasons:

1. Sandostatin LAR Depot is currently marketed, requires an additional step in product preparation compared to the proposed process, and exhibits similar types of issues.
2. The failures that occurred during Human Factors Usability Study are not unique to the proposed product and to the proposed changes for this product. There are multiple "depot" products requiring reconstitution that demonstrate the same type of issues (e.g., Invega Sustenna, Risperdal Consta, etc.)

4. RECOMMENDATIONS

Based on our evaluation, we recommend the following revisions be implemented prior to approval of this product:

3.1 Vial Label for Sandostatin LAR

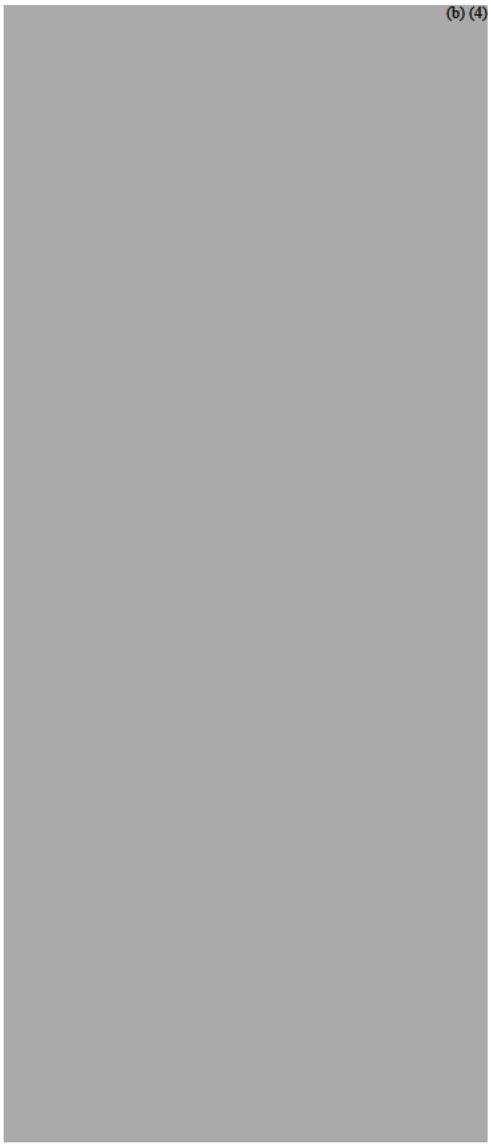
a. Relocate the route of administration to the principal display panel to increase its prominence. We have identified medication error cases with this product that reported administration of Sandostatin LAR via the wrong route.

3.2 Carton Labeling for Sandostatin LAR

a. Ensure the route of administration is placed on each panel including the principal display panel.

3.3 Instructions for Use (IFU)

- Design the IFU so that the instructions are in sequential order continuously in a vertical manner. For example:



- Increase the prominence of the critical tasks (i.e. 30 minute wait before reconstitution, 2 minute wait time for saturation, and shaking for 30 seconds) by using different color font, bolding, highlighting, and/or increasing font size.

If you have questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

4. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. Section 6 provides the methods and results for each material reviewed.

Table 1. Materials considered for review of the Applicant's Human Factors Validation Study, proposed Prescribing Information, container labels, and carton labeling

Section	Material Reviewed
6.1	Product Information/Prescribing Information
6.2	FDA Adverse Event Reporting System (FAERS)
6.3	Human Factors/Usability Study
6.4	Container Label, Carton Labeling, and Instructions for Use

5. DISCUSSION

The Human Factors Usability Study resulted in failures of the critical tasks required for the proper reconstitution of the product (i.e., failure to wait for a minimum of 30 minutes after removal from the refrigerator, failure to let the vial stand for a minimum of 2 minutes after reconstitution, and failure to shake the vial moderately for 30 seconds). These failures can result in the underdose of the medication for up to 15%. However, we note that Sandostatin LAR Depot is currently marketed and medication error data indicates that the same types of errors are occurring with the current formulation of this product. As a result, the failures in the Human Factors study are not related to the proposed changes of the product. (See Section 6.1 for the description of changes).

Additionally, the failures that occurred during Human Factors Usability Study are not unique to the product or to the proposed changes for this product. There are multiple "depot" products requiring reconstitution that demonstrate the same type of issues (e.g., Invega Sustenna, Risperdal Consta, etc.)

As a result, despite the fact that the Human Factors study failed, we find the proposed changes to the product's design acceptable. However, to help mitigate errors related to the proper reconstitution of the product, we recommend to ensure the critical steps outlined above are prominently placed in the IFU, on the carton labeling, tray label, and container label (if space permits).

6. METHODS AND RESULTS

6.1 Product Information

The user must reconstitute Sandostatin LAR Depot before administering intragluteally at 4-week intervals. Other Somatostatin analogs such as Signifor (Pasireotide) and Somatuline Depot (Lanreotide) do not require reconstitution. Table 2 provides product information for Sandostatin LAR Depot.

Table 2. Relevant Product Information for Sandostatin LAR Depot		
	Proposed	Currently Marketed
Active Ingredient	Octreotide Acetate	No change
Indication	For treatment in patients who have responded to and tolerated Sandostatin subcutaneous injection for acromegaly, malignant carcinoid syndrome, and VIPOMA	
Route of Administration	Intragluteal	No change
Dosage Form	Injectable suspension	No change
Strength	10 mg, 20 mg, and 30 mg	NO change
Dose and Frequency	20 mg intragluteally every 4 weeks for 3 months, then dose may be modified based upon response.	No change
How Supplied	Single-use kits containing: 5-mL vial of 10 mg, 20 mg, or 30 mg strength, ***pre-filled syringe containing 2 mL of diluent, safety injection needle, a vial adapter***, two alcohol pads, and instructions for use	Single-use kits containing: 5-mL vial of 10 mg, 20 mg, or 30 mg strength, ***a syringe containing 2.5 mL of diluent, two 1 ½" 19 gauge needles***, two alcohol wipes, and an instruction booklet.
Storage	Refrigerated temperatures between 2ºC to 8 ºC (36ºF to 46ºF) and protected from light until the time of use. ***The kit should remain at room temperature for*** (b) (4) ***minutes prior to reconstitution***. However, after reconstitution the drug must be administered immediately.	Refrigerated temperatures between 2°C-8°C (36°F-46°F) and protected from light until the time of use. ***The kit should remain at room temperature for 30-60 minutes prior to preparation*** of the drug suspension. However, after preparation the drug suspension must be administered immediately.

6.2 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 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.

