CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213224Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	September 24, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 213224
Product Name, Dosage Form, and Strength:	Bynfezia Pen (octreotide acetate) injection, 2,500 mcg/mL (2,500 mcg/mL octreotide in a 2.8 mL single-patient-use prefilled pen)
Applicant Name:	Sun Pharmaceutical Industries (Sun Pharma)
FDA Received Date:	September 24, 2024
TTT ID #:	2024-9104-2
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Sun Pharmaceutical Industries submitted revised container label and carton labeling received on September 24, 2024 for Bynfezia Pen. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Bynfezia Pen (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additionally, we collaborated with the Office of Pharmaceutical Quality (OPQ) and proposed additional recommendations to the Applicant to include the following statement on the container label: "After first use, store at 20°C to 25°C (68°F to 77°F)" and to truncate the manufacturer/distributor information[b].

2 CONCLUSION

Sun Pharmaceutical Industries implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Rahbani P. Label and Labeling Review for Bynfezia Pen (NDA 213224). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 Sep 19. TTT ID: 2024-9104-1.

[b] Cover Letter, Response to IR-Labeling Bynfezia Pen (NDA 213224). 2024 Sep 23 Available from: \\CDSESUB1\EVSPROD\nda213224\0120\m1\us\coverlettersign.pdf

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	September 19, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 213224
Product Name, Dosage Form, and Strength:	Bynfezia Pen (octreotide acetate) injection, 2,500 mcg/mL (2,500 mcg/mL octreotide in a 2.8 mL single-patient-use prefilled pen)
Applicant Name:	Sun Pharmaceutical Industries (Sun Pharma)
FDA Received Date:	September 16, 2024
TTT ID #:	2024-9104-1
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Sun Pharmaceutical Industries submitted revised container label and carton labeling received on September 16, 2024 for Bynfezia Pen. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Bynfezia Pen (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Sun Pharmaceutical Industries implemented most of our recommendations. Additionally, they addressed the following recommendation: "The use of the plural and singular designations of the word "pen" in the storage instructions" but they did not implement all the correlating changes accordingly on the two-pen carton labeling. Therefore, the revised carton labeling is unacceptable from a medication error perspective for the following reason:

- The use of the singular designation of the word "pen" in the storage statement: "(b) (4) (b) (4)." on the two-pen presentation does not account for possible scenarios where either one pen or both (two) pens need to be discarded if frozen.

We have additional recommendations for the container label:

- The inclusion of the (b) (4) in the upper right corner of the principal display panel (PDP) contributes to clutter and is redundant since the product strength (7,0000 mcg/2.8 mL) has been revised.
- The statement "(b) (4)" is not consistent and does not align with the PI and the carton which state to "Discard the pen 28 days after first use."

3 RECOMMENDATIONS FOR SUN PHARMACEUTICAL INDUSTRIES:

- Carton Labeling:
  - Revise the storage statement on the two-pen presentation to read: "Discard the pen(s) if frozen."
- Container Label:
  - Remove the (b) (4) in the upper right corner of the PDP.
  - Revise the statement "(b) (4)" to read "Date of first use."

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

[a] Rahbani P. Label and Labeling Review for Bynfezia Pen (NDA 213224). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 Aug 20. TTT ID: 2024-9104.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 18, 2024
To:	Jennifer Johnson Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	BYNFEZIA PEN (octreotide acetate)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 213224
Applicant:	Sun Pharmaceuticals Industries Limited

1 INTRODUCTION

On March 29, 2024, Sun Pharmaceuticals Industries Limited submitted for the Agency's review a Class 2 Resubmission for New Drug Application 213224 for BYNFEZIA PEN (octreotide acetate) injection, for subcutaneous use in response to a Complete Response letter issued by the Agency on May 19, 2021. The purpose of this submission is to address the facility deficiencies and the Applicant is proposing additional drug product manufacturing site, Stelis Biopharma Limited – Bengaluru.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on August 30, 2024 for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for BYNFEZIA PEN (octreotide acetate) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft BYNFEZIA PEN (octreotide acetate) IFU received on March 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 5, 2024.
- Draft BYNFEZIA PEN (octreotide acetate) Prescribing Information (PI) received on [Month Day, Year], revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 5, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and

Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022).

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	August 20, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 213224
Product Name, Dosage Form, and Strength:	Bynfezia Pen (octreotide acetate) injection, 2,500 mcg/mL (2,500 mcg/mL octreotide in a 2.8 mL single-patient-use prefilled pen)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Sun Pharmaceutical Industries (Sun Pharma)
FDA Received Date:	March 29, 2024
TTT ID #:	2024-9104
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Bynfezia Pen (octreotide acetate) injection, the Division of General Endocrinology (DGE) requested that we review the proposed Bynfezia Pen Prescribing Information (PI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

From January 28, 2020, to May 19, 2021, Bynfezia Pen, was previously marketed under NDA 213224.

On May 19, 2021, the Agency rescinded approval of the application and issued a Complete Response (CR) letter due to facility inspection deficiencies and noted that "the drug product may not be legally marketed until you have been notified in writing that this application is approved". Of note, Bynfezia Pen product characteristics remain accessible in commonly used drug databases.

On March 29, 2024, Sun Pharma submitted a class II resubmission addressing the deficiencies identified in the Complete Response letter[a] and submitted revised PI, IFU, container label, and carton labeling.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 213224.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Bynfezia Pen Instructions for Use, Prescribing Information (PI), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of General Endocrinology (DGE) in Section 4 and for Sun Pharmaceutical Industries in Section 5. Additionally, we collaborated with Office of Pharmaceutical Quality (OPQ) to revise the presentation of the product strength to align with the standard expression as a total quantity per total volume followed by the concentration per mL.

(b) (4)

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The product strength is not expressed as a total quantity per total volume followed by the concentration per mL.	A number of overdoses have occurred with small-volume parenteral because of health care practitioner or patient confusion when determining the quantity of drug in the container. In most cases, the user noticed the quantity per milliliter or concentration (e.g., 10 mg/mL) but failed to see the net quantity (e.g., 10 mL), which often appears in a different location on the container label.	We defer to OPQ to determine the appropriate strength presentation throughout labeling. We recommend revising the labeling to reflect the change in strength presentation.
Prescribing Information/Highlights/Section 3 Dosage Forms and Strengths			
1.	The "prefilled" description is missing when describing the pen	Elimination of "prefilled" could lead to confusion of the device characteristics (i.e., requirement of cartridge)	Consider revising "single-patient-use pen" to "single-patient-use prefilled pen" throughout the PI so it is consistent with section 16 and the carton and container.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16 does not include the statement "Dispense in the original sealed carton with the enclosed Instructions for Use" especially that the carton contains more than one device, and the	The lack of this statement may result in dispensing and administration errors. Dispensing the device without the carton circumvents the safety features of the carton labeling and has led to	Add the statement "Dispense in the original sealed carton with the enclosed Instructions for Use" to Section 16.

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	device is not intended for individual dispensing.	medication errors and other safety concerns.	
2.	The statement: "(b) (4) [redacted]" the first temperature numerical is missing the degree symbol	Lack of consistency.	Revise the sentence to read: "Before first use, store BYNFEZIA Pen in the refrigerator between 2° C to 8° C (36° F to 46° F) (b) (4) [redacted]."
Instructions for Use (IFU)			
1.	As currently displayed the product strength in the images of the pen does not reflect total quantity per total volume.	Inconsistency may lead to confusion.	We recommend revising the pen imagines in the IFU to reflect the new strength presentation.

5 RECOMMENDATIONS FOR SUN PHARMACEUTICAL INDUSTRIES

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, the proprietary name lacks prominence on the principal display panel. Additionally, the proprietary name and the (b) (4) are both displayed using the same (b) (4).	The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP)	We recommend increasing the prominence of the proprietary name. Consider the use of different font type or size, bolding, color, or other means (e.g., unbold the established name) to achieve increased prominence. Additionally, we recommend using an (b) (4) for the strength, so it does not coincide with the proprietary name. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
2.	The established name and dosage form presentation on the container label and carton labeling the name appears as (b) (4) which is not consistent with the prescribing information (PI) which appears as "(octreotide acetate) injection."	Inconsistent presentation of the established name and dosage form throughout the label and labeling may lead to confusion and wrong drug errors.	Ensure the presentation of the established name and dosage form is consistent throughout labeling.
3.	The statement 'For doses of 50 mcg, 100 mcg, 150 mcg, and 200 mcg' is unclear in intended meaning.	The statement may be misinterpreted to mean 'only doses of 50 mcg, 100 mcg, 150 mcg, and 200 mcg may be administered from	We recommend revising the statement to clarify the intended meaning, such as 'Delivers 50 mcg, 100 mcg, 150

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		this device' leading to potentially incomplete dosing administration for doses greater than 200 mcg.	mcg, or 200 mcg of octreotide per injection.'
4.	As currently presented, the "5xxxxxx" sequence competes in prominence with the barcode numerical sequence and adds cluster to the labels.	The "5xxxxxx" sequency is not minimally required information on a small container label and clutters the visual filed of the label. Additionally, "5xxxxxx" sequence on the carton labeling is in close proximity to the barcode's numerical sequency which may lead to confusion of the intended meaning of the sequence.	We recommend deleting the "5xxxxxx" sequence from the container labeling. Additionally, we recommend either deleting or decreasing its prominence on the carton labeling by moving the sequence away from the barcode and/or decreasing the font size.
Container Label			
1.	As currently presented, the NDC number is bolded.	The NDC competes with the prominence of important product information on label.	We recommend unbolding the NDC number.
2.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). Additionally, we recommend that the expiration date format matches the IFU displayed expiration date to prevent end-user confusion.
3.	As currently presented, the space for end-user to write the date of first use does not contain information to inform then end-user to throw away the pen 28 days after first use and is not consistent with the PI and IFU.	Lack of clarity in discard information may increase the risk of deteriorated drug medication errors	We recommend adding the statement "Throw away 28 days after first use."
Carton Labeling			
1.	The carton that contains two pens does not have	The lack of this statement may result in dispensing	We recommend adding the statement "Dispense in this

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	a statement “dispense in this sealed carton”.	and administration errors. Dispensing the device without the carton circumvents the safety features of the carton labeling and has led to medication errors and other safety concerns.	sealed carton” on the principal display panel of the carton.
2.	The use of the plural and singular designations of the word “pen” inconsistently throughout the storage instructions on the two-pen carton presentation: “Prior to first use, store pens refrigerated between 36°F and 46°F (2°C and 8°C) in the carton. Protect the pen from light. Do not freeze. Discard the pen if frozen. After first use, store pens at controlled room temperature between 68°F and 77°F (20°C and 25°C)”. Additionally, the plural designation “pens” is used on the one-pen carton presentation.	Using the plural and singular designations inconsistently may lead to confusion as to which pen the storage instructions are referring to in the two-pen presentation carton (e.g., “protect the pen from light” is unclear which pen requires light protection, “after first use, store pens at controlled room temperature”, it is unclear if both pens should be stored at room temperature together). The use of plural designation of “pens” in the one-pen presentation is inconsistent with the net quantity of the carton and alludes that the carton may contain more than one pen.	We recommend revising the storage statement to assure consistent and applicable use of the plural and singular designation of the word “pen” in the storage instructions as it applies to the one-pen and two-pen carton presentations.
3.	As currently presented in the storage instructions the temperature range is listed as Fahrenheit first followed by Celsius in parenthesis: “36°F and	Storage statement should be consistent with the PI to decrease confusion.	We recommend revising the storage instructions, so the temperature range aligns with the PI: 2°C and 8°C (36°F and 46°F)

Table 3. Identified Issues and Recommendations for Sun Pharmaceutical Industries (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	46°F (2°C and 8°C)" which is not consistent with the PI.		
4.	As currently presented on the carton with two-pen presentation there is only one space for the end-user to write the date of first use.	The carton containing the two-pen presentation with one space to document date of first may lead to confusion if the date of first use for the first pen is noted in the field. Patient may inadvertently discard the second pen which may contribute to missed doses.	Remove the following statement: (b) (4) Add the statement "Discard the pen 28 days after first use." Additionally, consider implementing the above changes on the one-pen carton presentation for consistency.
5.	The "Rx only" statement and NDC compete in prominence with other critical information (e.g., established name) on the PDP.	The "Rx only" statement and NDC should not compete in size and prominence with critical information on the PDP.	We recommend decreasing the font size and unbolding the "Rx only" and the NDC . See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
6.	As currently presented the (b) (4) is located after the strength on the PDP and as part of the statement (b) (4) on the side panel	The (b) (4) is commonly used (b) (4) Its use as part of the strength designation may lead to confusion as to the meaning of the presented strength.	Delete the (b) (4) from the strength presentation and the statement (b) (4) (b) (4)

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Bynfezia Pen received on March 29, 2024 from Sun Pharmaceutical Industries.

Table 4. Relevant Product Information for Bynfezia Pen	
Initial Approval Date	January 28, 2020, to May 19, 2021
Active Ingredient	octreotide acetate
Indication	Reduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [somatomedin C] in adult patients with acromegaly who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses Treatment of severe diarrhea/flushing episodes associated with metastatic carcinoid tumors in adult patients Treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adult patients
Dosage Form	injection
Strength	2500 mcg/mL
Route of Administration	subcutaneous
Dose and Frequency	Acromegaly: Dosage may be initiated at 50 mcg three times daily. The dose most commonly found to be effective is 100 mcg three times a day, but some patients require up to 500 mcg three times a day for maximum effectiveness. Doses greater than 300 mcg/day seldom result in additional biochemical benefit, and if an increase in dose fails to provide additional benefit, the dose should be reduced. Carcinoid Tumors: 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). VIP tumors: 200-300 mcg/day in 2-4 divided doses. Adjust the dosage to achieve a therapeutic response; daily dosage is 150 mcg to 750 mcg but usually doses above 450 mcg daily are not required.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Bynfezia Pen</th></tr>
<tr><td>How Supplied</td><td>2,500 mcg/mL octreotide as a clear, colorless solution in a 2.8 mL single-patient-use pen.
<table>
<tr><th>Dosage Unit</th><th>Package Size</th><th>NDC #</th></tr>
<tr><td>2.8 mL single-patient-use prefilled pen</td><td>Carton of 1</td><td>NDC 62756-452-36</td></tr>
<tr><td>2.8 mL single-patient-use prefilled pen</td><td>Carton of 2</td><td>NDC 62756-452-37</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Store BYNFEZIA Pen in the refrigerator between 2° C to 8° C (36° to 46° F) in the carton. Protect the pen from light. After first use store pens at controlled room temperature between 20°C to 25°C (68°F to 77°F). Excursions between 15°C (59°F) and 30°C (86°F) are allowed for up to 28 days. Discard the pen 28 days after first use.</td></tr>
<tr><td>Container Closure</td><td>Prefilled cartridge contained inside a pen-injector.</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

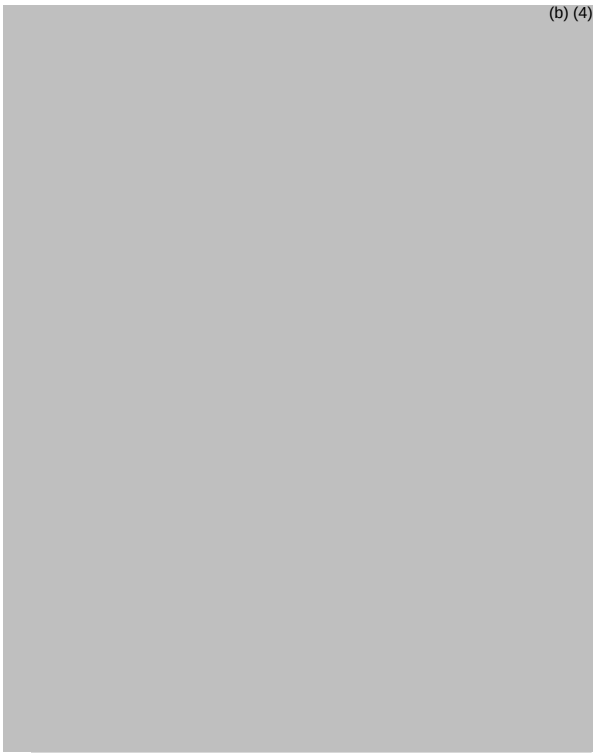
B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Bynfezia Pen labels and labeling submitted by Sun Pharmaceutical Industries.

