CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213224Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 213224
Supporting document/s:	1 (original NDA)
Applicant's letter date:	3/28/2019
CDER stamp date:	3/28/2019
Product:	Octreotide Acetate Injection
Indication:	Acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors (VIPomas)
Applicant:	Sun Pharmaceutical Industries Ltd
Review Division:	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer/Team Leader:	Federica Basso, PhD (acting)
Division Director:	Lisa Janoff, MD (acting)
Project Manager:	Meghna Jairath

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1 Executive Summary

1.1 Introduction

Sun Pharmaceutical submitted this NDA for Octreotide Acetate Injection 2.5 mg/mL, Pen injector 2.8 mL, via the 505(b)(2) regulatory pathway relying on the Agency's prior findings of safety and efficacy of Sandostatin®, the reference listed drug (RLD).

Sandostatin® is currently available at 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL concentration in single dose ampules and 0.2 mg/mL and 1 mg/mL concentration in 5 mL multiple-dose vials. Sun Pharmaceutical' proposed octreotide acetate injection is 2.5 times more concentrated than the highest available concentration of the RLD (2.5 mg/mL vs. 1 mg/mL) and will be provided in a multi-dose, variable dose disposable pen injector (2.8 mL) for subcutaneous delivery. The proposed indication, dose and route of administration of Sun Pharmaceutical's octreotide acetate are the same as for the RLD. The Applicant' proposed formulation contains the same excipients as the RLD at the same (lactic acid, phenol) or lower (mannitol) concentrations. No impurities, degradants or leachable of concerns have been identified.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were required or submitted in support of this NDA, as the proposed drug product formulation is similar to that of the RLD and no new impurities, degradants or leachables of concern were identified.

1.3 Recommendations

1.3.1 Approvability

Approval recommended from a nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Minor changes were made to the language in the nonclinical sections of the label to make it consistent with Sandostatin LAR label.

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2 Drug Information

2.1 Drug

CAS Registry Number
79517-01-4

Generic Name
Octreotide Acetate

Chemical Name
D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7)-disulfide (Octreotide is available as acetate salt)

Or

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

Or

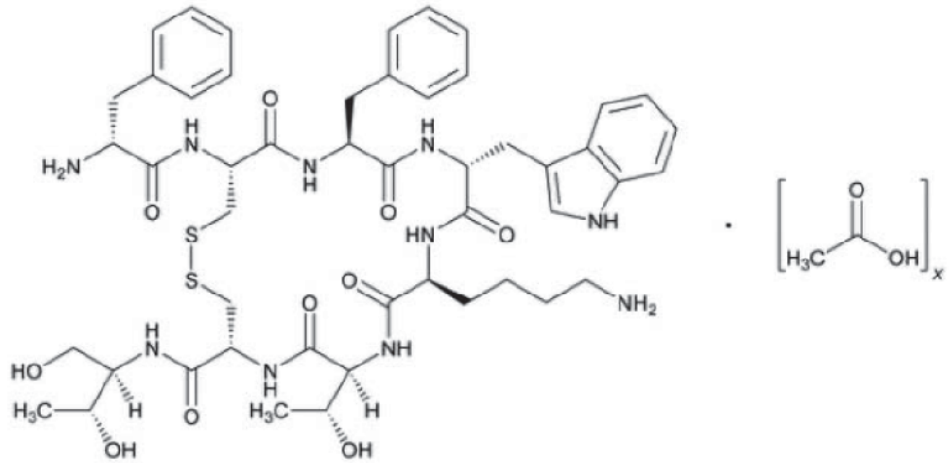
D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[(1R,2R)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7)-disulfide acetate (salt);

Or

D-Phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2→7)-disulfide acetate (salt)

Molecular Formula/Molecular Weight
$C_{49}H_{66}N_{10}O_{10}S_2$ (b) (4) / 1019.26 (Free peptide)

Structure or Biochemical Description



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Pharmacologic Class
Somatostatin analog

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 19667: Sandostatin
NDA 21008: Sandostatin LAR

2.3 Drug Formulation

The drug product formulation will be comprised of octreotide acetate as drug substance, and lactic acid, mannitol, and phenol as excipients. It will be filled in a plunger stoppered glass cartridge assembled in a light blue color pen injector.