6.2.1 Selection of Medication Error Cases

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	October 1, 2011 to October 29, 2013
Drug Names	Trade name: Sandostatin LAR Depot
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT Underdose (PT)

The FAERS database search identified 53 reports, respectively. Each report was reviewed for relevancy and duplication. After individual review, 12 cases were included in the analysis. However, 41 reports were not included in the final analysis for the following reasons:

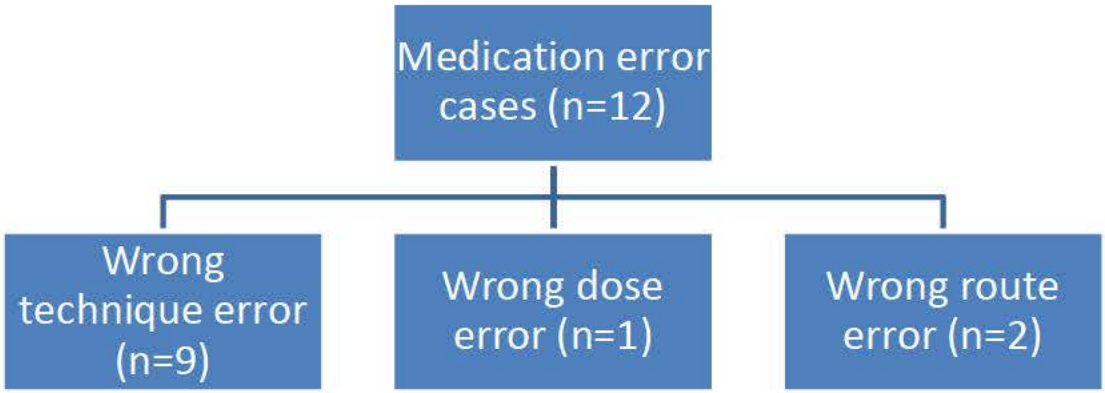
- Adverse events unrelated to medication error,
- Death due to disease progression,
- Patient did not receive full dose because nurse did not have full dose in stock,
- Report did not contain any information.

6.2.2 Medication Error Risk Assessment

Following exclusions as described in section 6.2.1, twelve (n=12) Sandostatin LAR Depot medication error cases remained for our detailed analysis. 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 sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix H provides listings of all case numbers for the cases summarized in this review.

[2] 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. Accessed June 1, 2011.

Figure 1: Sandostatin LAR Depot medication errors (n = 12) categorized by type of error



A. **Wrong Technique Error (n=9) (See Appendix A for detail summary)**
   1. Five cases (case #s: #8238090 V.6, #8647020 V.2, #8665726 V.3, #8765570 V.3, and #9338627 V.5) reported needle clogging or leaking during administration, resulting in underdose. In addition, one of these 5 cases also reported drug residue in vial. Contributing factors or patient outcomes were not reported.
   2. Two cases (case #s: #8671271 V.6 and #9194168 V.5) reported that the drug powder and diluent did not mix, resulting in incomplete reconstitution. Contributing factors or patient outcomes were not reported.
   3. Two cases (case #s: #8921443 V.1 and #9050478 V. 1) reported drug precipitate or residue in vial after injection, resulting in underdose. Contributing factors or patient outcomes were not reported.

B. **Wrong Dose Error (n=1,)**
   1. **Case** #9607666 V.3: The report stated that patient was administered 20 mg instead of 30 mg in error. The report stated that as a result of this error patients not feeling well. However, the causality of the error was not reported.

C. **Wrong Route Error (n=2)**
   1. Case #8261803 V.1: The report stated that the medication was given in the patient's via catheter's port intravenously. The order was entered correctly as intramuscular and sent in original kit. Neither root case nor an outcome of this error was reported.
   2. Case #9356749: The report stated that Sandostatin LAR was administered subcutaneously. Neither root cause nor an outcome of this error was reported.

6.3 Human Factors Validation Study

We reviewed the Human Factor validation study entitled, "Human Factors Engineering Summary Report for the SMS995L Delivery System," dated February 25, 2013 that the Applicant submitted on August 27, 2013.

6.3.1 Study Participants

The study included 30 participants:

1) 15 secondary care doctors who specialize in the fields of endocrinology or oncology
2) 15 secondary care nurses who specialize in the fields of endocrinology or oncology

Table 8 – Validation Study Participant Background Summary

Type	Average intragluteal injections per month:	
	Prepared	Administered
Group 1(n=15): Secondary care medical doctors (MDs)	12 (0 - 40)	8 (0 - 40)
Group 2 (n=15): Secondary care registered nurses (RNs)	30 (0 - 125)	29 (2 - 125)

Of the 30 participants, only 5 participants (all doctors) reported they did not ever prepare or administer any of the injections. All other participants prepared or administered at least one injection per month.

6.3.2 Study Design

Participants were given the delivery system in commercially-representative packaging, including the IFU and all system components, and were asked to prepare the injection using the delivery system and administer into an injection pad. The moderator and assessor each recorded performance on each use task (see Table 4) as 1) correct performance, 2) performance with difficulties, and 3) failed performance. In addition, each task was designated into one of three categories (see table 3).

Table 3 Criterion types

Designation	Criterion type	Criterion definition
C	Critical	Steps that are required for safe and effective use of the product.
N	Necessary	Steps that are required in order to complete the use process, but do not constitute a safety hazard if omitted or not performed correctly.
D	Desirable	Steps that are part of good clinical practice but are not directly related to the design or use of the specific product being investigated

Table 4 – User Performance Criteria

Step #	User Task	Criterion Type	Comments
1	Stated intent to wait a minimum of 30 minutes before reconstituting.	C	Medium risk. Lack of acclimatization could lead to incomplete reconstitution and up to 15% reduction in delivered dose. However, the clinical impact regarding the safety and efficacy is low. It was not realistic for participants to wait for the minimum of 30 minutes in this study. The participants were therefore required only to state their intent to wait a minimum of 30 minutes. Note that both the IFU and carton label highlight the need to acclimatize.
2	Peeled the lid film from the blister tray containing the injection kit.	N	Low risk of user being unable to peel off lid without use of tools.
3	Detached the flip-off cap from the vial containing the Sandostatin LAR® powder.	N	Low risk of user being unable to remove cap without use of tools. If user forgets this step, it will likely be detected in subsequent steps.
4	Cleaned the rubber stopper of the vial with an alcohol swab.	D	Medium risk. If vial stopper is not cleaned there is a chance of microbial contamination of drug product leading to infection of patient. (However, likelihood of infection is considered very low if stopper is not cleaned.)
5	Removed the lid film of the vial adapter packaging.	N	Low risk of user being unable to peel off lid without use of tools.