- Prescribing Information received on March 29, 2024, available from \\CDSESUB1\EVSPROD\nda213224\0104\m1\us\final-labeling-tc.docx
- Instructions for Use received on March 29, 2024, available from \\CDSESUB1\EVSPROD\nda213224\0104\m1\us\final-ifu-tc.docx
- Container label received on March 29, 2024
- Carton labeling received on March 29, 2024

B.2 Container Label(s) and Carton Labeling Images

Container label



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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On July 9, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, 'NDA 213224'. Our search identified one previous review[c] since the date of our last search on January 27, 2020, and we considered our previous recommendations to see if they are applicable for this current review.

[c] Schlick J. Label and Labeling Review for Bynfezia Pen (NDA 213224). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 27. OSE RCM No.: 2019-693 and 2019-694-2.

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	8/19/2024		
To:	OLUWAFUNMIKE AJOMALE		
Requesting Center/Office	CDER/OND	**Clinical Review Division**	N/A-OPQ/OSE led
From	Bingjie Liang OPEQ/OHT3/DHT3C		
Through (Team)	OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director, Injection Devices Team OPEQ/OHT3/DHT3C		
Subject	ICCR: 00985632 ICC: 2400435 Submission: NDA213224 Sponsor: Sun Pharmaceutical Industries Limited Drug/Biologic/Indications for Use: octreotide acetate injection for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors *Delivery Devices (e.g., autoinjector, non-insulin delivering infusion pump, nasal spray devices)		
Recommendation	Device constituent parts of Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL were approved on 1/14/2020 (ICC1900319). The sponsor proposed an additional drug product manufacturing site (Stelis Biopharma Limited – Bengaluru) in the resubmission. The sponsor proposed the same release specification for the functional testing of the finished combination product, and there are no changes to container closure system except updating (b) (4) of glass cartridge. In sequence 0112, the sponsor added the actual amount of dose in mcg highlighted in yellow in the specification of delivered dose accuracy, and provided a single regulatory finished drug product specification table that includes both the release and stability tests and acceptance criteria upon CDER's request in 3.2.P.5.1 as shown below.		

Parameters	Finished Product Specification		
	Release Limit	Shelf Life limit	Method Reference

Delivered Dose Accuracy (**)	Dose(mcg) = 50, Dose volume = 0.02 ml ± (b) (4) ml, K(actual) = Pass if K(actual) greater than equal to (b) (4) Actual amount of dose in mcg = 50 mcg ± (b) (4) mcg Dose(mcg) = 100, Dose volume = 0.04 ml ± (b) (4) ml, K(actual) = Pass if K(actual) greater than equal to (b) (4) Actual amount of dose in mcg = 100 mcg ± (b) (4) mcg Dose(mcg) = 200, Dose volume = 0.08 ml ± (b) (4) ml, K(actual) = Pass if K(actual) greater than equal to (b) (4) Actual amount of dose in mcg = 200 mcg ± (b) (4) mcg	Dose(mcg) = 50, Dose volume = 0.02 ml ± (b) (4) ml, K(actual) = Pass if K(actual) greater than equal to (b) (4) Actual amount of dose in mcg = 50 mcg ± (b) (4) mcg Dose(mcg) = 100, Dose volume = 0.04 ml ± (b) (4) ml, K(actual) = Pass if K(actual) greater than equal to (b) (4) Actual amount of dose in mcg = 100 mcg ± (b) (4) mcg Dose(mcg) = 200, Dose volume = 0.08 ml ± (b) (4) ml, K(actual) = Pass if K(actual) greater than equal to (b) (4) Actual amount of dose in mcg = 200 mcg ± (b) (4) mcg	In-house
Average Activation (Injection) Force Test	Average activation (injection) force shall be less than (b) (4) N for each pen injector.	Average activation (injection) force shall be less than (b) (4) N for each pen injector. (b) (4)	In-house

The functional testing of the finished combination product, i.e., delivered dose accuracy and average activation (injection) force, met their specifications at release and during stability study up to 3 months. The stability at the accelerated condition (6 months) and long-term condition (36 months) are on-going. CDRH has no further information request from the sponsor.

NOTEs to CDER:

In section 3.2.P.5.1, the sponsor noted that the emptied cartridge is used for break-loose force and glide force tests because current ISO 11608-3:2012 has been adopted. CDRH communicated this change to CDER during the NDA-213224-ORIG-1-RESUB-106, CMC Touch Point Meeting #1 on 5/22/2024, and defers the assessment for the testing methods and specifications of break-loose force and glide force tests to CDER.

CDER defers CDER to review the tighter individual specifications of delivered dose accuracy in mcg.

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Bingjie Liang -S Digitally signed by Bingjie Liang -S Date: 2024.08.19 17:31:32 -04'00'	Shruti N. Mistry -S	2024.08.19 17:41:03 -04'00'

1. PURPOSE

CDER is requesting review of the subject combination product that includes a pen injector. CDER sent the following consult:

This is a resubmission for NDA 213224 for Sun Pharmaceutical Industries Limited.

A previous consult was entered and deemed approvable – with conditions (ICCR SharePoint Tracking Number: ICC2019-04870, ICCR CTS Tracking Number: ICC1900362, previous reviewer: Christopher Brown). The application was effectively CR'd as the facility was out of compliance. In this resubmission, the applicant has changed the facility and now a CDRH consult is requested (Device remains the same compared to the previous submission).

The lead reviewer notes i) NDA 213224 was approved in 2020 and rescinded in 2021. ii) The consult ICC1900362 assessed the finished combination product manufacturer, (b) (4)

2. DEVICE DESCRIPTION

(b) (4)

Octreotide Acetate Injection, 2.5 mg/mL, is filled in 3 mL colorless USP type (b) (4) glass cartridges with 10 mm (b) (4) rubber plunger stopper and (b) (4) seal ((b) (4)). One filled and sealed cartridge of Octreotide Acetate Injection, 2.5 mg/mL, packed in one transparent cartridge holder and assembled with the help of blue body subassembly (dark blue button and white dose set knob) and (b) (4) blue cap for pen injector.

3. Review

Device Constituent Parts of the Combination Product were approved on 1/14/2020 (ICCR SharePoint Tracking Number: CCR2019-04781, ICCR CTS Tracking Number: ICC1900319, previous reviewer: Peter Petrochenko).

This consult focuses on evaluation if there are any changes to the functional testing specifications of finished combination product, container closure system, batch analysis and stability in the resubmission.

- Specification

The sponsor stated that release specification of Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL at proposed alternate drug product manufacturing site, Stelis are same as existing specifications of (b) (4) (b) (4) except minor change to break loose and glide force as mentioned table 3.2.P.5:1.

The lead reviewer verified the functional testing specifications at the proposed new site in sequence 0104 and at the existing site in sequence 0019, i.e., delivered dose accuracy and average activation (injection) force, are the same as shown as follows.

- Specification at proposed alternate drug product manufacturing site, Stelis provided in sequence 0104 received on 2024-03-29.

Stelis Biopharma Ltd

PRODUCT SPECIFICATION

Product Name: OCTREOTIDE ACETATE INJECTION 2500 mcg/ml 2.8 ml Pen Disposable Single Patient Use Prefilled Pens. [1'S] [SUN]					
Product code	:	**2000001620**	**Page**	:	3 OF 7
Specification No.	:	(b) (4)	**Version**	:	**3.0**

14.	Delivered Dose Accuracy (**)	Dose(mcg) = 50, Dose volume = 0.02 mL ± (b) (4) mL, K(actual) = Pass if K(actual) greater than equal to (b) (4) Dose(mcg) = 100, Dose volume = 0.04 mL ± (b) (4) mL, K(actual) = Pass if K(actual) greater than equal to (b) (4) Dose(mcg) = 200, Dose volume = 0.08 mL ± (b) (4) mL, K(actual) = Pass if K(actual) greater than equal to (b) (4)	IH
15.	Average Activation (Injection) Force Test	Average activation (injection) force shall be less than (b) (4) N for each pen injector. (b) (4)	IH

- existing specifications at [redacted] (b) (4) in sequence 0019 received on 2020-01-21.

[redacted] (b) (4)

The release specification of the functional testing of finished combination product is the same as the shelf-life specification in section 3.2.P.5.

Updates:

On June 12, 2024, CDER CMC sent the following IR to the sponsor:

- In the finished drug product release and stability specifications, for the Delivered Dose Accuracy test, you have included "K (actual) = Pass if K (actual) greater than equal to [redacted] (b) (4)" as the limit for each dose. In addition, we ask you to include an upper and lower limit for the actual amount (mcg) of the active ingredient present in the delivered dose. In the calculation for delivered dose (mcg), actual assay value of the injection solution and actual dispensed volume of the sample should be taken into consideration. Also, provide a

comparison of the results obtained for the drug product batches manufactured at [redacted] with those of the Stelis Biopharma Limited batches.

In the 6/21/2024 response in sequence 0108, the sponsor updated the release and stability specifications in 3.2.P.5.1 to include actual amount of dose in mcg for each dose highlighted in yellow and provided the delivered dose accuracy comparison between the existing and proposed specifications in Table 12.

Table 1: Existing and proposed specifications for delivered dose accuracy

Test	Existing specifications	Proposed specifications
Delivered Dose Accuracy (Release)	Dose (µg)=50, Dose volume=0.02 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Dose(µg)=100, Dose volume=0.04 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Dose(µg)=200, Dose volume=0.08 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted]	Dose (µg)=50, Dose volume=0.02 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Actual amount of dose in µg = 50 ± [redacted]µg Dose(µg)=100, Dose volume=0.04 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Actual amount of dose in µg = 100 ± [redacted]µg Dose(µg)=200, Dose volume=0.08 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Actual amount of dose in µg = 200 ± [redacted]µg
Delivered Dose Accuracy (Stability)	Dose (µg)=50 Dose volume=0.02mL ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Dose (µg)=100 Dose volume=0.04 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Dose (µg)=200 Dose volume=0.08mL ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted]	Dose (µg)=50 Dose volume=0.02 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Actual amount of dose in µg = 50 ± [redacted]µg Dose (µg)=100 Dose volume=0.04 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Actual amount of dose in µg = 100 ± [redacted] µg Dose (µg)=200 Dose volume=0.08 ± [redacted]mL, K(actual) = Pass if K(actual) greater than equal to [redacted] Actual amount of dose in µg = 200 ± [redacted]µg

The sponsor also provided comparative summary of actual amount of the drug delivered from Octreotide Acetate Injection-2.5 mg/ml, 2.8 ml in Table 2, and individual dose accuracy data for each dose of each lot in Tables 3 – 26.

Table 2: Comparative summary of actual amount of the drug delivered from Octreotide Acetate Injection-2.5 mg/ml, 2.8 ml PEN

	[redacted]									Stelis Biopharma Ltd, Bangalore								
Stage	[redacted]									B. No. 7000198			B. No. 7000199			B. No. 7000201		
	0M			0M			0M			0M			0M			0M		
	50 µg	100 µg	200 µg	50 µg	100 µg	200 µg	50 µg	100 µg	200 µg	50 µg	100 µg	200 µg	50 µg	100 µg	200 µg	50 µg	100 µg	200 µg
Limit	[redacted]																	
Min																		
Max																		
Mean	[redacted]									53.91	104.04	205.03	54.73	105.48	205.57	55.34	106.05	208.12
Stage	1M 25°C/60% RH			1M 25°C/60% RH			1M 25°C/60% RH			1M 25°C/60% RH			1M 25°C/60% RH			1M 25°C/60% RH		
Min	[redacted]																	
Max																		
Mean	[redacted]									54.04	103.89	201.73	56.34	106.89	206.20	59.42	109.76	209.58
Stage	3M 25°C/60% RH			3M 25°C/60% RH			3M 25°C/60% RH			3M 25°C/60% RH			3M 25°C/60% RH			3M 25°C/60% RH		
Min	[redacted]																	
Max																		
Mean	[redacted]									56.96	106.09	206.77	54.68	104.02	205.45	53.22	104.10	205.63
Stage	3M 2-8°C			3M 2-8°C			3M 2-8°C			3M 2-8°C			3M 2-8°C			3M 2-8°C		
Min	[redacted]																	
Max																		
Mean	[redacted]									55.09	105.86	207.64	56.51	107.12	207.30	55.03	106.41	208.17

Based on the summarised data, actual amount of dose delivered of exhibit batches manufactured at [redacted] and Stelis Biopharma are complying to proposed specifications for each dose of 50 µg, 100 µg and 200 µg.

Actual amount of dose delivered of exhibit batches manufactured at [redacted] and Stelis Biopharma met the proposed specifications for each dose of 50 µg, 100 µg and 200 µg.

CDER CMC summarized the observed minimum and maximum delivered dose (mcg) as follows and recommended tightening the specification of assay from [redacted]% - [redacted]% to 95% - 105% LC and recommended the specification of each target dose as shown below.

Dose Accuracy Results

		Observed values, mcg	
Dose setting, mcg	Proposed acceptance Range, mcg	Min	Max
50	[redacted]		
100			
200			

Assay	[redacted]% to [redacted]% LC
Target Dose	Individual Recommendation
50mcg	[redacted] mcg ([redacted]% LC)
100 mcg	[redacted] mcg ([redacted]% LC)
200mcg	[redacted] mcg ([redacted]% LC)

CDER CMC also discussed with CDRH if the delivered dose volume could be tightened to better control the drug delivery. We summarized the minimum and maximum drug delivered as follows,

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The observed range of drug delivered volumes are well within the proposed specifications for each dose as shown below. It seems that there is some room to tighten the proposed specifications in volume to align with CDER's proposal to tighten the individual specification.

Dose (µg)	Proposed Specifications (mL)	Observed Volume (mL)		Converted Tight Specification based on CDER's recommendation (mL)	
		min	max	min	Max
50	[redacted]				
100					
200					

CDRH issued the information request (IR) #1 along with CDER (IR#2) on 07/15/2024.

> IR #1- CDRH: The proposed dose volume accuracy specification is too wide, which does not comply with ISO 11608-1:2022. Please tighten the dose volume accuracy specification to meet both clinical acceptance and ISO 11608-1:2022 requirement.
>
> IR #2 - CDER: Based on the drug product pre-filled pen lot release and stability data provided, we recommend you tighten the proposed release and shelf-life acceptance criteria in the specification for the assay to [redacted]% to [redacted]% LC and the actual amount of dose in mcg under delivered dose accuracy test as suggested below:
>
> - For target delivery dose 50 mcg: [redacted] mcg to [redacted] mcg ([redacted]% to [redacted]% LC)
> - For target delivery dose 100 mcg: [redacted] mcg to [redacted] mcg ([redacted]% to [redacted]% LC)
> - For target delivery dose 200 mcg: [redacted] mcg to [redacted] mcg ([redacted]% to [redacted]% LC)

In sequence 0111 dated 7/16/2024, the sponsor noted that Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL prefilled Pen is variable dose pen having a minimum dialing resolution (RD) of [redacted] ml. Therefore, they calculated the transition point, P_T, per ISO 11608-1:2022 Rule 1.

> Rule 1: Absolute error, α, expressed in millilitres (ml), is equal to the RD (the minimum dialling resolution) of a variable dose NIS and is [redacted] ml for a fixed dose NIS. Absolute error is used to define the upper specification limit, USL, and lower specification limit, LSL, when Vset is equal to or below the P_T.
>
> Rule 2: Relative error, β, is equal to 5 % of Vset and is used to calculate the dose accuracy USL and LSL when Vset is above the PT.
>
> P_T is the volume (expressed in ml) at which the absolute error is equal to 5 % of Vset and is calculated using:
>
> P_T = (100 % x α) /5% = (100% x [redacted]ml)/5% = [redacted] ml.