Table 1. Drug Product Composition

Components	Function	Quality Standard	Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL		
			Amount		
			(mg/mL)	mg/pen	(%w/v)
Octreotide Acetate	Active drug substance	USP	2.5	(b) (4)	
Lactic Acid (b) (4)	(b) (4)	USP	3.4		
Mannitol (b) (4)		USP	22.5		
Phenol (b) (4)		USP	5.0		
Sodium Bicarbonate (b) (4)	For pH adjustment (b) (4)	USP	q.s. to pH		
Water for Injection (b) (4)		USP	q.s. to 1.0 mL		
(b) (4)		NF	(b) (4)		

2.4 Comments on Novel Excipients

The excipients are the same as in the RLD and comply with the FDA Inactive Ingredient Database limit for the subcutaneous route of administration.

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Table 2. Comparison of RLD with Sun's Octreotide Acetate Injection, 2.5 mg/mL

Product Name	RLD Sandostatin® (octreotide acetate) Injection 1000 mcg/mL, 5 mL multidose vial (Novartis Pharma Stein AG)	Sun's Drug Product Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL
	mg/mL	mg/mL
Active Ingredient		
Octreotide Acetate	1.0	2.5
Inactive Ingredients		
Lactic Acid (b) (4) (b) (4)	3.4	3.4
Mannitol (b) (4) (b) (4)	45.0	22.5
Phenol	5.0	5.0
Sodium Bicarbonate	q.s.	q.s.
Water for Injection	q.s.	q.s.
Dosage Form	Injectable	Injectable
Strength	1000 mcg/mL	2.5 mg/mL
Route of Administration	Subcutaneous or Intravenous	Subcutaneous
Container	5 mL multidose vial	2.8 mL Pen Injector

2.5 Comments on Impurities/Degradants of Concern

As per the CMC review team, there are no safety concerns for product impurities, degradants, or leachables from the container closure system.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indications and dosing regimen are identical to those of the reference product.

2.7 Regulatory Background

A pre-IND meeting request to discuss the sponsor's development plan for Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector was submitted to the Division of Metabolism and Endocrinology Products (DMEP) on October 9, 2018. The Division agreed that nonclinical studies were not required pending that the levels of impurities, degradants, and leachables met the appropriate ICH qualification thresholds or were adequately justified (PIND 141456, 12-7-2018).

3 Studies Submitted

No nonclinical studies were submitted.

Reference ID: 4552900

11 Integrated Summary and Safety Evaluation

Sun Pharmaceutical has submitted a 505(b)(2) NDA application for a more concentrated formulation of octreotide acetate (2.5 mg/mL) that relies on the Agency's prior findings of safety and efficacy of Sandostatin® (NDA 019667).

Octreotide is a synthetic octapeptide analog of the endogenous hormone somatostatin. Compared to somatostatin, octreotide is a more potent inhibitor of growth hormone, glucagon, and insulin. Like somatostatin, it also suppresses luteinizing hormone (LH) response to gonadotropin releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Sandostatin® was first approved in 1988 and is currently indicated to reduce blood levels of growth hormone and IGF-1 in acromegaly patients who have had inadequate response to, or cannot be treated with surgical resection, pituitary irradiation and/or bromocriptine mesylate at maximally tolerated doses. It is also indicated for the symptomatic treatment of metastatic carcinoid tumors and for the treatment of the profuse watery diarrhea associated with Vasoactive Intestinal Peptide Tumors (VIPomas)

Sandostatin® is currently available at concentrations up to 1 mg/mL. According to the applicant, its new octreotide presentation (2.5 mg/mL, 2.8 mL pen injector) is expected to enhance patient compliance due to self-administration. In addition, it offers dosing flexibility and lower volumes of administration, with subsequent less pain at the injection site. The applicant' octreotide formulation contains the same excipients as the RLD, at the same or lower concentrations. No impurities, degradants, or extractables/leachables of concern have been identified.

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/s/

FEDERICA BASSO
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