Step #	User Task	Criterion Type	Comments
6	Positioned the vial adapter on top of the vial and pushed it down so it snapped into place on the vial.	C	Medium risk. Possibility of leakage and therefore low dose if adapter not properly attached. Detectable immediately or in subsequent steps.
7	Lifted the packaging off the vial adapter with a vertical movement.	N	Low risk of user dislodging vial adapter leading to leaks during reconstitution. Detectable immediately or in subsequent steps.
8	Removed the cap from the pre-filled syringe containing the diluent	N	Low risk of user being unable to remove cap from the syringe.
9	Screwed the syringe onto the vial adapter	N	Medium risk. Leaks during reconstitution could lead to underdose but are likely to be detected.
10	Slowly pushed the plunger all the way down to transfer all the diluent solution in the vial.	C	Low risk. Entire solution should be transferred for reconstitution.
11	Let the vial stand for a minimum of 2 minutes, until powder is wetted.	C	Medium risk. Risk of incomplete reconstitution if left for less than 2 minutes leading to up to 7% reduction in delivered dose. However the clinical impact regarding the safety and efficacy is considered to be low. Risk is mitigated by a visual check of the solution after reconstitution.
12	Pressed the plunger all the way down in the syringe.	D	Low risk. If the plunger is not held down, the system is harder to hold while shaking.

Step #	User Task	Criterion Type	Comments
13	Kept the plunger pressed and shook the vial moderately in a horizontal direction for about 30 seconds. (Minimum of 30 seconds total shaking time)	C	Medium. Risk of incomplete reconstitution if not shaken for 30s leading to sub-optimal reconstitution and needle clogging. Risk is mitigated by visual check of the solution in the vial to ensure detection of sub-optimal reconstitution during the preparation process.
14	Turned the syringe and vial upside-down.	N	Low risk. Leak leading to underdose considered very unlikely.
15	Slowly pulled plunger out and drew the entire content from the vial into the syringe.	C	Low risk. Leak leading to underdose considered very unlikely.
16	Unscrewed the syringe from the vial adapter.	N	Low risk. Leak leading to underdose considered very unlikely.
17	Removed the safety injection needle from its blister	N	Low risk. Risk of microbial contamination of needle hub leading to infection of patient (however, likelihood of infection is considered very low if user observes aseptic technique and / or washes hands or wears gloves).
18	Screwed the safety injection needle onto the syringe.	N	Low risk. Leak leading to underdose considered very unlikely.
19	Pulled the protective cover straight off the needle.	N	Medium risk. Risk of needle stick injury. Risk of microbial contamination of drug product leading to infection of patient (however, likelihood of infection is considered low and very low if user washes hands or wears gloves).

Step #	User Task	Criterion Type	Comments
20	Expelled air or visible bubbles from the syringe.	D	Medium risk. Potential for air injected into patient leading to increased pain. Risk of unsterile air being injected into patient leading to infection (only if user draws in ambient air during priming). Risk of underdose due to drug being expelled during priming.
21	Stated intent to clean the injection site with an alcohol swab.	D	Low risk. Risk of microbial contamination leading to infection of patient (however, likelihood of infection is considered low if this step is omitted).
22	Inserted the needle into the injection pad.	C	Low risk. Possibility of needle stick injury.
23	Slowly depressed the plunger rod to inject the entire dose.	C	Low risk. Potential increase in pain on injection if injected too quickly. Potential for underdose if full dose is not injected.
24	Withdrew needle from injection site and activated the safety guard over the needle.	D	Medium risk. Risk of needle stick injury / infection of HCP if this step is not completed correctly, and disposal in sharps container not completed correctly.
25	Disposed of the syringe with needle immediately in a sharps container.	D	Low risk. Risk of needle stick injury / infection of HCP is very low if needle safety guard activated successfully.

6.3.3 Study Results

A total of 12 participants (40%) experienced 15 failures across 3 different critical tasks.

1. Five participants (17%) failed to state intent to wait at least 30 minutes for the delivery system to reach room temperature (Task #1). Failure to perform this task could result in an incomplete reconstitution leading to up to 15% in reduction in delivered dose.

    a. Two reported that they would have waited 30 minutes but did not think they had to during the interview.
    b. Two reported they would wait 5-10 minutes only if the delivery system felt cold when they received it from the pharmacy

c. One did not notice that the IFU contained instructions to let the delivery system acclimatize.

2. Seven participants (23) failed to let the vial stand for a minimum of 2 minutes until the powder was wetted (Task #11). Failure to perform this task could result in incomplete reconstitution leading to up to 7% reduction in delivered dose.

    a. Three stated they would normally wait 2 minutes but did not wait for the full 2 minutes because they did not believe they were supposed to.
    b. Two did not wait the full 2 minutes during the interview, but said that they would leave the vial to sit while they were doing other tasks.
    c. Once said she would shake the vial first then wait 2 minutes, though she did not wait 2 minutes during the interview
    d. One reported she would likely skip the 2 minutes in normal practice as she did not find it important to do.

3. Three participants (10%) failed to shake the vial for 30 seconds (Task #13). Failure to perform this task could result in incomplete reconstitution and needle clogging.

    a. Two gently rocked the vial during the wetting period but never shook the vial.
        i. One reported the product looked fully reconstituted after wetting for 2 minutes and 50 seconds, and therefore did not need shaking.
        ii. One reported the product looked fully reconstituted after wetting for almost 9 minutes and further noted that she would not feel comfortable shaking even though the IFU said because she had been taught to never shake
    b. One reported she knew she had shaken for less than 30 second (~15 seconds) but felt it was fully reconstituted based on visual check.

6.4 Labels and Labeling Review

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarketing medication error data, we evaluated the following materials that the Applicant submitted on December 23, 2013:

- Sandostatin LAR Depot container labels (section 6.4.1)
- Diluent Syringe Label (section 6.4.2)
- Tray Labeling (section 6.4.3)
- Sandostatin LAR Depot carton labeling (section 6.4.4)
- Sandostatin LAR Depot Instructions for Use (section 6.4.5)

Appendix A: Detailed Summary of Wrong Technique Errors.

- Case #8238090 V.6: During administration, the needle was plugged up and patient received 2/3 of the medication, resulting in underdose. Patient was initially on Sandostatin LAR Depot 20 mg every 2 weeks and was switched to 30 mg every 3 weeks due to disease progression. Causality, seriousness and outcome were not reported.
- Case #8647020 V.2: Nurse reported mixing Sandostatin LAR according to instructions but didn't go through a blockage. The needle was changed and patient only received 3/4 of medication, resulting in underdose. The root cause of the event seemed to be linked to the suspended microsphere. The events outcome, seriousness and causality were not reported.
- Case #8665726 V.3: First try: Sandostatin LAR came around the needle in spite of going through the needle and syringe. Second try: Sandostatin LAR was prepared but was leaking around and was not going into the patient after three attempts. At a later date, a new batch was correctly administered without any issues. The event was considered as serious by the reporter and event outcome was recovered and was suspected to the Sandostatin therapy. The seriousness, causality, and outcome for the event syringe fault were not reported.
- Case #8671271 V.6: The diluent and the powder didn't mix. The dose was out of fridge for about 1 hour and the nurse tried to mix for 45 to 60 minutes. Patient passed due to disease progression. The seriousness and causality of the events were not reported.
- Case #8765570 V.3: Patient was receiving a dose of 60 mg once a month. On an unknown date, the patient found that since she had changed nurse, the needle was clogging and it caused the nurse to prick her more. The patient mentioned as it was very painful and that one dose was cloudy. Patient complained of right gluteal pain (last injection site) shooting down the whole leg, followed by swollen ankles. The patient wanted to know if the clogging was due to the drug or the nurse. The seriousness, outcome and causality of events were not provided.
- Case #8921443 V.1: The patient received her medication at the doctor's office. She was not able to receive her full dose because the medication at the bottom of the bottle would not come out. The patient was not feeling well and had a hard time standing. The patient complained that the Sandostatin LAR was not properly injected. The seriousness, outcome and causality of events were not provided.
- Case #9050478 V. 1: On an unknown date, the patient experienced tumor increased a lot and the drug precipitated and due to this, the patient did not receive the correct dosage of the medication. The patient mentioned that the last administration, the medication precipitated during the application and the needle clogged. The treatment with Sandostatin LAR was ongoing. The outcome and causality of the event were not reported.