The Vmin, Vmid, and Vmax doses for the Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Prefilled Pen are [redacted] ml, [redacted] ml, and [redacted] ml respectively. Each of the doses are less than calculated transition point, P_T. According to ISO 11608-1:2022, section no. 7.4.2.1, upper and lower specifications limit are provided in below Table 1:

> If Vset ≤ P_T, then:
> $V_{USL} = V_{set} + \alpha$
> $V_{USL} = V_{set} - \alpha$

Table 1: Upper and lower specification limit for delivered dose accuracy (ml)

Delivered dose	Lower specification limit ($V_{set} - \alpha$)	Upper specification limit ($V_{set} + \alpha$)
0.02 ml	(b) (4)	
0.04 ml		
0.08 ml		

It appears that the proposed specification for delivered dose volume accuracy is in accordance with ISO 11608-1:2022. Meanwhile, the sponsor accepted to tighten specification limit for 'Assay of Octreotide Acetate eq. to Octreotide' to (b) (4)% -(b) (4)% LC for release and shelf life. They provided the following calculations to demonstrate that the proposed specifications are already tightened and within the theoretical specifications (when amount of drug in delivered dose is calculated considering assay of octreotide (as octreotide acetate) as (b) (4)%-(b) (4)%). CDER defers CDER to review the tighter individual specifications of delivered dose accuracy in mcg.

	Considering 100% Assay for octreotide (as octreotide acetate)		Considering (b) (4)% Assay for octreotide (as octreotide acetate)	Considering (b) (4)% Assay for octreotide (as octreotide acetate)
Delivered dose	Proposed Lower specification limit ($V_{set} - \alpha$)	Proposed Upper specification limit ($V_{set} + \alpha$)	Lower specification limit	Upper specification limit
50 µg	(b) (4)			
100 µg				
200 µg				

The sponsor noted that the existing method for break loose and glide force submitted in the original application was in accordance with ISO 11608-3:2000 in which filled cartridges were used in analysis. This ISO 11608-3:2000 has been withdrawn hence current ISO 11608-3:2012 has been adopted and as per this ISO, break loose and glide force analysis has been performed on emptied cartridge. CDRH communicated this change to CDER during the meeting on 5/22/2024 and defers the assessment for minor changes to the testing methods of break loose and glide force to CDER.

- Container closure system

In section 3.2.P.7, the sponsor stated container closure system at existing manufacturing site, (b) (4) and at proposed alternate drug product manufacturing site, Stelis are the same except updating (b) (4) of glass cartridge. The class cartridge is primary container. CDRH defers the change to glass cartridge to CDER.

- Batch analysis

In section 3.2.P.5.4, the results of delivered dose accuracy and average activation (injection) force of three registration batches met their specifications.

- Stability

In the resubmission, the stability testing data are available up to 3 months. In section 3.2.P.8.3, the results of three registration batches met the specifications of delivered dose accuracy and average activation (injection) force.

Conclusion: there are no changes to the specifications of delivered dose volume accuracy and average activation (injection) force, and container closure system except updating (b) (4) of glass cartridge. Upon CDER's

requests, the sponsor added delivered dose accuracy in mcg in the specification, and provided a single regulatory finished drug product specification table that includes both the release and stability tests and acceptance criteria. The batch analysis and stability testing results showed that the delivered dose accuracy and average activation (injection) force met their specifications at release and during stability study up to 3 months. CDRH has no further information request from the sponsor.

<<END OF REVIEW>>

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/s/

OLUWAFUNMIKE O AJOMALE
08/20/2024 08:45:17 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	5/24/2024		
To:	OLUWAFUNMIKE AJOMALE		
Requesting Center/Office	CDER/OND	**Clinical Review Division**	Choose an item.
From	Bingjie Liang OPEQ/OHT3/DHT3C		
Through (Team)	OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director, Injection Devices Team OPEQ/OHT3/DHT3C		
Subject	ICCR: 00985632 ICC: 2400435 Submission: NDA213224 Sponsor: Sun Pharmaceutical Industries Limited Drug/Biologic/Indications for Use: octreotide acetate injection for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors *Delivery Devices (e.g., autoinjector, non-insulin delivering infusion pump, nasal spray devices)		
Recommendation	Device constituent parts of Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL were approved on 1/14/2020 (ICC1900319). The sponsor proposed an additional drug product manufacturing site (Stelis Biopharma Limited – Bengaluru) in the resubmission. The sponsor proposed the same release specification for the functional testing of the finished combination product, and there are no changes to container closure system except updating (b) (4) of glass cartridge. The functional testing of the finished combination product, i.e., delivered dose accuracy and average activation (injection) force, met their specifications at release and during stability study up to 3 months. The stability at the accelerated condition (6 months) and long-term condition (36 months) are on-going. CDRH has no further information request from the sponsor. **NOTE to CDER**: In section 3.2.P.5.1, the sponsor noted that the emptied cartridge is used for break-loose force and glide force tests because current ISO 11608-3:2012 has been adopted. CDRH communicated this change to CDER during the NDA-213224-ORIG-1-RESUB-106, CMC Touch Point Meeting #1 on 5/22/2024, and defers the assessment for the testing methods and specifications of break-loose force and glide force tests to CDER.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Bingjie Liang -S Digitally signed by Bingjie Liang -S Date: 2024.05.24 15:05:56 -04'00'	Shruti N. Mistry -S 2024.05.24 15:09:50 -04'00'	

1. PURPOSE

CDER is requesting review of the subject combination product that includes a pen injector. CDER sent the following consult:

This is a resubmission for NDA 213224 for Sun Pharmaceutical Industries Limited.

A previous consult was entered and deemed approvable – with conditions (ICCR SharePoint Tracking Number: ICC2019-04870, ICCR CTS Tracking Number: ICC1900362, previous reviewer: Christopher Brown). The application was effectively CR'd as the facility was out of compliance. In this resubmission, the applicant has changed the facility and now a CDRH consult is requested (Device remains the same compared to the previous submission).

The lead reviewer notes i) NDA 213224 was approved in 2020 and rescinded in 2021. ii) The consult ICC1900362 assessed the finished combination product manufacturer, (b) (4)

2. DEVICE DESCRIPTION

(b) (4)

Octreotide Acetate Injection, 2.5 mg/mL, is filled in 3 mL colorless USP type (b) (4) glass cartridges with 10 mm (b) (4) rubber plunger stopper and (b) (4) seal ((b) (4)). One filled and sealed cartridge of Octreotide Acetate Injection, 2.5 mg/mL, packed in one transparent cartridge holder and assembled with the help of blue body subassembly (dark blue button and white dose set knob) and (b) (4) blue cap for pen injector.

3. Review

Device Constituent Parts of the Combination Product were approved on 1/14/2020 (ICCR SharePoint Tracking Number: CCR2019-04781, ICCR CTS Tracking Number: ICC1900319, previous reviewer: Peter Petrochenko).

This consult focuses on evaluation if there are any changes to the functional testing specifications of finished combination product, container closure system, batch analysis and stability in the resubmission.

- Specification

The sponsor stated that release specification of Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL at proposed alternate drug product manufacturing site, Stelis are same as existing specifications of (b) (4) (b) (4) except minor change to break loose and glide force as mentioned table 3.2.P.5:1.

The lead reviewer verified the functional testing specifications at the proposed new site in sequence 0104 and at the existing site in sequence 0019, i.e., delivered dose accuracy and average activation (injection) force, are the same as shown as follows.

- Specification at proposed alternate drug product manufacturing site, Stelis provided in sequence 0104 received on 2024-03-29.

Stelis Biopharma Ltd

PRODUCT SPECIFICATION

Product Name: OCTREOTIDE ACETATE INJECTION 2500 mcg/ml 2.8 ml Pen Disposable Single Patient Use Prefilled Pens. [1'S] [SUN]					
Product code	:	**2000001620**	**Page**	:	3 OF 7
Specification No.	:	(b) (4)	**Version**	:	**3.0**

14.	Delivered Dose Accuracy (**)	Dose(mcg) = 50, Dose volume = 0.02 mL ± (b) (4) mL, K(actual) = Pass if K(actual) greater than equal to (b) (4) Dose(mcg) = 100, Dose volume = 0.04 mL ± (b) (4) mL, K(actual) = Pass if K(actual) greater than equal to (b) (4) Dose(mcg) = 200, Dose volume = 0.08 mL ± (b) (4) mL, K(actual) = Pass if K(actual) greater than equal to (b) (4)	IH
15.	Average Activation (Injection) Force Test	Average activation (injection) force shall be less than (b) (4) N for each pen injector. (b) (4)	IH

- existing specifications at (b) (4) n sequence 0019 received on 2020-01-21.

(b) (4)

The release specification of the functional testing of finished combination product is the same as the shelf-life specification in section 3.2.P.5.

The sponsor noted that the existing method for break loose and glide force submitted in the original application was in accordance with ISO 11608-3:2000 in which filled cartridges were used in analysis. This ISO 11608-3:2000 has been withdrawn hence current ISO 11608-3:2012 has been adopted and as per this ISO, break loose and glide force analysis has been performed on emptied cartridge. CDRH communicated this change to CDER during the meeting on 5/22/2024 and defers the assessment for minor changes to the testing methods of break loose and glide force to CDER.

- Container closure system

In section 3.2.P.7, the sponsor stated container closure system at existing manufacturing site, (b) (4) and at proposed alternate drug product manufacturing site, Stelis are the same except updating (b) (4) of glass cartridge. The (b) (4) cartridge is primary container. CDRH defers the change to glass cartridge to CDER.

- Batch analysis

In section 3.2.P.5.4, the results of delivered dose accuracy and average activation (injection) force of three registration batches met their specifications.

- Stability

In the resubmission, the stability testing data are available up to 3 months. In section 3.2.P.8.3, the results of three registration batches met the specifications of delivered dose accuracy and average activation (injection) force.

Conclusion: there are no changes to the specifications of delivered dose accuracy and average activation (injection) force, and container closure system except updating (b) (4) of glass cartridge. The batch analysis and stability testing results showed that the delivered dose accuracy and average activation (injection) force met their specifications at release and during stability study up to 3 months. CDRH has no further information request from the sponsor.

<<END OF REVIEW>>

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/s/

OLUWAFUNMIKE O AJOMALE
05/24/2024 03:24:41 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 4, 2024

FROM: Geanina Roman-Popoveniuc, MD Medical Officer, Division of General Endocrinology (DGE)

THROUGH: Marina Zemskova, MD, Deputy Director for Safety, DGE

TO: File (NDAs 19667, 21008, 22074, 215395, 203255, 200677, 208232)

SUBJECT: This memorandum is a review of the safety signal of Pancreatic Exocrine Insufficiency (PEI) associated with somatostatin analogs (SAs), including recommendations proposed by the Office of Surveillance and Epidemiology (OSE), Division of Oncology 2 (DO2) and Division of Gastroenterology (DG) for safety labeling changes for SAs pertaining to PEI

Background and Regulatory History:

Somatostatin analogs (SAs, also known as somatostatin receptor ligands) are indicated for the treatment of acromegaly, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), symptoms (i.e., severe diarrhea/flushing) associated with metastatic carcinoid syndrome, diarrhea associated with vasoactive intestinal peptide tumors (VIPomas), and Cushing's disease. SAs are synthetic analogues of endogenous somatostatin. There are eight currently approved SAs in the U.S., namely octreotide acetate (Sandostatin, NDA019667; Sandostatin LAR, NDA 021008; and Mycapssa, NDA 208232), lanreotide acetate (Somatuline Depot, NDA 022074 and Lanreotide Acetate, NDA 215395), and pasireotide diaspartate/pamoate (Signifor, NDA 200677 and Signifor LAR, NDA 203255, respectively) (refer to Table 1, Appendix, for a summary of approved doses and indications of each product).

In July 2021, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) identified the risk of PEI associated with octreotide products in patients with neuroendocrine tumors (NETs) and subsequently recommended its inclusion in the European Union (EU) Summary of Product Characteristics (SmPC) Section 4.4 "Special warnings and precautions for use" for octreotide products to alert prescribers about the risk of PEI in patients with GEP-NETs, as follows:

"Pancreatic function
Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving octreotide therapy for gastroenteropancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating, and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients."

The signal was triggered by a medical literature report describing a seven-month and three-week-old male who developed PEI, vitamin K deficiency and cutaneous hemorrhagic syndrome after receiving octreotide [1], which was followed by a review of the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) database that identified 21 spontaneous cases of PEI occurring after octreotide treatment in patients with NETs.

Pancreatic exocrine insufficiency (PEI) is defined as reduced or inappropriate secretion of pancreatic enzymes (i.e., pancreatic lipase, amylase) which are required to maintain normal digestion, resulting in malabsorption of dietary fats and other nutrients such as lipid soluble vitamins (vitamins A, D, E and K, and B12). Clinical symptoms related to PEI include steatorrhea, loose stools or diarrhea, flatulence, abdominal discomfort, weight loss, and fatigue. The most common etiologies of PEI include chronic, or acute pancreatitis, pancreatic cancer, cystic fibrosis, as well as other extra-pancreatic disorders such as type 1 diabetes, inflammatory bowel disease, celiac disease, gastrointestinal surgery, HIV syndrome, Sjögren syndrome, and tobacco and alcohol use. It should be noted that the underlying etiologies of PEI, such as malabsorption conditions (celiac disease, Chron's disease, short gut syndrome), infectious (giardiasis), liver diseases (cholangitis, liver cirrhosis, gallstones), or alcohol use, manifest similar symptoms as PEI: i.e., steatorrhea, fat malabsorption, and abdominal pain may be due to the other . Therefore, the diagnosis of PEI is challenging and should be based not only on symptoms, but also on other testing, such as measurement of fecal elastase (decreased) and/or imaging (CT scan, ultrasound, magnetic resonance cholangiopancreatography). The main treatment of PEI is Pancreatic Enzyme Replacement Therapy (PERT).[2]

SAs have inhibitory actions on digestive enzymes and bile acid secretions (i.e., pancreatic polypeptide, lipase, amylase, gastrin, and cholecystokinin), resulting in alteration of intestinal motility, digestion and absorption of dietary fats.[3] Therefore, PEI and associated symptoms of steatorrhea and fat malabsorption are expected events with SAs use based on the drug class mechanism of action. In fact, malabsorption of dietary fats is a labeled risk associated with octreotide products (i.e., Sandostatin s.c., Sandostatin LAR, and Mycapssa, Section 5). Gastrointestinal symptoms of diarrhea, flatulence, loose stools, abdominal pain and nausea are listed adverse reactions for all octreotide, lanreotide and pasireotide products. Additionally, steatorrhea is a labeled adverse reaction in the Postmarketing experience section of the lanreotide products label (i.e., Somatuline Depot, Lanreotide Acetate). However, PEI itself is

[1] Ros-Perez P, et al. Octreotide-related exocrine pancreatic insufficiency in congenital hyperinsulinism. J Pediatr Endocrinol Metab 2020; 33: 947-950
[2] Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol. 2013; 19:7258-7266.
[3] Khan MS, et al. Differential diagnosis of diarrhea in patients with neuroendocrine tumours: A systematic review. World J Gastroenterol. 2020; 26: 4537-4556

not labeled adverse reaction to date. Patients with uncontrolled NET manifest similar symptoms as seen in PEI (i.e., steatorrhea, flatulence, nausea). Since octreotide and lanreotide products are indicated for the treatment of diarrhea associated with NET, it is difficult to differentiate whether these symptoms are due to the drug itself or poor control of the underlying disease in patients with NET.

Based on the EMA PRAC report and EU SmPC octreotide label, the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE), in conjunction with Division of General Endocrinology (DGE), started to investigate the signal of PEI associated with the use SAs.

On May 31, 2022, DGE and DPV issued information requests (IRs) to the NDA application holders of SAs to submit a comprehensive assessment of PEI cases associated with the use of their product from clinical trials, postmarketing experiences, and the medical literature. Sponsors of the SA products reviewed their safety databases and responded by providing detailed information and summaries of PEI cases (summarized in Table 2 in the Appendix).