- Case #9194168 V.5: The drug was taken out the fridge 2 hour before the reconstitution and was injected just after the reconstitution. The third Sandostatin LAR injection, the reconstituted product did not have the usual aspect and was granular. Nevertheless, the injection was performed and all the product was injected in one go. The patient experienced pain after injection irradiating all the hemi body. The physician reported that patient had some difficulties to bend her hand for 48 hours after the third injection. The physician mentioned that the product was hard to reconstitute, which did not allow having a homogenous solution. The seriousness and causality of the other events were not reported.
- Case #9338627 V.5: Patient stated that the needle clogged four times and there was some residue left behind in the vial. The patient also informed that she did not get the full dose as some of it was leaking on her leg. On an unspecified date, the patient experienced a state of fatigue. Two or three days after Sandostatin injections, she experienced abdominal cramping and constipation. It was then reported that during the injection, the medication was crystallized in the needle and the nurse changed the needle and she received her injection. From that injection, the patient had a lump at the injection site for 3 weeks. Patient stated that she was experiencing all the side effects of Sandostatin. Sandostatin was later discontinued. The outcome for syringe issue, reaction from injection and underdose was not reported

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

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
01/21/2014

YELENA L MASLOV
01/22/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021008/S-030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Johnson, Jennifer
To:	"Munir, Omer"
Bcc:	Johnson, Jennifer
Subject:	NDA 21008/S-030: Sandostatin LAR new diluent - *Final agreed-upon labels and labeling*
Date:	Wednesday, July 02, 2014 3:42:00 PM
Attachments:	NDA 21008 S030 Sandostatin LAR PI FINAL 02 July 2014.doc NDA 21008 S030 Sandostatin LAR Final Labeling 02 July 2014.pdf

Hi Omer,

Thank you for confirming, and for the update.

I have attached the final agreed-upon (clean) PI in Word format, as well as the labeling and labels to be attached to the action letter, and will document in that letter the agreed-upon changes to be made to the carton/container labels in the final printed labeling submission.

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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Tuesday, July 01, 2014 6:58 PM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Jennifer,
Sorry for the delay.
Yes, all of the changes/updates in the PI are acceptable. I am hoping to have final carton labeling for you this week also.
Thanks!
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, July 01, 2014 2:44 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

I'm following up on the email I sent to you last Thursday 6/26.
Are you in agreement with all points stated below and the package insert I had attached to that email?
Please confirm, as we would like to act on S-030 this week. Thank you!

Kind Regards,
Jennifer

From: Johnson, Jennifer
Sent: Thursday, June 26, 2014 3:03 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

Thanks for confirming, and for clarifying the Novartis position. I have discussed with my review team, and we agree with your rationale for the "safety needle" description. Therefore, we have reinserted "safety needle" into the relevant sections (2, 3 and 16) of the package insert, in accordance with the package insert approved with S-028.

The only other revision that has been made is deletion of the [redacted] (b) (4) in the second bullet point of the second paragraph in Section 2.2 (Carcinoid Tumors and VIPomas, Patients Currently Receiving Sandostatin Injection). [redacted] (b) (4)

I have attached the package insert (updated from the one I sent to you on Friday, June 20th), with these revisions shown in tracked changes. If your team has no further questions or comments, then this can be considered the final agreed-upon package insert for S-030.

Also, you may disregard the request made in my email on June 20th to remove "safety needle" from the carton/tray labeling and Instruction Booklets (IFU) in the final printed labeling submission.

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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Tuesday, June 24, 2014 4:47 PM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Jennifer,
Yes, correct.
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, June 24, 2014 4:41 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

Thanks for the quick response. I was able to open that attachment (and view the one you sent previously via my clinical team leader's computer as we discussed this issue). If I understand correctly, this means that you're using an already approved safety needle device (in this case the (b) (4) needle) for your new product presentation.
Therefore, you're stating that the package insert I sent to you on June 6th (that had the "safety" descriptor removed from Sections 2, 3 and 16) needs to be corrected (i.e., "safety" re-inserted per the label approved with S-028)? Please confirm.

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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Tuesday, June 24, 2014 4:27 PM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Jennifer,
Yes, we disagree with the removal of 'safety' on the components, as they are not promotional in nature. It accurately describes the new needle in the new Sandostatin LAR presentation, as well as the former S-028 approval.
The term 'safety needle' is recognized as its own type of needle device, different than a standard (non-safety) needle for injection.
See attachment.

Kind Regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, June 24, 2014 3:58 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

I'm working on finalizing the review of all labels/labeling and discussing with my team leader. Before I call you back, though, I want to be clear as to which revisions you and your team disagree with FDA.
On June 6, 2014, I sent you the attached PI.
(Unfortunately, I have not been able to open the 2 jpg attachments. Would you mind trying to send them again?)

You stated that you agreed with all of the changes, including the removal of the term "safety" from the labeling after we discussed and determined that it was promotional in nature. I realized that I had forgotten to request its removal from the Instruction Booklets (IFU) and carton/tray labels when I sent the other revision requests (as a condition of approval); the reason for the request was to be consistent with the PI. **Are you saying that you disagree with the removal of "safety" from the PI, or from the Instruction Booklets and carton/tray labels, or from all pieces of labeling (PI/IFU/labels)?**

If you could clarify for me, that would be appreciated.

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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Monday, June 23, 2014 5:23 PM
To: Johnson, Jennifer
Cc: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Jennifer,
We would like to have a TC with the Division Director and the CMC reviewer if necessary to discuss the timing and appropriateness of these comments received. It was our understanding that the round of labeling comments were final, and we have just completed final labeling for submission to the Division.

Please see attachments:

The term 'safety' is an accurate description of the needle now supplied in the drug kit. Image 1 shows the difference from non-safety to safety needle approved in S-028, where the needle is described as 'safety' in its packaging. The [redacted] (b) (4) needle is packaged as a safety needle per the manufacturer and therefore not promotional in nature.

Image 2 shows the updated Sandostatin LAR package, where the new 20G needle is also included by the same manufacturer and is labeled as a safety needle.

The term safety needle is well recognized in the medical community as a different type of needle and is therefore appropriately described in the Sandostatin LAR packaging components.

My TC number is below. Please let me know, to coordinate timing if needed to gain approval on this supplement.
Thanks,
Best regards,
Omer

TC Dial in Information:

USA/Canada : (b) (4)
USA/Canada (free phone) : (b) (4)

Participant Passcode: (b) (4)

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Friday, June 20, 2014 5:26 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

Thank you very much for the information – that was very helpful. I've been working on wrapping up my review. My supervisor has been out of the office this week but is scheduled to return on Monday so I will discuss further with her and obtain concurrence at the beginning of next week, as well as from my clinical team leader.

Regarding the labels and labeling:

1. Yes, you are correct that the (b) (4) needs to be defined on the syringe labels (both trade and demo kits) as well.

2. I also meant to mention that the carton and tray labels (both trade and demo kits) will need to have the word "safety" removed (re: "safety injection needle") as well to harmonize them with deletion of the word "safety" that appeared in the package insert, to which you agreed to on June 6th. This deletion request also applies to the instruction

booklets (both trade and demo kits): under the package contents description and Step 8 (demo kit booklet)/Step 9 (trade kit booklet).

3. Finally, I'm attaching a copy of the clean agreed-upon Word version of the PI following your agreement to the changes.
   I fixed the formatting issues in the FPI: Contents section on the first page.
   The identifier at the end of the last page still does need to be updated, though.

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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Friday, June 13, 2014 2:06 PM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Jennifer,
The current approved carton and container presentation had FPL sent on April 12, 2004 with the approval letter (combined S-06 and S-10 attached) appending approved FPL dated April 19, 2004.

The (more recent) lastly currently approved carton, container labeling for all components with any annual reportable changes to present was sent with the NDA 21-008 annual report on January 18, 2013 Serial No. 31.

A note also – we will define the [redacted] (b) (4) in the LAR diluent syringes also. Was not mentioned with reviewer's comments but understood this is the case.

Thanks, anything you can do to expedite this letter – appreciated.
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation

Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, June 12, 2014 6:50 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

Thanks for confirming and agreeing to the changes. I also received your follow-up voicemail this afternoon.

At this point, we are working on wrapping up the final reviews and action letter.
I'm working on my review of all labeling and labels, an internal requirement before taking action on S-030.
That means a detailed comparison of the final agreed-upon labeling/labels to what is currently approved.
Obviously, since we just approved S-028, the package insert is straightforward.

However, it would be helpful to me and expedite my review if you could confirm what are the currently approved carton and container labels/IFU. By "currently approved", we mean labels that were approved in the original NDA or supplement (and ideally, attached to the approval letter). I realize that some labels are too old to be attached to an approval letter (especially during the pre-electronic era), so if an approval letter stated that XX labels are being approved but the labels weren't attached, and a letter issued after approval stating that the final printed labeling (FPL) is acceptable – then pointing me to the FPL submission and the subsequent "FPL acceptable" letter would be helpful.

Specifically, I'm referring to the following currently approved:

- Sandostatin LAR kit: carton and container (vial/syringe/tray) labels
- Instructions for use (IFU)/instruction booklet (unless the final agreed-upon healthcare practitioner IFU is the first one you've created)
- Demonstration kit: carton and container (vial/syringe/tray) labels + instruction booklet

I'm happy to explain further over the phone if that helps. Let me know if you have any questions.

Thanks,
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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Friday, June 06, 2014 6:37 PM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Jennifer,
Thanks for your reply and expediting.

The changes in your attached PI and the changes below are all acceptable. Since it will take time to mock-up new carton/vial labeling (EU offices are closed Monday), in the interest of time, we commit to the changes and will send all this final labeling with FDA requested changes as part of the final labeling post-approval.

Looking forward to the approval letter.

Thanks again,
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Friday, June 06, 2014 5:35 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*

Hi Omer,

No problem – thanks for letting me know.

We have discussed the package insert that was submitted on August 27, 2013, and have made some edits.
See the attached revised PI, which includes our edits and comments.

After further consultation with our CMC colleagues (and follow-up concurrence from DMEPA), we also have the following additional revision requests for the carton and container labels:

Revised Carton label submitted on March 24, 2014:

1) Under "Each diluent syringe contains", [redacted] (b) (4)
2) Under STORAGE: Change [redacted] (b) (4)

To

"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light"

Revised Vial label submitted on March 24, 2014:

Under STORAGE: Change "[redacted] (b) (4)

To

"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light"

Demo-Carton label submitted on February 10, 2014:

Under "Each diluent syringe contains", [redacted] (b) (4)

Demo-Syringe label submitted on February 10, 2014:

[redacted] (b) (4)

Note: if the revisions to the carton and container labels can be made quickly and submitted to me via email, then please do that. Otherwise, we are fine with you committing to make the revisions to the labels (in the final printed labeling submission post-approval) now via email and then documenting that agreement in the action letter.

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

From: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Wednesday, June 04, 2014 9:52 AM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent

Hi Jennifer,
Sorry for the delay, I've been out of office until today.
Please let me know what edits are requested for approval.
Thanks,
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, May 29, 2014 12:27 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent

Hi Omer,

I'm following up on this supplement, and apologize again for the delay.
Reviews are complete and we're just finishing up the labeling.
We've been discussing the package insert and have some edits, which I hope to send you by the end of the day.
I also have some minor carton/container label comments, which I'll send shortly in another email.

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: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Wednesday, May 14, 2014 6:09 PM
To: Johnson, Jennifer
Subject: NDA 21008/S-030: Sandostatin LAR new diluent

Hi Jennifer,

Following up on the action for this supplement, if you still anticipate by the end of this week.
Thanks for your understanding.
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

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

07/03/2014

Email chain between RPM and applicant documenting discussion re: labels and labeling, as well as final agreed-upon versions for manufacturing CMC supplement with labeling (NDA 21008/S-030)

From:	Johnson, Jennifer
To:	"Munir, Omer"
Bcc:	Johnson, Jennifer
Subject:	RE: NDA 21008/S-030: Sandostatin LAR new diluent - *FDA revisions to package insert and carton/container labels*
Date:	Friday, June 06, 2014 5:34:00 PM
Attachments:	NDA 21008 S030 Sandostatin LAR PI to Novartis FDA edits 06 June 2014.doc

Hi Omer,

No problem – thanks for letting me know.

We have discussed the package insert that was submitted on August 27, 2013, and have made some edits.
See the attached revised PI, which includes our edits and comments.