On August 3, 2022, DPV opened a newly identified safety signal (NISS, ID #1004917) and moved it to the evaluation phase after conferring with DGE.

On June 13, 2022, DGE consulted Division of Oncology 2 (DO2) to provide their assessment regarding a possible causal relationship association between octreotide-containing products and risk of Pancreatic Exocrine Insufficient (PEI) in patients with gastroenteropancreatic- neuroendocrine tumors (GEP-NETs) based on the data submitted.

On March 20, 2023, DGE consulted Division of Gastroenterology (DG) requesting their input regarding the proposal for labeling of PEI in the Postmarketing Experience section of the US Prescribing Information (PI) for octreotide and lanreotide products, as well as other PEI-related revisions for the USPI. DGE also requested input regarding the labeling language to best differentiate the symptoms of PEI from those related to the underlying disease (i.e., GEP-NET) and proposed mitigation strategies.

Of note, on January 29, 2023, Ipsen Pharm submitted a labeling supplement proposing to add PEI to multiple sections of the Somatuline Depot USPI, due to reasonable causal evidence that the relationship between exposure to lanreotide and development of PEI (refer to Table 2, Appendix for details):

(b) (4)

(b) (4)

Section 6. ADVERSE REACTIONS, Postmarketing Experience:

"Gastrointestinal disorders: Pancreatic exocrine insufficiency"

Following below is a summary of the DGE clinical reviewer assessment of the data submitted by the Sponsors in response to the Division's information request, as well as a summary of OSE, DO2 and DG's findings and recommendations.

- **Medical Officer's Review of the Sponsors' data included in the responses to the Information Request Letters issued on May 31, 2022**

Somatuline Depot (lanreotide), NDA 22074, Ipsen Bioscience

On June 30, 2022, the Sponsor submitted data regarding PEI from the global safety database search cumulative until May 31, 2022. The search identified 52 cases of PEI, of which 29 cases were considered relevant for review. The remaining 23 cases were not evaluated further because they either described pre-existing PEI that did not worsen on treatment with lanreotide, or the case did not meet criteria for PEI. This Medical Officer reviewed all 29 cases. Fifteen of the 29 cases lacked sufficient information (i.e., time to onset, test results, medical history, concomitant medications, treatment and/or outcome) to conduct an informed assessment and conclusion on a causality relationship between the drug(s) and event(s), and as such, these cases are not discussed below. The remaining 14 cases for which sufficient information was provided were further reviewed in detail by this clinical reviewer (refer to Table 3, Appendix) and a summary of the findings is provided below.

The indication for lanreotide therapy in these 14 cases were: NET (10 cases), acromegaly (2 cases), carcinoid syndrome (1 case) and unknown in one case. The dose of lanreotide was 120 mg monthly in 9 cases, 90 mg monthly in 3 cases and 60 mg monthly in 2 cases. All 14 cases had one or more confounding factors complicating the assessment of causality, with most common being represented by underlying NET with pancreatic lesions in 11 cases (including the case of carcinoid syndrome), previous use of octreotide formulation(s) in 5 cases, diabetes mellitus that may affect exocrine pancreatic function (4 cases) and pancreatic surgery in 4 cases. Since the mechanistic rationale of SA-induced PEI is related to functional reversible inhibition of pancreatic enzymes secretion, a shorter duration of event onset (i.e., days- months) may be considered a positive temporal association, while a longer duration of event onset (i.e., years) would suggest more likely an organic, alternative etiology. In 9 cases where a temporal relationship was

reported, the event occurred within ≤ 12 months in 7 cases, while in the other 2 cases, the event was reported after > 2 years and 5 years, respectively. While de-challenge information was not available in the majority of cases, 2 cases reported a positive de-challenge results. It should be noted that only one of the 14 cases had a confirmatory stool test positive for PEI, while the remaining 13 subjects did not have either the stool test/imaging studies performed, or results were not reported (one case only). However, 10 out of the 14 subjects were treated with PERT following symptoms onset, suggestive of suspected exocrine pancreatic insufficiency.

Because PEI-related symptoms in subjects with NET may be due to the drug itself or to the poor control of the disease, it is complicated to establish the relationship between the drug and the event in this population. However, PEI in acromegalic patients, who typically do not manifest gastrointestinal symptoms due to their underlying disease, in general, is more likely to be related to the drug. Therefore, this Medical Officer reviewed PEI cases reported in acromegalic patients in details in order to establish the relationship between the drug and the event of PEI. Although strong confounding factors, such as NET, were not presented in these two patients, both cases of acromegaly were confounded by diabetes (1 case) and by previous octreotide use (1 case). The cases of PEI in subjects that occurred in the two subjects with acromegaly are briefly reviewed below.

(1) Case 2016-11484 is a solicited case received from a physician in Japan regarding a patient enrolled in a drug use special survey. The subject was a 60 years old female with history of acromegaly, with past medical history of type 2 diabetes, diabetic nephropathy stage II, hypertension, hypercholesterolemia and hypophysectomy. Concomitant medications included rosuvastatin calcium, azelnidipine and Humulin 3/7 (human insulin). Previous medications included cabergoline. On (b) (6) (b) (6), the subject started Somatuline Depot 90 mg subcutaneous every 4 weeks for treatment of acromegaly. Laboratory evaluation before Somatuline Depot initiation showed total protein was 7.3 g/dL (normal range 6.7-8.3) and glycated hemoglobin (HbA1C) 7.9%. In (b) (6) (unspecified day), the patient experienced worsening hyperglycemia. No corrective treatment was provided. On (b) (6), 28 days after initiation of Somatuline Depot, the patient reported whitish stools. On the same day, HbA1C levels was 8.3% and blood glucose was elevated at 251 mg/d (normal range not provided), while total protein was 7.2 g/dL (normal range 6.7-8.3). On (b) (6), HbA1C was noted to be further elevated at 9.6% and total protein was 6.9 g/dL (normal range 6.7-8.3). On (b) (6), the patient received her last Somatuline Depot injection. On (b) (6), 183 days after starting treatment with Somatuline Depot, and 30 days after drug last dose, the patient reported soft feces, diarrhea, and fat in stools. The patient also noted weight loss of 2 kg to 48 kg in one month. On the same day, the result of pancreatic function diagnostic test (details of the specific test not provided) was 28.1% (normal range not provided), and pancreatic exocrine hypofunction was suspected by the treating physician. On the same day, HbA1c was reported to be elevated at 9.8% (normal range 6.7-8.3), and total protein was decreased at 6.6 g/dL (normal range 6.7-8.3). The patient was switched to pegvisomant, while insulin dosage was adjusted. On (b) (6) the patient recovered from the event of diarrhea. Laboratory evaluation during the following 3 months ((b) (6)) revealed continuously

elevated HbA1c (range 9.7% - 10%), and normal total protein levels. The outcome of all other events was not reported. The company assessed the event of 'suspected pancreatic exocrine hypofunction' as likely related to the drug.

Clinical reviewer's comments:
This clinical reviewer concurs with company assessment of causality assessment as probably related, in light of positive temporal relationship, positive de-challenge test, and mechanistic rationale i.e., somatostatin physiologically inhibits pancreatic exocrine function). While diabetes is a confounder factor, the event improved (i.e., diarrhea resolved) after discontinuation of Somatuline, despite diabetes control continuing to be poor, suggesting a Somatuline-related adverse reaction. While it is not clear that a diagnosis of PEI was made, as it is unknown what "28% pancreatic function test" represents since the normal ranges were not reported, the clinical symptoms of diarrhea, fatty stools and decreased total proteins along with physician assessment of "suspected pancreatic exocrine hypofunction" are all indicative of PEI.

(2) Case 2021-20369 is a 78 year-old female with acromegaly and past history of trans-sphenoidal hypophysectomy, hypertension, panhypopituitarism, and microadenoma. Concomitant medications included cabergoline, hydrocortisone, esomeprazole, levothyroxine, lisinopril, denosumab, risedronate, calcium, vitamin B complex, ascorbic acid, and ergocalciferol. The patient started therapy with Somatuline Depot 120 mg every 4 weeks (unknown date and indication). The report also indicates patient started therapy with Sandostatin LAR 30 mg every 3 weeks (unknown date) for the treatment of acromegaly. On an unspecified date, the patient was diagnosed with fat malabsorption, pancreatic insufficiency, cholelithiasis, diarrhea and lack of efficacy for the medication. However, there were no reported positive diagnostic tests performed, such as fecal test, or imaging studies. The patient underwent treatment with pancrelipase and cholecystectomy. Action taken with lanreotide was not reported.

Clinical reviewer's comments: In the absence information regarding timing of events, limited information regarding confirmatory diagnostic test results, use of octreotide (another somatostatin analog) and presence of cholelithiasis as a risk factor for pancreatitis and subsequent pancreatic insufficiency, which are both, significant confounding factors, a causal assessment between the event of pancreatic insufficiency and Somatuline Depot cannot be performed.

In summary, while confounding factors were present in all cases of PEI and Somatuline Depot, the clinical reviewer deemed that a causal relationship was as probable or possible in 6/14 cases (one case of acromegaly, 2016-11484 and 5 cases of NET, 2011-2029, 2012-3952, 2013-5816, 2018-15733, 2019-00074, 2021-20369, Table 3). One of these 6 subjects (2011-2029 with NET with metastasis to liver) was reported from US, all others were non-US cases. However, it is important to note that only one of these 6 cases had a possible positive confirmatory stool test (Case 2016-11484, "pancreatic function test" was 28.1%, although the normal

reference range was not provided), while the remaining 5 subjects did not have either the stool test/imaging studies performed, or if performed, results were not reported (one case only). In the remaining 8/14 cases, the presence of more plausible alternative etiologies makes the causality relationship between the event and the drug less likely, although it cannot be ruled out completely (due to temporal relationship).

Lanreotide Acetate, NDA 215395, InvaGen

In their response to the Information Request letter from July 5, 2022, the Sponsor stated that no case reports of pancreatic insufficiency associated with lanreotide acetate were identified from the global safety database search cumulative until May 31, 2022.

Sandostatin/Sandostatin LAR, NDAs 19667/21008, Novartis

On July 15, 2022, the Applicant submitted data regarding PEI cases associated with Sandostatin, or Sandostatin LAR use. The Sponsor identified a total of 30 cases of PEI: 4 cases from 16 clinical trials, one from compassionate use program, and 25 cases from the global safety database search cumulative until May 31, 2022.

The 4 cases from clinical trials, which include more reliable data due to pre-defined and structured safety monitoring and reporting, are briefly described below.

(1) Patient (b) (6) was a 44-year-old female with acromegaly, with past medical history of hypogonadism, hypothyroidism, goiter, diabetes, cholelithiasis and pituitary surgery (in (b) (6)). Patient has been treated with Sandostatin s.c. since (b) (6) (b) (6) (discontinuation date not reported). On (b) (6), the patient started octreotide LAR treatment (dose not reported) in Study CSOM230C2422[4]. The patient was diagnosed with Grade 2 pancreatic insufficiency on Study Day 115 (information regarding the diagnostic tests performed was not provided). On the same day, the patient was given pancreatin. The treatment with study drug was continued. On Study Day 141, the patient completed the core phase of the study with octreotide LAR and continued to extension phase crossing over to treatment with pasireotide LAR. At the time of crossover, the PEI event was not resolved. No further information provided regarding the event outcome once the subject was switched to pasireotide LAR therapy. The event was considered to be related to study drug by the investigator.

Clinical reviewer's comment: While a causal assessment between the event and octreotide LAR is possible in light of positive temporal relationship, and mechanistic rationale (i.e., somatostatin physiologically inhibits pancreatic exocrine function), the

[4] A Phase III, Multicenter, Randomized, Parallel-group Study to Assess the Efficacy and Safety of Double-blind Pasireotide LAR 40 mg and Pasireotide LAR 60 mg Versus Open-label Octreotide LAR or Lanreotide ATG in Patients With Inadequately Controlled Acromegaly (Phase III)

case lacks sufficient information (e.g., information regarding the diagnostic test performed) and is also confounded by other factors (e.g., history of diabetes, cholelithiasis) to adequately establish a positive causality.

(2) Patient (b) (6) was a 38-year-old male with carcinoid tumor of the lung, with past medical of hypercholesterolemia, hypocalcemia and bone pain. The patient was treated with fluorouracil and dacarbazine for carcinoid tumor. The subject started treatment with everolimus and octreotide LAR in Study CRAD001C2325[5] due to disease progression with metastases to lung, liver and left adrenal cortex. On Study day 57, the investigator reported Grade 1 pancreatic insufficiency. The case report did not include information regarding the confirmatory diagnostic tests performed. No action was taken for study drugs (the patient continued treatment with everolimus and octreotide LAR). The patient was treated with pancreatin from Study day 89 to Study day 229 due to pancreatic insufficiency. The patient received the last dose of everolimus on Study day 220 and discontinued the drug due to Grade 4 jaundice and Grade 4 bone pain. Treatment with octreotide LAR was discontinued on Study day 225. On Study day 285, the patient died due to disease progression. The event of PEI was not resolved at the end of safety follow up. The event was not considered to be related to study treatment by the investigator.

Clinical reviewer's comment: A casual association between PEI and octreotide LAR cannot be ruled out completely given positive temporal relationship and known mechanistic rationale. However, without information regarding confirmatory tests for PEI and the presence of confounding factors such as underlying metastatic disease (although pancreatic involvement was not reported) that may be associated with pancreatitis, the concomitant medication everolimus, which may cause pancreatitis, diabetes and hepatobiliary disorders (cholangitis, cholestasis, a causal relationship is less likely to be related to study drug, but more likely due to the progression of cancer/use of everolimus.

(3) Patient (b) (6) was an 80-year-old female diagnosed with a well differentiated neuroendocrine carcinoma of the small intestine treated with hemicolectomy and a partial ileum resection, followed by chemotherapy including 5-fluorouracil, bevacizumab, and irinotecan. Prior medical treatment for carcinoid included long-acting octreotide ((b) (6) (b) (6)). The patient was then enrolled in study CSOM230C2303[6] when the neuroendocrine carcinoma metastasized to liver, pancreas, and bone (thoracic vertebrae, sacrum, pelvis). The patient experienced bile duct obstruction (Grade 4) as well as worsening of cholestasis (Grade 4) and pancreatitis (Grade 4) from Day -22 to Day -16, and the first dose of study medication

[5] A Randomized, Double-blind Placebo-controlled, Multicenter Phase III Study in Patients With Advanced Carcinoid Tumor Receiving Octreotide Depot and Everolimus 10 mg/Day or Octreotide Depot and Placebo (Phase III)

[6] A Multicenter, Randomized, Blinded Efficacy and Safety Study of Pasireotide LAR vs Octreotide LAR in Patients With Metastatic Carcinoid Tumors Whose Disease-related Symptoms Are Inadequately Controlled by Somatostatin Analogues (Phase III)

(octreotide LAR) was subsequently received on [redacted] (Day 1). On Day 71, the investigator reported Grade 4 ALP and GGT increase (levels are not provided) and on Day 84, Grade 3 "increase of diarrhea due to PEI" was reported. The case report did not include information regarding the confirmatory diagnostic tests performed. The patient was treated with pancreatin from Day 84 onwards due to "increased suspected pancreatic insufficiency". The patient discontinued long-acting octreotide due to withdrawal of consent, with the last dose received on Day 84. On Day 85 the patient experienced complications of ductus hepato-choledochal stent dislocation, cholestasis and cholangitis, treated with antibiotic therapy. The events of cholestasis and cholangitis resolved 23 days after the last dose of octreotide. The outcome of the PEI event was not reported. The event of PEI was not considered to be related to study drug by the investigator.

Clinical reviewer's comment: While a casual association between PEI and octreotide cannot be excluded completely, given positive temporal relationship and known mechanistic rationale, the case is confounded by the underlying metastatic disease to the pancreas, as well as the associated comorbidities of hepatobiliary disorders and pancreatitis, which are known risk factors for PEI.

(4) Patient [redacted] was a 71-year-old female with a functionally active, metastasized, locally inoperable neuroendocrine tumor of the ileum with liver metastases diagnosed in 1979. The patient had primary tumor resection in [redacted]. Neither prior antineoplastic therapy nor symptom control therapy was reported. Past medical history included glaucoma, hypertension and atrial fibrillation. Relevant medications included lisinopril, hydrochlorothiazide and clopidogrel. The patient was enrolled in Study CSMS995ADE05[7] and received her first dose of octreotide LAR on [redacted] (Day 1). Grade 2 pancreatic insufficiency was reported on Day 9. The case report did not include information regarding the confirmatory diagnostic tests performed. No action was taken for study drug and the patient continued treatment with long-acting octreotide. The patient was treated with pancreatin from Day 29 onwards due to pancreatic insufficiency. On Day 517, the patient received her last dose of study medication (long-acting octreotide) as per protocol and continued with post-study long-acting octreotide. The event of pancreatic insufficiency was not resolved at the end of safety follow up for the study. The event was considered to be related to study drug by the investigator.

Clinical reviewer's comment: This clinical reviewer concurs with the Investigator's assessment that a causal relationship between the event and the drug cannot be ruled out completely, in light of positive temporal relationship, and mechanistic rationale (i.e., somatostatin physiologically inhibits pancreatic exocrine function). However, the case is confounded by the underlying metastatic disease (although pancreatic involvement was not reported), as well as the concomitant medications

[7] Placebo-controlled prospective randomized study on the antiproliferative efficacy of octreotide in patients with metastasized neuroendocrine tumors of the midgut (PROMID, Phase IIIb)

lisinopril and clopidogrel, which may cause pancreatitis. In addition, the limited/absent information on confirmatory tests for PEI (fecal tests, laboratory findings, imaging results) further complicates the assessment.

Of the 25 cases of PEI identified in the global safety database search, 11 cases lacked sufficient information (i.e., time to onset, test results, medical history, concomitant medications, primary location of NETs, progression of underlying disease, treatment and/or outcome) to conduct an informed assessment of a causality relationship, and as such, these cases were not further reviewed. In one case, the patient developed multi-organ failure following infection and thus the Applicant did not consider PEI to be related to octreotide. The remaining 13 cases, for which sufficient information was provided, were further reviewed in detail by this clinical reviewer (refer to Table 4, Appendix) and are summarized below.

The indications for Sandostatin/Sandostatin LAR therapy in these 13 cases were NET (6 cases), carcinoid syndrome (3 cases), pancreatic cancer (1 case), hepatocellular cancer (1 case) and hypoglycemia (2 cases) (the last 3 conditions are unapproved indications). Six subjects received US formulations while 7 subjects received non-US formulations of the drug. Dosing information was only available in 8 out of 13 cases, with 6 subjects receiving 30 mg (3 subjects-monthly and 3 subjects-unknown regimen), and 2 subjects receiving 80 mg (frequency not specified). Confounding factors were present in all subjects including severe underlying pancreatic conditions [i.e., pancreatic cancer (3 cases), pancreatic surgery/atrophy (3 cases), advanced pancreatic NET (2 cases), pancreatic atrophy (1 case)], or advanced NET (4 cases). Information regarding temporal relationship was present in 10 out of the 13 cases, with event occurring within ≤ 12 months in 5 cases, while in the other 5 cases, the event was reported after 18 months in 2 cases, and after >2 years in thew other 3 cases (29 months, 30 months and 36 months, respectively). While de-challenge information was not available in the majority of cases, 2 cases reported a positive de-challenge test.

In summary, of the 17 cases of PEI (4 cases of PEI identified in clinical trials and the 13 cases of PEI from the global safety database), the clinical reviewer deemed 3 cases from clinical trials to be possibly or probably related to the drug in light of positive temporal relationship and mechanistic rationale (one case of acromegaly (b) (6) and two cases of NET (b) (6)). None of these cases had reported confirmatory diagnostic testing of PEI (i.e., stool test, imaging studies), therefore, it remains unclear whether these were true cases of PEI, or other, milder forms of intestinal malabsorption. In the remaining 14 cases (one from clinical trial and 13 cases from global safety database) a causality assessment could not be determined because the cases were confounded by other significant risk factors (i.e., underlying neoplastic disease with pancreatic involvement, pancreatic surgery), or not sufficient information was provided.

Mycapssa (octreotide acetate) oral capsule, NDA 208232

In their response to the Information Request letter from June 29, 2022, the Sponsor stated that no case reports of pancreatic insufficiency associated with Mycapssa were identified from the global safety database search cumulative until May 31, 2022.

Signifor and Signifor LAR (pasireotide)

Pasireotide is a somatostatin analog indicated for the treatment of Cushing's disease (CD) and acromegaly only. Therefore, a causal association between events of PEI or PEI-like symptoms may be easier to assess, since acromegaly and CD do not manifest with PEI-like gastrointestinal symptoms (e.g., fatty stools, diarrhea, abdominal pain).

Signifor (pasireotide), NDA 200677

The Applicant has not identified any cases of PEI associated with the use of Signifor.

Signifor LAR (pasireotide), NDA 203255

The Sponsor identified five (5) cases from post marketing experience: one (1) case had a SAE of pancreatic failure (case (b) (6)) and 4 cases ((b) (6)) had non-serious AEs of signs and symptoms suggestive of pancreatic insufficiency. The cases are further reviewed below.

(1) Pancreatic failure

Case (b) (6) was a 46-year-old male who received pasireotide LAR for the treatment of acromegaly (unknown start date, unknown dose, unknown route). Significant past medical history included diabetes mellitus, pancreatitis chronic, alcoholism, drug dependence, ex-tobacco user, pancreatic pseudocyst, biliary pseudocyst, ketoacidosis, gastrointestinal disorder. Aside from cannabis, no other concomitant medications were provided. On (b) (6), the patient developed pancreatic insufficiency and was treated with pancreatic extract (Creon). Symptoms of pancreatic insufficiency and diagnostic test were not reported. The patient also developed hepatic steatosis, weight loss and steatorrhea. No additional information was provided with regards to diagnostic evaluation, action taken with study drug, and outcome of the event.

Clinical reviewer's comments: The case lacks sufficient information to allow for evaluation of a potential causal relationship between the event of pancreatic failure and pasireotide, such as time to onset, adequacy of diagnostic tests, action taken with study drug, de-challenge/ rechallenge information. In addition, the case is confounded by many comorbid conditions known to cause pancreatic insufficiency, such as diabetes mellitus, pancreatitis chronic, alcoholism, drug dependence, pancreatic pseudocyst, hepatic steatosis. Therefore, a causality assessment cannot be performed.

Non-serious cases with symptoms potentially related to PEI :

(2) Pancreatic disorder

Case [redacted] (b) (6) was a 34-year-old male from US with acromegaly and inoperable pituitary tumor who was treated with pasireotide (unknown date, unknown formulation and dose, frequency and route) for acromegaly. No other past medical history was reported, however, concomitant medications included levothyroxine, testosterone and hydrocortisone. The patient was reported to have experienced reduced pancreatic function, "upset stomach", fatigue and headaches 7 years after initiation of pasireotide. The symptoms improved after pasireotide dose was decreased, and he also received "full replacement therapy".

Clinical reviewer's comments: A causal association between the event of decreased pancreatic function and pasireotide cannot be ruled out completely due its mechanism of action and positive de-challenge test, although the improvement in symptoms could also have been a result of pancreatic enzymes replacement therapy. However, since the mechanism of inhibition of pancreatic secretory function of SAs via somatostatin receptor activation is a functional and reversible process with drug discontinuation rather than an organic process of tissue damage, the time to onset is expected to be closely related to the time point of drug initiation. As such, an onset of the event after 7 years of treatment is more suggestive of other than drug-induced etiologies of pancreatitis.

(3) Steatorrhea

Case [redacted] (b) (6) was a 62-year-old male who was treated with pasireotide LAR (unknown date, unknown dose, frequency and route) for acromegaly. Past medical history include diabetes mellitus, hypertension, hypopituitarism and hypothyroidism. Concomitant medications included tolbutamide, hydrocortisone, levothyroxine. The patient developed steatorrhea and he was treated with pancreatin, which resolved the steatorrhea. No additional information was provided. The Sponsor assessed the causality relationship between pasireotide LAR and the event of steatorrhea as related.

Clinical reviewer's comments: A causal relationship between the event of steatorrhea and pasireotide cannot be excluded completely due to possible positive temporal association, however, there is insufficient information to make such a determination. Overall, in the absence of details on the timing of events and also giving the presence of confounding factors, such as diabetes, a causal relationship determination between the event of steatorrhea and pasireotide cannot be made.

(4) Steatorrhea, Fatigue

Case [redacted] (b) (6) was a 44-year-old female who received pasireotide LAR for the treatment of acromegaly. Past medical history included congenital deafness and asthma, while concomitant medications included octreotide, and levothyroxine. The patient also had a listed AE of hyperglycemia. The patient developed fatigue and later, steatorrhea, for which she received pancreatin at a dose of 150 mg. The patient recovered from steatorrhea after treatment with pancreatin. No other information was provided. The Sponsor assessed the causality relationship between pasireotide LAR and the events of fatigue and steatorrhea as related.

Clinical reviewer's comments: There is insufficient information provided including absence of information regarding the timing of events, to evaluate for causality between pasireotide and the events of fatigue and steatorrhea. Confounding factors include concomitant use of octreotide, another SA analog and presence of hyperglycemia, suggestive of underlying diabetes.

(5) Steatorrhea

Case (b) (6) was a 30-year-old male patient who was started on pasireotide LAR 20 mg once a month in 2017, for acromegaly. Past medical history included arrhythmia. No concomitant medications were reported. The patient experienced various digestive issues, such as dyspepsia, gallbladder disorder, discolored stools, and flatulence. In 2022, the patient reported that he continued to have undigested fats in the stool "caused by pasireotide". His physician suggested him to take pancreatic enzymes, but it was unknown whether the patient had started taking it or not, and action taken with pasireotide was unknown. The event of undigested fats in stool was reported as not resolved. The case was reported by patient and it was not medically confirmed. The Sponsor assessed the causal relationship between pasireotide LAR and the event steatorrhea as not related, because of the presence of other gastro-intestinal disorders (i.e., gallbladder disorder), which were confounding factors.

Clinical reviewer's comments: The case lacks sufficient information to determine a causal association between pasireotide and the event of steatorrhea. Additionally, the case is confounded by other gastro-intestinal disorders that may induce pancreatitis. Lastly, the case was reported by patient and not medically confirmed.

Overall, no clearly defined cases of PEI were reported with use of pasireotide LAR. There were 5 cases (1 case from US, and 4 non-US cases) with symptoms suggestive of pancreatic insufficiency reported with pasireotide LAR (4 cases of steatorrhea and one case of "pancreatic insufficiency" without specified symptoms/test) in the post-marketing setting, however all cases lacked sufficient information to conduct an adequate causality assessment between the drug and the events of interest. All cases were also confounded by use of other drugs that potentially induce pancreatitis/pancreatic insufficiency and/or had underlying medical conditions that may be associated with pancreatitis/ pancreatic insufficiency. Lastly, without confirmatory tests results for PEI (e.g., lab results, imaging studies, fecal tests) it is complicated to conclude that steatorrhea is pancreas-related (and due to the drug) since steatorrhea may be caused by many other conditions including bile salt deficiency and liver disease, intestinal malabsorption itself, infections (giardiasis).

In summary, no firm conclusion can be made based on the information provided regarding causal relationship between the drug and pancreatic insufficiency and whether the observed cases were due to PEI or other causes given limited information provided and the fact that none of the cases had reported positive confirmatory diagnostic tests for PEI (i.e., stool fat test, imaging studies). However, the event cannot be ruled out completely given the drug mechanism of action. Pasireotide, a second generation SA, exerts its pharmacological activity via binding to somatostatin receptors (SSTRs), similar to first generation SAs (octreotide and lanreotide).

There are 5 isoforms of SSTRs: 1-5. Pasireotide binds with high affinity to SSTRs 1-4 and with lower affinity to SSTR5 compared to endogenous somatostatin [27] and first generation SAs (octreotide and lanreotide), which have high affinity for SSTRs 2 and 5. Data from in vitro studies demonstrate that pasireotide can decrease the release of trypsin, while data from in vivo animal and human studies have shown decreased pancreatic exocrine secretion and decreased intestinal proteolytic activity in association with its use.[8, 9, 10] In clinical trials, pasireotide demonstrated similar gastrointestinal adverse reactions (i.e., pancreatitis, cholelithiasis and complications of cholelithiasis, diarrhea, abdominal pain, abdominal distension, flatulence) to other SAs (i.e., octreotide, lanreotide), which are a result of somatostatin receptors-mediated inhibitory effect on gastrointestinal and pancreatic exocrine enzyme secretion. Therefore, while there was no clear clinical evidence to date of pasireotide-induced PEI, data suggest the effect of pasireotide on fat malabsorption, is a pharmacodynamic property shared by all somatostatin analogs.

- **Office of Surveillance and Epidemiology (OSE) summary and recommendations (Refer to OSE review in DARRTS, dated 7/28/2023, for details)**

The OSE conducted an independent evaluation of PEI associated with the use of SAs from the FDA Adverse Event Reporting System (FAERS) and medical literature (refer to review in DARRTS, dated 7/28/2023). The review identified 27 cases in FAERS of PEI associated with the use of SAs, including 14 cases of octreotide and 13 cases of lanreotide, with most, but not all of them, being identified by the Sponsors as well. Of these, OSE identified 7 representative cases supporting a causal role between the SAs and PEI, as follows:

(1) One case (FAERS 7602892, Case 2010-2883) concerned a 77-year-old male patient enrolled in a phase III, multi-center, prospective, exploratory, open label study to assess the efficacy and safety of lanreotide acetate 120 mg in the symptomatic treatment of patients with refractory diarrhea. This case was not reported by the Sponsor. The patient did not have any relevant medical history. Concomitant medications included mebeverine, tamsulosin, and olanzapine. One day after receiving treatment with study drug, the patient experienced “severe” steatorrhea requiring hospitalization. Treatment for the event included Creon 150 mg three times a day and a low-fat diet. Treatment with study drug was discontinued due to the adverse event. Four days later, the event severity changed to mild and three weeks later the event “completely” resolved.

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[8] Fu Q, et al. Preclinical evaluation of Som230 as a radiation mitigator in a mouse model: postexposure time window and mechanism of action. Radiat Res 2011; 175: 728-735

[9] Fu Q, et al. The somatostatin analog SOM230 (pasireotide) ameliorates injury of the intestinal mucosa and increases survival after total body irradiation by inhibiting exocrine pancreatic secretion. Radiat Res 2009; 171: 698-707.

[10] Allen PJ, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med. 2014; 370(21): 2014-2022.

(2) Five cases (PHHY2011US95004, PHHY2011US95871, PHHY2011US95882, PHHY2011US95887, PHHY2011US95888) identified in a cohort case report of 43 subjects with NET [11]. These cases were also submitted to FAERS (FAERS#s: 8222206, 8222216, 8222210, 8222205, 8222224). These 5 subjects who were previously well-controlled on octreotide therapy (formulations are unknown) had worsening of diarrhea, weight loss, gas problems and bloating without improvement in symptomatology with octreotide dose escalation. Follow up testing with fecal stool test confirmed PEI, while symptoms improved with PERT, which also allowed octreotide dose reduction in 2 subjects without symptoms recurrence. There were no other relevant medical problems or medications, and no evidence of disease progression by imaging studies was noted in the case report.