After further consultation with our CMC colleagues (and follow-up concurrence from DMEPA), we also have the following additional revision requests for the carton and container labels:

Revised Carton label submitted on March 24, 2014:

1) Under "Each diluent syringe contains", spell out (b) (4)
2) Under STORAGE: (b) (4)

To
"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light"

Revised Vial label submitted on March 24, 2014:

Under STORAGE: Change (b) (4)

To
"Refrigerate at 2 °C to 8 °C (36 °F to 46°F). Protect from light"

Demo-Carton label submitted on February 10, 2014:

Under "Each diluent syringe contains", (b) (4)

Demo-Syringe label submitted on February 10, 2014:

Spell out (b) (4)

Note: if the revisions to the carton and container labels can be made quickly and submitted to me via email, then please do that. Otherwise, we are fine with you committing to make the revisions to the labels (in the final printed labeling submission post-approval) now via email and then documenting that agreement in the action letter.

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

From: Munir, Omer [mailto:omer.munir@novartis.com]
Sent: Wednesday, June 04, 2014 9:52 AM
To: Johnson, Jennifer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent

Hi Jennifer,
Sorry for the delay, I've been out of office until today.
Please let me know what edits are requested for approval.
Thanks,
Kind regards,
Omer

Omer A. Munir, RPh.
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
Phone +1 862 7783485
(b) (6)
omer.munir@novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, May 29, 2014 12:27 PM
To: Munir, Omer
Subject: RE: NDA 21008/S-030: Sandostatin LAR new diluent

Hi Omer,

I'm following up on this supplement, and apologize again for the delay.
Reviews are complete and we're just finishing up the labeling.
We've been discussing the package insert and have some edits, which I hope to send you by the end of the day.
I also have some minor carton/container label comments, which I'll send shortly in another email.

Kind Regards,
Jennifer

Jennifer Johnson

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/s/

JENNIFER L JOHNSON
06/06/2014

From:	Johnson, Jennifer
To:	"Munir, Omer"
Cc:	Ganeshan, Shanthi; Stamatis, Demetre
Bcc:	Johnson, Jennifer
Subject:	NDA 21008/S-030: Sandostatin LAR new diluent - *Requested revisions to carton/container labels + IFU*
Date:	Friday, March 07, 2014 6:35:00 PM
Attachments:	NDA 21008 Consolidated Comments.docx

Dear Omer,

For pending NDA 21008/S-030, we have the following comments and requests for revision to your currently proposed carton and container labels and Instructions for Use (IFU). Please see the attached document, which includes consolidated comments from DMEPA and CDRH.

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

NDA 21008/S-030: Consolidated Comments from DMEPA and CDRH

Instructions for Use (IFU)

1. The Human Factors validation study results showed that multiple participants failed to perform critical tasks where participants needed to wait for a specific amount of time prior to completing a particular task. For example, 5 participants failed to state intent to wait at least 30 minutes for the delivery system to reach room temperature (Task 1), or 7 participants (23%) failed to let the vial stand for a minimum of 2 minutes until the powder was wetted (Task 11), or 3 participants (10%) failed to shake the vial for 30 seconds (Task 13).

   Your finalized IFU includes an attention box in red as follows before it provides individual user steps:

   However, the same information did not seem to be emphasized in the same manner in the individual task description. For example, the Attention in step 1 is shown below:

   We also note that the use of terminology was not used consistently in the IFU. In the red box, you indicate that there are three critical steps. In the individual task, you use the term essential.

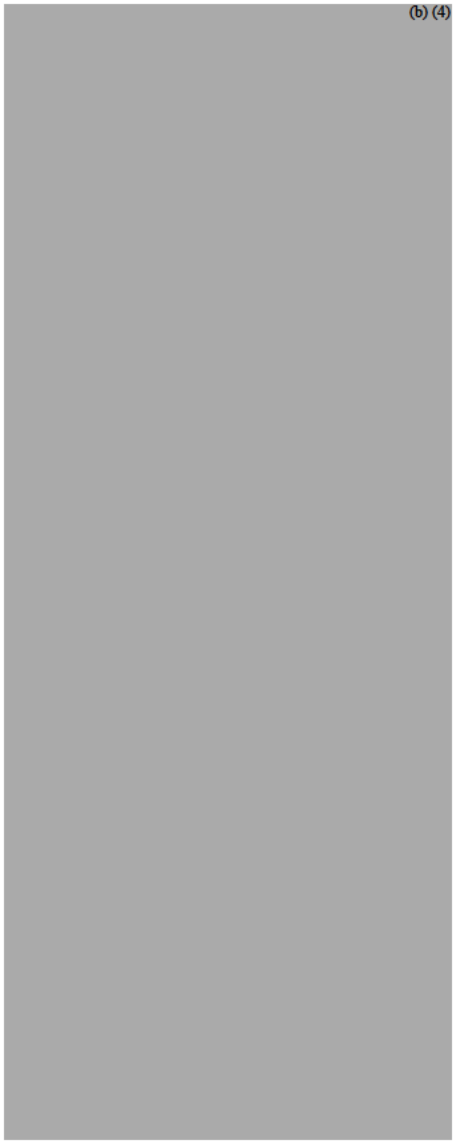
   In addition, there were two other task failures where 2 participants (7%) failed to clean the rubber stopper of the vial with an alcohol swab (Task 4), and 5 participants (17%) failed to

dispose of the syringe in a sharps container (Task 25). However, your finalized IFU did not appear to include these steps.

Please address the following:

a. You stated in your submission dated November 27, 2013, that the finalized IFU was used in the validation study. If that is the case, we recommend that the IFU includes consistent terminology (i.e., critical/essential).
b. Further emphasize the attention section in all the individual steps (tasks 1, 11, 13 described above) to call the user's attention to the wait time associated with each step.
c. Revise your IFU to include tasks 4 and 25 (described above).

d. Design the IFU so that the instructions are in sequential order continuously in a vertical manner. For example:



e. Increase the prominence of the critical tasks (i.e., 30-minute wait before reconstitution, 2-minute wait time for saturation, and shaking for 30 seconds) by using different color font, bolding, highlighting, and/or increasing font size.

f. Due to the nature of the changes, we do not need to see additional human factors data. We ask that you submit a revised IFU implementing the above requested changes.

Vial Labels for Sandostatin LAR

Relocate the route of administration to the principal display panel to increase its prominence. We have identified medication error cases with this product that reported administration of Sandostatin LAR via the wrong route.

Carton Labeling for Sandostatin LAR

Ensure that the route of administration is placed on each panel including the principal display panel.

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/s/

JENNIFER L JOHNSON
03/07/2014
Consolidated comments from CDRH and DMEPA (carton/container labels + IFU)

From:	Johnson, Jennifer
To:	Munir, Omer (omer.munir@novartis.com)
Bcc:	Johnson, Jennifer
Subject:	NDA 21008/S-030 (Sandostatin LAR Depot): Human Factors Study Information Requests
Date:	Thursday, November 14, 2013 3:13:00 PM

Dear Omer,

Regarding your NDA 21008/S-030 (Sandostatin LAR Depot) currently under review, we need a few items clarified regarding the Human Factors Study:

1. On page 18 of the Human Factors Engineering Summary Report for the SMS995L Delivery System, it states "Once a participant had expressed the intent to let the delivery system sit at room temperature for a minimum of 30 minutes after removing it from the refrigerator, the study moderator swapped the cold delivery system for one that was at room temperature and instructed the participants to continue as though the 30 minutes had passed."
    a. Question: It is unclear how Task # 1: Stated intent to wait a minimum of 30 minutes before reconstituting was verified. Were the participants asked an open ended question on how long they need to wait prior to reconstitution or did the participants have to verbally state the intent to wait 30 minutes without probing?
2. In the Validation Testing, was the test performed using the 1) Final Instruction for Use and 2) Revised Carton and Container Labeling, found in the Appendix of the Human Factors Report?
3. Under 6.2 Test participants, the background summary shows that participants have prior experience with preparation and administration of intragluteal injections. Can you further clarify whether these participants are previous Sandostatin preparers/administrators or non-Sandostatin users?

Let me know if you have any questions – thanks in advance for your help.

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
11/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021008/S-030

**REVIEW EXTENSION –
CMC SUPPLEMENT**

Novartis Pharmaceuticals Corporation
Attention: Omer A. Munir, R.Ph.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Munir:

Please refer to your August 27, 2013, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sandostatin LAR Depot (octreotide acetate for injectable suspension), 10 mg, 20 mg, 30 mg.

On October 11, 2013, we received your major amendment to this application. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is **February 27, 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
11/08/2013
Concurrence from Acting Director Jean-Marc Guettier, M.D.

From:	Johnson, Jennifer
To:	Munir, Omer (omer.munir@novartis.com)
Bcc:	Johnson, Jennifer
Subject:	NDA 21008/S-030 (Sandostatin LAR Depot): Update + Information Requests
Date:	Friday, November 08, 2013 1:43:00 PM
Attachments:	NDA 21008 S030 Review Extension- CMC Supp Major Amendment.pdf

Dear Omer,

I'm following up regarding pending CMC supplement 030 submitted to NDA 21008 (Sandostatin LAR Depot) on August 27, 2013. We are continuing to review this supplement and have recently made a decision to extend the review clock by two months in order to allow sufficient time for review of the application. As you know, review of this supplement involves input by numerous disciplines outside the Division and required the requested information that you submitted in amendments on September 24th, October 9th and 11th. Today we issued a review extension letter (see attached), which will be also sent to you via U.S. mail. The new user fee goal date is **February 27, 2014**.

We also have a request for the following two items:

1. We note that you did not yet submit color mock-ups of your proposed carton and container labels included with the original submission on August 27th. (Only descriptions of the proposed changes to these labels were included.) Please submit the color mock-ups of your proposed carton and container labels as soon as possible so that we may complete our review.

2. We received a Word version of the Instructions for Use (IFU) in your October 9th submission per our request sent via email on September 20th. We are also requesting a stand-alone pdf version that you plan to enclose in the injection kit and distribute to healthcare practitioners with the product. Currently the only one we can find in the application is included as part of the Human Factors Study Report.

Feel free to contact me with any questions or concerns – thank you in advance for your help.

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
11/08/2013
Information requests from DMEPA reviewer

From:	Johnson, Jennifer
To:	Munir, Omer (omer.munir@novartis.com)
Bcc:	Johnson, Jennifer
Subject:	NDA 21008/S-030 (Sandostatin LAR Depot): Biopharmaceutics Information Requests
Date:	Friday, October 04, 2013 5:53:00 PM

Dear Omer,

For Sandostatin LAR Depot NDA 21008/S-030, we have the following biopharmaceutics information requests.

Provide the locations of the following items in your submission (Module, Volume, Section, and Page Numbers), or submit the missing items if they were not included in the submission:

1. In order to confirm your BE assessment/conclusion, SAS xpt files or datasets in Excel format ready for the Phoenix program are needed.

2. In order to waive the *in vivo* BE studies for the two lower strengths (10 and 20 mg/vial) with the new vehicle, comparative drug release profiles/data (using the currently FDA approved dissolution method, USP IV method) of the two lower strengths compared with the biolot of the highest strength (30 mg) used in the BE study (No. CSMS995L2106) are needed.

3. A biowaiver request for the two lower strengths is also needed.

Please submit an official response by next **Friday, October 11th**.
Let me know if you have any questions – thanks in advance.

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
10/04/2013
Information request from Biopharmaceutics Reviewer Tien-Mien (Albert) Chen on 10/4/13

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: Immo Zadezensky, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
REVIEW DATE: 10/04/2013	IND No.: Serial No.:	NDA No. 21008 S-030	SUBMISSION DATE : **08/27/2013**	
NAME OF DRUG: Sandostatin Depot (octreotide acetate) injection	PRIORITY CONSIDERATION **S**		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Novartis Pharmaceuticals Corp.

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PHASE I PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☒ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW):* []
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*: [ ]
(Check as appropriate and attach e-mail)		

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS: The sponsor submitted this CMC supplement on 8/27/13, which provides for a new diluent (including supportive bioequivalence (BE) study report). Revised labeling, healthcare provider IFU and human factors study results were also submitted. The supportive BE study report and results will be evaluated by ONDQA.

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/s/

IMMO ZADEZENSKY
10/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: **Priyanka Kumar Regulatory Project Manager (240) 402-3722**

PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/1/2013	**N/A**	**21008/S-030**	**Electronic**	**8/27/2013**

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
SANDOSTATIN LAR(OCTREOTIDE ACETATE)DEPOT		**12/27/2013**	**12/1/2013**

NAME OF APPLICANT OR SPONSOR: **Novartis**

GENERAL PROVISIONS IN APPLICATION

☐ 30-DAY SAFETY REVIEW NEEDED

☐ NDA FILING REVIEW NEEDED BY: _____

☐ BUNDLED

☐ DOCUMENT IN EDR

PAS

☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

This Prior approval supplement provides for a new diluent for product reconstitution (new pharmaceutically equivalent vehicle and presentation). Submission includes CMC data, bioequivalence data from Study CSMS995L2106 (protocol submitted on 10/11/2011 to IND 37768), human factors study (protocol submitted on 10/3/2011, IND 37,768) results and revised PI, carton/container and health care practitioner IFU (instructions for use). This is OND managed. OND PM is Jennifer Johnson.