(3) One case (FAERS 18056692, 2020R1-253615)[12] concerns a seven month and three-week-old male treated with octreotide for off label indication, i.e., congenital hyperinsulinism. The patient was diagnosed with vitamin K (a fat-soluble vitamin) deficiency 2 months after initiation of octreotide therapy by laboratory findings, while levels of the other fat-soluble vitamins (A, D, E) were within the normal range. Bruising disappeared and coagulopathy resolved with a three-day course of vitamin K treatment. Further investigation at an unspecified date revealed steatorrhea and a decrease in fecal elastase (FE-1)(125 μg/g)] in repeated measurements, which was diagnostic of PEI. Other causes of PEI, such as cystic fibrosis and pancreatic hypoplasia were excluded, the latter based on PET scan findings. The child also developed cholelithiasis requiring ursodeoxycholic acid therapy. At 12 months of age, the patient required up to 12.7 mcg/kg/day of octreotide to maintain capillary blood glucose levels above 65–70 mg/dL. He has also needed PERT, oral iron supplementation, and dietary supplements with fat-soluble vitamins (vitamins A, D, E, K).

This medical reviewer agrees with OSE reviewer's assessment of causal relationship between octreotide and PEI in 5 patients reported in the literature, which is supported by absence of symptomatology improvement with octreotide dose escalation (to presumably treat progression of underlying disease), confirmation of PEI diagnosis with stool studies, improvement of symptoms with PERT therapy and octreotide dose de-escalation in 2 subjects. The assessment of drug-induced PEI is complicated in the remaining 2 cases due to the multiple factors including use of the drug for unapproved indications (e.g., refractory diarrhea and hyperinsulinemia) using unapproved doses (i.e., hyperinsulinemia), and absence of PEI confirmatory tests (1 case).

[11] Saif MW, et al. Chronic octreotide therapy can induce pancreatic insufficiency: a common but under-recognized adverse effect. Expert Opinion on Drug Saf. 2010; 9(6): 867-873

[12] Ros-Perez P, et al. Octreotide-related exocrine pancreatic insufficiency in congenital hyperinsulinism. J Pediatr Endocrinol Metab 2020;33(7): 947-950

OSE also identified six articles [13,14, 15, 16, 17, 18] from the medical literature that included clinical trial evidence that pancreatic exocrine function was decreased by octreotide and lanreotide, most notably in patients with NET/GEP-NETs. However, the OSE reviewer concluded that interpretation of these studies was limited by study design issues (e.g., lack of baseline pancreatic function, lack of comparator group, no confirmatory fecal elastase -1, FE-1, levels) to assess the development of SA-induced PEI.

In summary, OSE concluded that while interpretation of causality relationship between octreotide and lanreotide was limited in majority of cases due to confounding factors (i.e., underlying disease symptomatology overlaps with symptoms of PEI, majority of cases being reported in subjects with underlying advanced or metastatic NET, pancreatic atrophy, pancreatic surgery), or limited information available, there was sufficient data to support an association between PEI and octreotide/lanreotide, based on temporal relationship, positive de-challenge, and plausible biologic mechanism. OSE did not identify any postmarketing cases of PEI and pasireotide. Thus, OSE could not make a causal association determination between PEI and pasireotide. However, OSE noted that lack of identified cases may be related to the low drug utilization of pasireotide compared to the other SAs, since the number of patients with an indication for pasireotide is less than patients with GEP-NET indications for other SAs. According to OSE review, "*about 10 to 15 new cases per million people are diagnosed with Cushing's disease in the US each year, where most are treated surgically and do not need pasireotide, compared to more than 12,000 people [36 new cases per million people] diagnosed with GEP-NET in US each year*".

Overall, the OSE recommended to update labels only for octreotide and lanreotide formulations with new safety information. OSE recommended to add or modify to the WARNINGS AND PRECAUTIONS section of the octreotide and lanreotide USPI to inform health care professionals that if new or worsening steatorrhea, weight loss, or malnutrition is reported, evaluate patients for pancreatic exocrine insufficiency and manage accordingly. OSE also recommended to update the Postmarketing Experience section of the octreotide and lanreotide USPI to include pancreatic exocrine insufficiency.

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[13]Caplin ME, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014; 371(3): 224–233

[14] Khan MS, et al. Long-term results of treatment of malignant carcinoid syndrome with prolonged release Lanreotide (Somatuline Autogel). Aliment Pharmacol Ther 2011; 34(2): 235-242

[15] Lamarca A, et al. Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study. Expet Rev Gastroenterol Hepatol 2018; 12:723-731

[16] Rinzivillo M, et al. Occurrence of exocrine pancreatic insufficiency in patients with advanced neuroendocrine tumors treated with somatostatin analogs. Pancreatology 2020; 20 (5): 875-879

[17] Saif MW, et al. Chronic Use of Long-Acting Somatostatin Analogues (SAs) and Exocrine Pancreatic Insufficiency (EPI) in Patients with Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): An Under-recognized Adverse Effect. Cancer Med J 2020; 3(2): 75-84

[18] Hall LA, et al. Casting a Wider NET: Pancreatic Exocrine Insufficiency Induced by Somatostatin Analogues among Patients with Neuroendocrine Tumours? Cancers. 2023;15 (7).

- **Division of Oncology 2 (DO2) review summary and recommendations (Refer to DO2 review in DARRTS, dated 8/17/2022, under NDA 21008, for details)**

DO2 reviewer evaluated the data submitted by all the Sponsor of all SAs products and noted that while a causal association between somatostatin analogues and PEI was possible, given the multiple confounding factors that can occurs in patients with GEP-NETs [i.e., the presence of the tumor in the pancreas causing symptoms similar to PEI, and/or concomitant medications with similar adverse reactions and diseases (e.g. diabetes) that may present similarly to PEI], a causality determination could not be definitively established. DO2 concluded that since the symptoms of PEI may be misinterpreted as adverse reactions to octreotide or as lack of efficacy, it might be useful to inform patients and providers that PEI may occur. DO2 recommended inclusion of PEI in Section 6 of the label as a post-marketing event.

- **Division of Gastroenterology (DG) review summary and recommendations (Refer to DG review in DARRTS, dated 8/4/2023, for details)**

Upon review of data submitted by all the Sponsor of all SAs products and OSE review, DG agreed that there was sufficient evidence to support addition of the PEI to the label of octreotide and lanreotide products. DG's assessment was based primarily on the known mechanism of action of SAs, and available pharmacovigilance reports from FAERS and clinical trial data from literature publications, which support the association between SA use and PEI. DG agreed with DO2 and DPV assessment that many of the reported cases (especially from patients with GEP-NETs) had multiple confounding factors; however, DG concluded that four cases of patients without underlying GEP-NETs (Case 2010-2883 of the 77 years old male with refractory diarrhea treated with lanreotide, Case 2020R1-253615 of the seven month and three-week-old male treated with octreotide for congenital hyperinsulinism, and the two cases of acromegaly treated with lanreotide; all reviewed above) that reported new onset steatorrhea in close temporal relationship to treatment with octreotide/lanreotide support a causal relationship between the drug and the event.

As such, DG recommended adding the term "pancreatic exocrine insufficiency" to the Adverse Reactions, Postmarketing Experience subsection in the USPI for octreotide and lanreotide products. In addition, DG recommended modifying the existing labeling language in the SA products WARNINGS AND PRECAUTIONS section in order to harmonize and mitigate risk of steatorrhea and malabsorption of dietary fat (well-known call adverse events based on mechanism of action of Sas) by recommending healthcare providers perform appropriate clinical workup and offer treatment to patients, as needed. However, given the limitations of the available case reports and published literature that complicates the assessment of pancreatic-related ethology of steatorrhea, DG recommended the subsection focus on the malabsorption of dietary fats and the resulting occurrence of steatorrhea:

5.x. Steatorrhea and Malabsorption of Dietary Fats

Octreotide [lanreotide] may inhibit the absorption of dietary fats. Octreotide [lanreotide], a somatostatin analog, reversibly inhibits secretion of pancreatic enzymes and bile acids. New onset steatorrhea and stool discoloration have been reported in patients receiving somatostatin analogs for various conditions. If new or worsening steatorrhea, and/or other sign(s) and/or symptom(s) of malabsorption of dietary fats is reported, evaluate patients for potential pancreatic exocrine insufficiency and manage appropriately.

Lastly, DG noted there is insufficient postmarketing information to determine whether labeling changes for pasireotide were warranted at this time.

DGE's Conclusions:

After the review of the Sponsor's data and published literature, DGE agrees with OSE, DO2 and DG conclusions that there is evidence of a possible association between the event of PEI and octreotide/lanreotide products. This assessment is based on a plausible mechanistic rationale, and a small number of cases (one case of acromegaly with lanreotide use; one case of hypoglycemia due to congenital hyperinsulinism with octreotide use; and five cases of NETs with octreotide use) from pharmacovigilance reports and from published clinical trial data from literature supporting an association between octreotide/lanreotide use and PEI. In all other cases discussed above a clear causality assessment could not be performed due to presence of confounding factors, absence of confirmatory diagnostic testing for PEI and overall limited information provided. It is important to note that symptoms of steatorrhea and fat malabsorption are expected events with SAs use based on the drug class mechanism of action. In fact, malabsorption of dietary fats is a labeled risk associated with octreotide products (i.e., Sandostatin, Sandostatin LAR, and Mycapssa, Section 5), while gastrointestinal symptoms of diarrhea, flatulence, loose stools, abdominal pain and nausea are listed adverse reactions for all octreotide, lanreotide and pasireotide products in Section 6 Adverse Reactions. Additionally, steatorrhea is a labeled adverse reaction in the Postmarketing experience section of the lanreotide products label (i.e., Somatuline Depot, Lanreotide Acetate).

Overall, DGE concludes that the risks of steatorrhea and fat malabsorption is supported by the existing data and should be included in all SA labels. DGE recommends using FDAAA Safety Labeling Changes (SLC) to require manufacturers to harmonize the risks of severe gastrointestinal symptoms related to fat malabsorption, such as steatorrhea, stool discoloration and loose stool that may be suggestive of PEI in all somatostatin analog product labels, including pasireotide. DGE also agrees with DO/DG recommendations to include the adverse event of PEI in current SA labels. However, since the event was observed mostly in patients with NET, it is complicated to conclude whether the event is due to the mechanism of action of the drug or due to the flare of the underlying disease. DGE recommends including the adverse event of PEI in Section 6.2 Postmarketing Adverse Reactions of all but Mycapssa and pasireotide products label to inform prescribers about this potential risk. The prescribers should evaluate and provide recommendations based on individual case assessment. Since no PEI cases were identified in postmarketing setting in relation to

Mycapssa, pasireotide and pasireotide LAR to date, DGE does not recommend including the adverse events of PEI in labels for these products.

DGE's Recommendations:
DGE recommends updates to Section 5. WARNING AND PRECAUTIONS, and Section 6. ADVERSE REACTIONS as follows:

Section 5. WARNING AND PRECAUTIONS

5.x. Steatorrhea and Malabsorption of Dietary Fats

New onset steatorrhea, stool discoloration and loose stool have been reported in patients receiving somatostatin analogs, including DRUG NAME[19]. Somatostatin analogs reversibly inhibit secretion of pancreatic enzymes and bile acids, which may result in malabsorption of dietary fats and subsequent symptoms of steatorrhea, loose stools, abdominal bloating, and weight loss. If new or worsening steatorrhea, and/or other sign(s) and/or symptom(s) of malabsorption of dietary fats is reported in patient receiving DRUG NAME, evaluate patients for potential pancreatic exocrine insufficiency and manage accordingly.

Section 6. ADVERSE REACTIONS

6.x. Postmarketing experience

Gastrointestinal disorders: Pancreatic exocrine insufficiency[20]

[19] for NDAs 019667, 021008, 022074, to include trade names of Sandostatin, SANDOSTATIN LAR DEPOT, and SOMATULINE DEPOT, respectively as DRUG NAME; for NDAs 208232, 215395, 200677 and 203255, to include octreotide, lanreotide acetate and pasireotide products, respectively, as DRUG NAME.
[20] Not to be included in NDA 200677 (Signifor), NDA 203255 (Signifor LAR) and NDA 208232 (Mycapssa).

Appendix

Table 1. FDA-approved Somatostatin Analogues (SAs)

Active Ingredient	**Lanreotide acetate**	**Octreotide acetate**	**Octreotide acetate**	**Octreotide acetate**	**Lanreotide acetate**	**Pasireotide diaspartate**	**Pasireotide pamoate**
Trade name	Lanreotide Acetate[21]	Mycapssa[22]	Sandostatin[23]	Sandostatin LAR[24]	Somatuline Depot[25]	Signifor[26]	Signifor LAR Kit[27]
Application NDA	215395	208232	019667	021008	022074	200677	203255
Approval	12/17/2021	6/26/2020	10/21/1988	11/25/1998	8/30/2007	12/14/2012	12/15/2014
Dosage form	SQ injection	Oral capsule	SQ, IV injection	IM injection	SQ injection	SQ injection	IM injection

[21] Lanreotide acetate (12/17/2021): https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215395s000lbl.pdf
[22] Mycapssa (dated 6/26/20): https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208232s000lbl.pdf
[23] Sandostatin (dated 10/4/22): https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/019667s073lbl.pdf
[24] Sandostatin LAR (dated 2/9/23): https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021008s041lbl.pdf
[25] Somatuline Depot (dated 4/11/19): https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022074s024lbl.pdf
[26] Signifor (1/15/2020): https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/200677s006lbl.pdf
[27] Signifor LAR (7/9/2020): https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203255s008lbl.pdf

Dose	90 mg Q4WK (acromegaly) 120 mg Q 4WK (GEP-NETs)	20 mg BID (acromegaly)	50 mcg TID (acromegaly) 1500 mcg daily (carcinoid tumor) 450 mcg daily (VIPoma)	50 mcg TID (acromegaly) 600 mcg daily (carcinoid tumor, VIPoma)	60-120 mg Q4WK (acromegaly) 120 mg Q 4WK (GEP-NETs and Carcinoid Syndrome)	0.3-0.9 mg BID (Cushing's disease)	40 mg Q 4WK (acromegaly) 10 mg Q 4WK (Cushing's disease)
Indications	Acromegaly, GEP-NET	Acromegaly	Acromegaly, Carcinoid Tumors, Vasoactive Intestinal Peptide Tumors (VIPomas)	Acromegaly, Carcinoid Tumors, Vasoactive Intestinal Peptide Tumors (VIPomas)	Acromegaly, GEP-NET, Carcinoid Tumors	Cushing's disease	Acromegaly, Cushing's disease
Safety	Section 6: Adverse reactions: Diarrhea, abdominal pain, flatulence, loose stools. Section 6.3. Postmarketing experience: Steatorrhea	Section 5: Warning and Precautions: May alter absorption of dietary fats. Section 6: Diarrhea, abdominal discomfort	Section 5: Warning and Precautions: May alter absorption of dietary fats in some patients. Section 6: Adverse reactions: Diarrhea, loose stools, abnormal stools, abdominal discomfort, flatulence.	Section 5: Warning and Precautions: May alter absorption of dietary fats. Section 6.1: Adverse reactions: Diarrhea, abdominal pain, flatulence.	Section 6.1: Adverse reactions: Diarrhea, abdominal pain, flatulence, loose stools. Section 6.3. Postmarketing experience: Steatorrhea	Section 6: Adverse reactions: Diarrhea, abdominal pain, abdominal distension	Section 6: Adverse reactions: Diarrhea, abdominal pain, abdominal distension, flatulence

Source: Adapted from DPV review in DARRTS (dated 07/27/2023)

Table 2. Summary of Events of PEI in Patients Treated with SAs

Sponsor	Product	Sources Reviewed	Number of cases	Sponsor response and conclusion
Novartis[28]	Sandostatin/Sandostatin LAR (octreotide)	16 clinical trials and 1 compassionate use program	4 cases of PEIs	-2 cases, the investigators did not suspect the causality of PEI to octreotide. -2 cases were suspected to be treatment-related by investigator, but Novartis considered that causality could not be confirmed due to various confounders such as prior octreotide use without reporting PEI events, underlying condition (diabetes), concomitant medications potentially causing pancreatitis (lisinopril/hydrochlorothiazide and clopidogrel).
		Novartis global safety database ((b) (4))	25 cases w/ individual case safety reports	-13 cases, the causal role of octreotide with event PEI was considered unlikely as they were confounded: advanced NET stage IV of the pancreas (n=2), ileum (n=2), and of unknown primary origin (n=1), subtotal pancreatectomy metastases to pancreas; 1 case of progression of hepatocellular carcinoma pancreatic atrophy and another patient had preexisting PEI. -11 cases, the information was limited regarding time to onset, medical history, concomitant medications, primary location of NETs, evolution of underlying disease, laboratory investigations (including baseline pancreatic functions), action taken with octreotide and event outcome. -1 case, the patient developed multi-organ failure following infections not related to octreotide therapy.
		Scientific literature review	7 publications	Sponsor states the observational studies in patients with advanced/metastatic GEP-NETs do not provide compelling evidence of a causal association between SAs, including octreotide, and PEI. Sponsor states these studies do not include a control or comparative arm and there is an inadequate analysis of confounding factors (including primary location of tumor, information on the location of metastases, history of GI surgery, prevalence of functioning vs non-functioning tumors etc.) in patients diagnosed with PEI compared with those who were not.
	In conclusion, the Sponsor states that there is no evidence of a causal relationship between octreotide treatment and the risk of PEI, potentially associated malabsorption, and nutritional deficiencies. Given the absence of evidence of a causal relationship, and against the high background incidence of PEI in the patient population typically receiving octreotide, an update of the USPI to include PEI would neither appear warranted nor provide clinically relevant information.			
Ipsen Bioscience	Somatuline Depot	Global safety database search	52 cases	A total of 52 cases were identified for the PEI review.

[28] IR response (submitted 7/15/22): \\CDSESUB1\EVSPROD\nda019667\0099\m1\us\fda-response-clinical-20220531.pdf

Sponsor	Product	Sources Reviewed	Number of cases	Sponsor response and conclusion
, Inc[29]	(Lanreotide)			• 1 case was excluded because it did not include confirmation of PEI. • 22 cases described patients with pre-existing PEI which did not worsen following treatment with lanreotide. • 15 cases reported a temporal association between PEI diagnosis and lanreotide treatment, however, these cases did not contain sufficient detail to confirm whether there were other more likely causes of the PEI. • 14 cases that indicated a temporal association between PEI and lanreotide. Each case contained one or more confounders: concomitant/past use of octreotide (6 cases), concurrent diabetes mellitus (5 cases), pancreatic NET (5 cases), pancreatic gastrinoma (1 case), pancreaticoduodenectomy surgery (3 cases), left pancreatectomy (1 case), pre-existing diarrhea (3 cases) and disease progression (2 cases). Although these cases were confounded, in 11 of the 14 cases, a causal association between lanreotide and PEI cannot be ruled out.
		Clinical Trial Data		Lanreotide company core data sheet (CCDS) version 3.0 dated 9 March 2022, mentions in the Undesirable effects, section 4.8: pancreatic enzymes decreased (common for GEP-NET/NET) and other related symptoms: loose stools (very common for acromegaly), steatorrhea (common for GEP-NET/NET), flatulence, abdominal distension and weight decreased (all common for acromegaly and GEP-NET/NET). Pancreatic insufficiency was reported as drug-related TEAE in 0.8% (3/378) of the subjects in the GEP-NET/NET pool (lanreotide Autogel formulation neuroendocrine tumor submission dated 30 April 2014). Lanreotide CCDS version 3.0 dated 9 March 2022, mentions in the Pharmacodynamic effects, section 5.1: “ Lanreotide, like somatostatin, exhibits a general exocrine anti-secretory action. It inhibits the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide but has no significant effect on fasting secretin or gastrin secretion.” and “Lanreotide inhibits postprandial secretion of pancreatic polypeptide, gastrin, and cholecystokinin (CCK).”

[29] IR response (submitted 6/30/2022): \\CDSESUB1\evsprod\NDA022074\0213\ response-ir.pdf

Sponsor	Product	Sources Reviewed	Number of cases	Sponsor response and conclusion
		Literature Review		Seven publications, i.e., five studies, one retrospective chart and pharmacy review and one literature review, reported convincing data regarding SA and a causal association with pancreatic insufficiency.
	In conclusion, the sponsor states PEI has been validated as a signal for lanreotide by the Company and the evaluation is currently ongoing.			
InvaGen Pharmaceuticals, Inc. [30]	Lanreotide Injection	Safety database search		No cases reported
		Literature search	3 article	Study 1: The study demonstrated that the occurrence of PEI was at a higher rate than previously reported and was estimated to occur in 1 in 4 patients with Wd-NETs treated with SAs and screening with fecal elastase-1 (FE1) in symptomatic patients was recommend. Study 2: It concluded that SA-related PEI occurs in 34% patients of the 160 treated patients. It also highlighted that SAs may inhibit secretion and release of amylase, trypsin, lipase, secretin, CCK, motilin, bile acid leading to PEI. Study 3: Of the 50 eligible patients in the study, 22% developed SA-induced PEI and concluded the occurrence in 1:4 patients.
Recordati Rare Diseases[31]	Signifor (pasireotide)	Global safety database: search for narratives, search in EMA database EVDAS, and literature search.		-No case of PEI identified in the RRD global safety database. -No cases reporting pancreatic insufficiency were retrieved in EVDAS. -A literature search was performed in PubMed. No case reports describing pancreatic exocrine insufficiency and no clinical evidence of a link between Signifor use and PEI were identified in the literature for pasireotide.
	Signifor LAR (pasireotide)	Global safety database: search for narratives, search in EMA	5 cases	-1 case reporting pancreatic insufficiency -1 case was assessed as not related because of the presence of multiple other gastro-intestinal disorders that were confounding factor.

[30] IR response (submitted 7/5/2022): \\CDSESUB1\evsprod\NDA215395\0029\ cover-letter-0029-ir-response.pdf
[31] IR response (submitted 7/8/2022): \\CDSESUB1\EVSPROD\nda203255\0108\m1\us\111-info-amend\response-to-fda-ir-pei-may2022.pdf

Sponsor	Product	Sources Reviewed	Number of cases	Sponsor response and conclusion
		database EVDAS, and literature search		-3 cases were considered related to Signifor LAR. • 1/3 cases: the patient's symptom pertaining to reduced pancreatic function was steatorrhea and the condition improved with administration of pancreatic enzyme replacement therapy (PERT). • 2/3 cases: time to onset unknown.
	In conclusion, the Sponsor states that the investigation did not retrieve any case of Pancreatic Exocrine Insufficiency related to the use of pasireotide and there is no clinical evidence that PEI might be associated with Signifor, or Signifor LAR use.			
Amryt Pharma[32]	Mycapssa	Safety database and literature search.		No relevant cases from clinical trials, post-marketing experience, or medical literature were identified.

Table 3. Summary of the 14 Cases of PEI in Subjects Receiving Somatuline Depot in Whom Detailed Information Was Available

Case ID/ Report type/ Gender/ Age (years)/Country	Indication/ Dose/ Route of administration	Events of interest (MedDRA PT) / Symptoms	Event date/ TTO/ Action taken/ Outcome	Treatment received for events of interest	Relevant lab values and diagnostic criteria	De-challenge/ Re-challenge	Relevant Medical history/ Concomitant medication	Confounding/ risk factors	Summary/ Sponsor assessment of causality
2011-2029/62/M/ United States	Neuroendocrine cancer with metastasis to the liver /120mg/ every 14 days	Pancreatic failure/Flatulence/ diarrhea/Abdominal pain/Weight decreased	Approx. 2-3 months/Cont./ Ongoing	PERT	Stool analysis, colonoscopy and endoscopy performed - no results provided	Not performed/ Not performed	Two intestinal resections, gall bladder removal, BPH, abdominal pain, bloating, weight loss, diarrhea, gas/ Creon (pancrelipase) - co-suspect, loperamide, cholestyramine powder	Previous octreotide treatment (duration and formulation unknown)	Patient had pre-existing symptoms of diarrhea, gas and weight loss which worsened approximately one month after start of lanreotide (120mg/2 weeks). Pancreatic insufficiency was reported after one month. Clinical course was unclear. Treatment with pancrelipase at varying doses. Lanreotide treatment continued. Sponsor's causality assessment: Related. The patient had pre-existing symptoms,

[32] IR response (submitted 6/29/2022): NDA208232 (208232 - 0076 - (240) - 2022-06-29 - ORIG-1 /Clinical/Response To Information Request) - response-29jun2020-SN0076

									however PEI worsened after starting lanreotide 120 mg administered every two weeks. Although the patient had previously received octreotide, a causal association between the event and lanreotide 120 mg administered every two weeks cannot be ruled out.
Clinical reviewer's comment: Causal relationship possible due to positive temporal relationship (i.e., PEI worsened after starting lanreotide 120 mg administered every two weeks), however confounding factors include pre-existent symptoms, use of octreotide and underlying disease.									
2012-3952/49/M/ Israel	Pancreatic neuroendocrine tumor/60mg/ Monthly	Pancreatic failure	Approx 10 months /Discontinued/ Ongoing	NA	NA	NA	Adrenalectomy due to pheochromocytoma, parathyroid adenoma removal/ Simvastatin, diazepam, propranolol, metamizole	GEP-NET but lack of information to determine other confounding or risk factors	Patient experienced fatty stools and abdominal pain and was diagnosed with pancreatic insufficiency 10 months after start of lanreotide (60mg/month). Details on diagnosis, clinical course and treatment were not provided. Treatment with lanreotide discontinued. Event ongoing at time of reporting. Sponsor's causality assessment: Related. Although pancreatic NET was a confounder in this case, a causal association between the event and lanreotide cannot be ruled out.
Clinical reviewer's comment: Causal relationship possible due to positive temporal relationship (i.e., PEI diagnosed 10 months after starting lanreotide), with confounding factor including underlying disease (pancreatic NET)									
2013-5816/NA/F/ Australia	NA/120mg/ monthly	Pancreatic failure/malabsorption	NA/NA/NA	PERT	NA	NA	Not reported/Sandostatin LAR (octreotide), cabergoline, hydrocortisone, esomeprazole, calcium, risedronate sodium, thyroxine sodium, thyroxine sodium, paracetamol, lisinopril, denosumab, unspecified vitamin B, vitamin C and vitamin D	Octreotide long-acting release (30mg, frequency unknown)	Patient experienced fat malabsorption and pancreatic insufficiency at an unspecified time after lanreotide (120mg/4 weeks) initiation. Medical history not reported. Treatment with pancrelipase. Action taken with lanreotide was not reported. Sponsor's causality assessment: Related. Although documentation in this case was incomplete and octreotide was reported as co-suspect medication, a causal association between the event and lanreotide cannot be ruled out.

Clinical reviewer's comment: Causal relationship possible due to PEI occurring after initiation of lanreotide (although timing of events not available), with confounding factor including previous use of octreotide. The underlying indication for treatment with lanreotide unknown.									
2016-11484/60/F/ Japan	Acromegaly/90 mg/ monthly	Pancreatic failure/Steatorrhea/Diarrhea/Protein total decreased/Weight decreased	6 months/ Discontinued/ NA	NA	Pancreatic function diagnostic test was 28.1% (normal range not provided). No other results provided	Positive dechallenge	Diabetic nephropathy stage II, hypertension, diabetes mellitus, hypercholesterolemia and hypophysectomy/ rosuvastatin calcium, azelnidipine, and Humulin 3/7 (insulin human (genetic recombination)). Past medications included bromocriptine and cabergoline	Diabetes mellitus	Patient experienced white-ish stools 28 days after first lanreotide dose (90mg/28 days). Six months after first dose, soft feces, diarrhea, and fat in stools. Weight decreased by 2 kg to 48 kg in one month. Pancreatic function diagnostic test was 28.1% (normal range not provided) and pancreatic exocrine hypofunction was suspected. Lanreotide discontinued and 12 days later diarrhea had resolved (positive dechallenge). Details on outcome of other events, treatment and follow-up diagnostics not reported. Sponsor's causality assessment: Related. Although the patient had underlying risk factors for PEI (diabetes), symptoms of diarrhea resolved following discontinuation of lanreotide, therefore a causal association between the event and lanreotide cannot be ruled out.
Clinical reviewer's comment: A causal relationship is probable due to positive temporal relationship (i.e., PEI diagnosed 6 months after lanreotide initiation), and positive de-challenge test. In addition, while presence of diabetes is a confounder factor, the patient was treated with lanreotide for acromegaly, therefore underlying pancreatic NET was not present as a confounder in this case.									
2017-06129/70/F/ United States	Pancreatic neuroendocrine tumor/120mg/ monthly	Diarrhea/abdominal pain/Flatulence/ Weight decreased	NA/Discontinued/ Improved	No	NA	NA	Pancreatic insufficiency, obesity , gall stones, cholecystectomy, abdominal symptoms, belching, diabetes mellitus, Whipple's surgery/ Creon (pancreatin), Reg's Activ Detox and liver Health + probiotics (Lactobacillus	Disease progression, pancreaticoduodenectomy 2 years before LAN start & diabetes	Although reported that pancreatic insufficiency treated with pancrelipase was pre-existing, the information provided suggests that symptoms occurred after the start of treatment. The patient experienced diarrhea/frequent stools, sharp stabbing pain in stomach, increased blood pressure, and decreased appetite 28 days after lanreotide (120mg/month) initiation. One month later she had increased flatulence. Around the same time, lanreotide was discontinued due to disease progression. The patient was then treated with sunitinib and on same day experienced

							fermentum ME-3, L-selenothionine, L-methionine and N-Acetyl-cysteine, milk thistle extract), losartan, hydrochlorothiazide, metformin, pantoprazole, lorazepam, prochlorperazine		diarrhea. Diarrhea improved an unspecified time later. These abdominal symptoms were not reported as associated with pancreatic insufficiency. No relevant lab or diagnostic data. No details of treatment for diarrhea were provided. Sponsor's causality assessment: Related. There were multiple risk factors in this case and the clinical evolution of the case is unclear, however a causal association between the event and lanreotide cannot be ruled out.
Clinical reviewer's comment: Limited information provided (i.e., no clear symptomatic evidence of PEI, no diagnosis, no treatment with pancreatic enzymes, no diagnostic evaluation) to suspect lanreotide-induced PEI in this case. Additionally, multiple confounding factor were present (i.e., underlying progressive disease, pancreatectomy, diabetes).									
2017-10891/57/F/ United Kingdom	Carcinoid syndrome/120 mg/ monthly	Pancreatic failure/Abdominal pain/Flatulence	5 year/ Continued/NA	PERT	NA	NA	Flushing, diarrhea, hypertension, hyperthyroidism, post-menopausal, intermittent sciatica, lymphoedema, lymph node metastases and neuroendocrine tumor/ Telotristat etiprate, carbimazole, Penicillin, warfarin, loperamide, senna, candesartan, phenoxymethylpenicillin	Pre-existing diarrhea, time to onset of over 5 years and pancreatic NET evolution.	Medical history including diarrhea. Patient developed flatulence 5 years after first lanreotide (120mg/28 days) dose and 3 weeks later was diagnosed with pancreatic insufficiency and treated with pancrelipase. Lanreotide treatment continued. Five months later the patient was treated with interferon due to progressive pancreatic disease. Reported term was 'pancreatic insufficiency/progressive pancreatic disease'. The patient died due to progressive disease. It was not reported whether lanreotide treatment was maintained during these events. Sponsor's causality assessment: Related. Although this case is confounded by progression of pancreatic NET and a prolonged time to onset, a causal association between the event and lanreotide cannot be ruled out.
Clinical reviewer's comment: Although this case is confounded by progression of pancreatic NET and a prolonged time to onset, a causal association between the event of PEI and lanreotide cannot be ruled out.									