SIGNATURE OF REQUESTER

Priyanka Kumar

REVIEW REQUEST DELIVERED BY (Check one):
X DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):
X EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

PRIYANKA KUMAR
10/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021008/S-030

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attention: Demetre Stamatis, Pharm.D.
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Stamatis:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021008

SUPPLEMENT NUMBER: 030

PRODUCT NAME: Sandostatin LAR Depot (octreotide acetate) intramuscular injection; 10 mg, 20 mg, 30 mg

DATE OF SUBMISSION: August 27, 2013

DATE OF RECEIPT: August 27, 2013

This supplemental application proposes the following changes: a new diluent for product reconstitution (pharmaceutically equivalent vehicle) and product presentation, including a simplified administration kit. Revisions have also been proposed to the package insert, healthcare practitioner instructions for use, and carton and container labels.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 26, 2013, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be **December 27, 2013**.

If you have not already done so, promptly submit the 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have 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
09/04/2013

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
Division: ODE/DAGID/GHDB
Mail Code: HF
Consulting Reviewer Name: 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:

From (Originating Center):
Center: CDER
Division: Division of Metabolism and Endocrin
Mail Code: HF D-510
Requesting Reviewer Name: Jennifer Johnson, RPM
Building/Room #: WO22 Room 3114
Phone#: 301-796-2194
Fax #: 301-796-2290
Email Address: jennifer.johnson@fda hhs.gov
RPM/CSO Name and Mail Code:
Requesting Reviewer's Concurring Supervisor's Name: Julie Marchick (CPMS)

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: September 3, 2013

Requested Completion Date: November 15, 201

Submission/Application Number: NDA 21008/S-030
(Not Barcode Number)

Submission Type: Prior Approval CMC supplemen
(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: August 27, 2013

Official Submission Due Date: December 27, 201

Name of Product: Sandostatin LAR Depot (octreotide acetate for

Name of Firm: Novartis Pharmaceuticals Corp.

Intended Use: Approved for the treatment of patients with acromegaly, metastatic carcinoid tumors and vasoactive intestinal peptide tumors (no new indications being sought)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

This Prior Approval CMC supplement provides for a new diluent for product reconstitution (pharmaceutically equivalent vehicle and presentation). Submission includes CMC data, bioequivalence data from Study CSMS995L2106, human factors study results and revised PI, carton/container labels and health care practitioner IFU. This supplement is OND-managed. Direct link to EDR submission: \\CDSESUB1\evsprod\NDA021008\0035

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

Please review and comment on the new proposed device. Along with the new vehicle, the sponsor proposes a simplified administration kit with one safety engineered needle and a vial adapter (instead of 2 needles), a lower injection volume (2 mL instead of 2.5 mL) and a smaller needle diameter (0.9 mm instead of 1.1 mm). Recall that we held a Type C pre-sNDA guidance meeting with the sponsor on 5/10/11 (refer to meeting minutes which issued on 6/9/11 under NDA 21008). Also refer to the CDRH review dated 5/2/11. CDRH (Quynh Nguyen) and OSE/DMEPA are being consulted for input on the Human Factors Study results and IFU.

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/s/

JENNIFER L JOHNSON
09/03/2013

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
Division: ODE/DAGID/GHDB
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: CDER
Division: Division of Metabolism and Endocrin
Mail Code: HF D-510
Requesting Reviewer Name: Jennifer Johnson, RPM
Building/Room #: WO22 Room 3114
Phone#: 301-796-2194
Fax #: 301-796-2290
Email Address: jennifer.johnson@fda hhs.gov
RPM/CSO Name and Mail Code:
Requesting Reviewer's Concurring Supervisor's Name: Julie Marchick (CPMS)

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: September 3, 2013

Requested Completion Date: November 15, 201

Submission/Application Number: NDA 21008/S-030
(Not Barcode Number)

Submission Type: Prior Approval CMC supplemen
(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: August 27, 2013

Official Submission Due Date: December 27, 201

Name of Product: Sandostatin LAR Depot (octreotide acetate for

Name of Firm: Novartis Pharmaceuticals Corp.

Intended Use: Approved for the treatment of patients with acromegaly, metastatic carcinoid tumors and vasoactive intestinal peptide tumors (no new indications being sought)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

This Prior Approval CMC supplement provides for a new diluent for product reconstitution (pharmaceutically equivalent vehicle and presentation). Submission includes CMC data, bioequivalence data from Study CSMS995L2106, human factors study results and revised PI, carton/container labels and health care practitioner IFU. This supplement is OND-managed. Direct link to EDR submission: \\CDSESUB1\evsprod\NDA021008\0035

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

Please review and comment on the Human Factors Study report and IFU. located in Module 5, section 5.3.5.4. Along with the new vehicle, the sponsor proposes a simplified administration kit with one safety engineered needle and a vial adapter (instead of 2 needles), a lower injection volume (2 mL instead of 2.5 mL) and a smaller needle diameter (0.9 mm instead of 1.1 mm). Recall that we held a Type C pre-sNDA guidance meeting with the sponsor on 5/10/11 (refer to meeting minutes which issued on 6/9/11 under NDA 21008). Also refer to the CDRH review dated 5/2/11. CDRH is being consulted for the new proposed device and OSE/DMEPA is being consulted for input on the Human Factors Study results and IFU.

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/s/

JENNIFER L JOHNSON
09/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Margarita Tossa, OSE Regulatory Project Manager, WO22 Rm 3461, (301) 796-4053
Mail: OSE

FROM: Jennifer Johnson, Regulatory Health Project Manager, DMEP, WO22 Rm 3114, (301) 796-2194

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 3, 2013	(related IND 37768)	21008/S-030	Prior Approval CMC supplement	August 27, 2013

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Sandostatin LAR Depot (octreotide acetate for injectable suspension)	Standard	Somatostatin analog	November 15, 2013

NAME OF FIRM: Novartis Pharmaceuticals Corp.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the human factors study report, health care provider instructions for use, proposed package insert and carton/container labels submitted with this Prior Approval CMC supplement, which provides for a new diluent for product reconstitution (pharmaceutically equivalent vehicle and presentation). Along with the new vehicle, the sponsor proposes a simplified administration kit with one safety engineered needle and a vial adapter (instead of 2 needles), a lower injection volume (2 mL instead of 2.5 mL) and a smaller needle diameter (0.9 mm instead of 1.1 mm). Recall that we held a Type C pre-sNDA guidance meeting with the sponsor on 5/10/11 (refer to meeting minutes which issued on 6/9/11 under NDA 21008). CDRH is also being consulted for input on the human factors study results and revised IFU (Quynh Nguyen), and for the proposed device. This supplement is on a 4-month review clock (PDUFA date = December 27, 2013), so we are requesting review completion by November 15th if possible to allow enough time for team discussion and revisions to the IFU, labeling and labels.

Direct EDR link to the submission: \\CDSESUB1\evsprod\NDA021008\0035

Let me know if you have any questions or need further information. Many thanks, Jennifer

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jennifer Johnson	X DARRTS/EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

JENNIFER L JOHNSON
09/03/2013