2018-10311/77/M/ Netherlands	Ileocecal NET/90mg/ monthly	Pancreatic failure	< 2 years/NA/NA	PERT	NA	NA	Paroxysmal atrial fibrillation, hypertension, carcinoid tumor of the cecum, metastases to lymph nodes, metastases of liver, diarrhea, hypercholesterolemia, carcinoid syndrome, prostatic hyperplasia/ ketoconazole, telmisartan, tamsulosine, simvastatin, metoprolol, fenprocoumon, amlodipine, goserelin and multivitamins (ergocalciferol, ascorbic acid, pyridoxine hydrochloride, thiamine hydrochloride, retinol, riboflavin, nicotinamide, calcium pantothenate	Medical history included diarrhea.	Patient experienced pancreatic insufficiency at an unspecified time after lanreotide (90mg/28 days) initiation. Approximately 2 years after start of lanreotide treatment the patient was treated with pancrelipase. No diagnostic information or details on clinical course or outcome. Action taken with lanreotide was not reported. Sponsor's causality assessment: Related. Time to onset is not clear in this case, however the patient had pre-existing diarrhea and was diagnosed with PEI sometime after initiation of lanreotide, therefore a causal association cannot be ruled out.
Clinical reviewer's comment: While the time to onset is not clear in this case and the patient had pre-existing diarrhea, the diagnosis of PEI was made approx. 2 years after initiation of lanreotide, therefore a causal association cannot be ruled out completely.									
2018-15733/25/F/ Brazil	Neuroendocrine tumor (liver)/ 120mg/ monthly	Pancreatic failure/Diarrhea	<27days/ Discontinued/ Improved	PERT	NA	Positive dechallenge	Hypertension, scleroderma, anemia/ nifedipine, enalapril, omeprazole, cerazette, denosumab, pregabalin, amitriptyline, hydrochlorothiazide, prednisone, simvastatin. Past	Past octreotide use (dose, duration and frequency not reported).	One month after lanreotide (120mg/30 days) initiation, the patient developed diarrhea and vomiting and 'pathology in pancreas (stopped working)' was reported. Treatment with pancrelipase was started. Due to insurance issues, lanreotide treatment was interrupted for several months and during this time, diarrhea frequency improved. Sponsor's causality assessment: Related. Although the case is confounded by past octreotide use, the time to onset and improvement of

							medication included octreotide		symptoms following lanreotide discontinuation suggest a causal association.
Clinical reviewer's comment: A causal relationship between lanreotide and PEI is possible given positive temporal relationship and positive de-challenge test, however, past use of octreotide is a confounder factor.									
2019-00074/66/F/ United Kingdom	Neuroendocrine tumor/120mg/ monthly	Pancreatic failure/Steatorrhea/Diarrhea/Abdominal pain/Flatulence	3 days/ Continued/NA	PERT	No	NA	Not reported/ clopidogrel, lansoprazole, metformin, gliclazide, felodipine, losartan and levothyroxine	Diabetes (as suggested by metformin and gliclazide)	On the same day as the first injection of lanreotide (120mg/28 days), the patient experienced nausea, cramping, and bloating which lasted for several days. Three days later, the patient experienced loose, fatty stools which lasted for 20 days. The patient was diagnosed with PEI and treated with PER). Lanreotide treatment continued. Sponsor's causality assessment: Related. Despite risk factors for PEI, the time to onset in this case is convincing, therefore a causal association between the event and lanreotide cannot be excluded.
Clinical reviewer's comment: A causal relationship between lanreotide and PEI is possible given positive temporal relationship, with diabetes and underlying disease representing confounding factors.									
2019-09219/80/F/ Japan	Pancreatic neuroendocrine tumor/120mg/ monthly	Pancreatic failure	12 months/ Continued/ Improving/resolving	PERT	NA	NA	Pancreatic exocrine insufficiency, diabetes mellitus, glaucoma, chronic gastritis, tumor excision/ everolimus, Lipacreaon (pancrealipase)	Pancreatic NET, Diabetes mellitus	Patient with pre-existing PEI treated with pancrelipase experienced aggravation of PEI one year after start of lanreotide (120mg/28 days). Treatment with enteral nutrition. Lanreotide was continued. Concomitant treatment: everolimus. Sponsor's causality assessment: Related. This case is confounded, however an association between the event and lanreotide cannot be ruled out.
Clinical reviewer's comment: An association between the event and lanreotide cannot be ruled out due to temporal relationship, but the case is confounded by pre-existing condition of PEI, underlying disease and diabetes.									
2020-04020/56/F/ Japan	Pancreatic gastrinoma/ 120mg/monthly	Pancreatic failure	3 months /Continued/ Ongoing	PERT	NA	NA	Not reported/ Takecab, Miya BM (clostridium butyricum) and Nexium.	Pancreaticoduodenectomy and pancreatic gastrinoma.	Received first dose of lanreotide (120mg/28days) which was then temporarily interrupted for three-month while patient underwent pancreaticoduodenectomy and hepatic subsegmentectomy. Two months after lanreotide was resumed, the patient

									experienced “postoperative PEI” (reporter’s term) and was treated with pancrelipase. Treatment with lanreotide continued. Sponsor’s causality assessment: Unrelated. The pancreaticoduodenectomy provides a more likely cause of the PEI in this case.
Clinical reviewer’s comment: While a causal relationship between lanreotide and PEI cannot be excluded, the case is heavily confounded by the pancreaticoduodenectomy, which provides a more likely cause of the PEI in this case.									
2021-03254/52/M/ Israel	Pancreatic neuroendocrine tumor/90mg/ monthly	NA	NA/NA/NA	PERT	NA	NA	Whipple surgery (Oct2011), Endocrine and exocrine pancreatic insufficiency secondary to surgery in combination with somatostatin treatment since Aug-2012 (Pancreatic insufficiency), diabetes mellitus/ Creon (pancreatin)	Pancreaticoduodenectomy, pancreatic NET and diabetes mellitus	Medical history included pancreaticoduodenectomy and PEI treated with pancrelipase. On an unknown date, after lanreotide (90mg/month) initiation, the patient had excessive bowel movements for about one week, despite pancrelipase. Pancrelipase dose increased. Not reported as an ADR. Outcome and action taken with lanreotide not reported. Sponsor’s causality assessment: Related. Although this case is heavily confounded, an association between the event and lanreotide cannot be ruled out.
Clinical reviewer’s comment: An association between the event and lanreotide cannot be ruled out, however, the case is heavily confounded by pancreaticoduodenectomy, pancreatic NET and diabetes mellitus.									
2021-20369/76/F/ Australia	Acromegaly/ 120mg/ monthly	Pancreatic failure/Malabsorption/Diarrhea	NA/NA/NA	PERT	NA	No	hypertension, panhypopituitarism, hypophysectomy trans-sphenoidal in 2001, microadenoma in 2001/ Esomeprazole, levothyroxine, paracetamol, lisinopril, denosumab, risedronate, hydrocortisone	Octreotide long-acting release (30mg/3 weeks) was a concomitant medication and co-suspect. Lack of information to determine any other confounders/risk factors.	Patient experienced fat malabsorption, pancreatic insufficiency, cholelithiasis, diarrhea and lack of efficacy an unspecified time after lanreotide (120mg/28 days) initiation. The patient underwent cholecystectomy. Treatment included pancrelipase. Action taken with lanreotide was not reported. Sponsor’s causality assessment: Unrelated. Although this case lacks information regarding time to onset and any other confounders/risk factors, if any, an association between the event and lanreotide cannot be ruled out.

Clinical reviewer's comment: An association between the event and lanreotide cannot be ruled out, however, the case is confounded by use of octreotide and presence of cholelithiasis,which is a risk factor for pancreatitis and subsequent pancreatic insufficiency.									
2022-15539/76/F/ Switzerland	Pancreatic endocrine tumor/ 120mg/ monthly	Pancreatic failure	NA/Continued /NA	NA	NA	NA	Caudal pancreatectomy, splenectomy, atypical gastrectomy and partial hepatic segmentectomy VI, radiofrequency of segment III metastasis, cholecystectomy, left pancreatectomy/ Not reported	Complex medical history, concurrent condition of pancreatic (7 mm pancreatic head) NET progression and left pancreatectomy. Past octreotide treatment for 10 months.	An unspecified time after lanreotide (120mg/month) initiation, the patient experienced renal failure on probable interstitial calcium oxalate deposits in the context of PEI (maldigestion, steatorrhea), hyperoxaluria, hypocalciuria, hypomagnesuria, hypocitraturia, metabolic acidosis, secondary hyperparathyroidism of mixed origin, iterative hypoglycemia on relative hyperinsulinism in the context of dumping syndrome, Hashimoto's thyroiditis and arterial hypertension. No treatment was reported for the PEI. No action taken with lanreotide. Sponsor's causality assessment: Unrelated. The patient's underlying pancreatic head NET progression and left pancreatectomy are more likely causes for the PEI than lanreotide treatment.
Clinical reviewer's comment: While a causal association between lanreotide and the event cannot be excluded, this case is heavily confounded by the patient's underlying pancreatic head NET progression, left pancreatectomy, and previous use of octreotide.									

Abbreviations: F, female; M, male; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TTO, time to onset; NA, not available; NET, neuroendocrine tumor; PERT, pancreatic enzyme replacement therapy.

Table 4. Summary of 13 Cases of PEI in Subjects Receiving Sandostatin/Sandostatin LAR in Whom More Detailed Information Was Available

Case ID/ Report type/ Gender/ Age (years)/Country	Indication/ Dose/ Route of administration	Events of interest (MedDRA PT) / Symptoms	TTO*/ Action taken/ Outcome	Treatment received for events of interest	Relevant lab values and diagnostic criteria	De-challenge/ Re-challenge	Relevant Medical history/ Concomitant medication	Confounding/risk factors	Comments/Sponsor's assessment

PHBS2003FI13210 / 61/F/ Finland	Carcinoid syndrome/NA/ NA	Pancreatic failure/diarrhea	NA/NA/Complete recovery	PERT	Decreased fecal elastase; Imaging: pancreatic atrophy	NA/NA	NA/NA	Pancreatic atrophy	Confounded by pancreatic atrophy, hence causal role of octreotide therapy is considered unlikely.
Clinical reviewer's comment: A causal assessment is difficult to make due to limited information provided; pancreatic atrophy represents a confounding factor, since the effect of octreotide on pancreatic function is believed to be functional and not organic in nature.									
PHEH2000US03221/ M/80/ United States	Carcinoid syndrome/NA/ NA	Pancreatic failure/diarrhea/ abdominal cramps	Approx 150 days/NA/NA	PERT	NA	NA/NA	Surgery for intestinal carcinoid tumor 4 years prior	Prior gastrointestinal surgery	The case was confounded by prior gastrointestinal surgery which is a significant risk for the patient to develop exocrine pancreatic insufficiency. Of note, the patient developed symptoms prior to octreotide treatment and hence a causal role of the drug was considered unlikely.
Clinical reviewer's comment: A causal assessment is difficult to make due to limited information provided; the case is confounded by history of prior gastrointestinal surgery.									
PHHO2004BE02957/69/M/ Belgium	Hepatocellular carcinoma progression/NA/NA	Pancreatic failure	886 days/NA/Fatal with malignant neoplasm progression		NA	NA/NA	Hepato-pancreatic insufficiency with jaundice and encephalopathy/NA	Progression of underlying disease	Progression of underlying malignancy is a significant confounder and causal role of octreotide therapy is unlikely. The investigator considered the event was due to progression of the hepatocellular carcinoma.
Clinical reviewer's comment: A causal assessment is difficult to make due to limited information provided; the case is confounded by progression of hepatocellular carcinoma.									
PHHY2009JP47129/ 2 months/NA/ Japan	Hyperinsulinemic hypoglycemia/ NA/ subcutaneous	Pancreatic failure/steatorrhea	NA/NA/NA	PERT	NA	NA/NA	Subtotal pancreatectomy 5 months after birth/Diazoxide	Subtotal pancreatectomy	The patient developed exocrine pancreatic insufficiency post subtotal pancreatectomy and hence the event is considered not related to octreotide.
Clinical reviewer's comment: A causal assessment is difficult to make due to limited information provided; the case is confounded by subtotal pancreatectomy.									
PHHY2011CA76243/ 65/F/ Canada	Carcinoid tumor/30 mg monthly/intramuscular	Pancreatic failure/diarrhea, flatulence	88 days/NA/NA	NA	NA	NA/NA	Metastases to pancreas and liver, diabetes/insulin	Metastases to pancreas and liver, diabetes	Case reported multiple confounders such as metastases to pancreas and liver, pancreatitis and uncontrolled diabetes; hence considered not related to octreotide.
Clinical reviewer's comment: While a causal relationship cannot be excluded, the case is confounded by the severe underlying disease with metastases to pancreas and liver, as well as presence of diabetes.									

PHHY2011US 95004/ 67/M/ United States	Stage 4 pancreatic NET/30 mg/NA	Pancreatic failure/Weight loss, flatulence, bloating	18 months/ Continued/Improved	PERT	Fecal stool test	NA/NA	NA/NA	Advanced pancreatic NET	The Sponsor considered that a causal relationship between octreotide and event was unlikely because the case was confounded by patient's advanced pancreatic cancer and the patient was improving with PERT with no change in octreotide therapy.
Clinical reviewer's comment: While a causal relationship cannot be excluded, the case is confounded by the patient's advanced pancreatic cancer.									
PHHY2011US 95871/64/F/ United States	Stage 4 NET of ileum/80 mg/NA	Pancreatic failure/diarrhea	36 months/ Dose decreased from 80 mg to 60 mg/ Improving	PERT	Fecal stool test	Positive/NA	NA/NA	Advanced NET	The Sponsor considered that a causal relationship between octreotide and event was unlikely because advanced NET and its complications can explain the event.
Clinical reviewer's comment: Although limited information is provided, a causal relationship cannot be excluded due to potentially positive de-challenge test (i.e., condition noted to be improving with octreotide dose reduction), although unsure whether the improvement was due to dose reduction versus treatment with PERT. Advanced underlying NET is a confounder factor.									
PHHY2011US 95882/53/F/ United States	Stage 4 NET of pancreas/30 mg/NA	Pancreatic failure/weight loss, flatulence and bloating	18 months/No change/Improving	PERT	Fecal stool test	NA/NA	NA/NA	Advanced pancreatic NET	The Sponsor considered that a causal relationship between octreotide and event was unlikely because of the advanced pancreatic cancer was a significant confounder and patient was improving with PERT with no change in octreotide therapy.
Clinical reviewer's comment: While a causal relationship cannot be excluded, the case is confounded by patient's advanced pancreatic cancer.									
PHHY2011US 95887/51/M/ United States	Stage 4 NET of ileum/80 mg/NA	Pancreatic failure/bloating	38 months/dose decreased from 80 to 60/Improving	PERT	Fecal stool test	NA/NA	NA/NA	Advanced NET	The Sponsor considered that a causal relationship between octreotide and event was unlikely because the advanced NET and its complications can explain the event.
Clinical reviewer's comment: While a causal relationship cannot be excluded, the case is confounded by patient's advanced underlying NET.									
PHHY2011US 95888/48/M/ United States	Stage 4 NET of unknown primary/30 mg monthly/intramuscular	Pancreatic failure/Weight loss, flatulence	12 month/No change/Improving	PERT	Fecal stool test	NA/NA	NA/NA	Advanced NET	The Sponsor considered that a causal relationship between octreotide and event was unlikely because the advanced NET was a significant confounder and the patient was improving with PERT with no change in octreotide therapy.
Clinical reviewer's comment: While a causal relationship cannot be excluded, the case is confounded by patient's advanced underlying NET.									

PHHY2013CA017753/NA/M/ Canada	Pancreatic cancer/30 mg every 4 weeks/intramuscular	Pancreatic failure/ steatorrhea, decreased weight	< 2 months/ Discontinued/Improving	PERT	Fecal stool test	Positive/NA	History of pancreatic insufficiency and noncompliance with PERT/NA	Pancreatic cancer	Sponsor assessed the case as not related to octreotide as patient had pancreatic cancer and he was non-complaint with PERT. The treated physician assessed the case as not related to octreotide.
Clinical reviewer's comment: While the case is confounded by patient's underlying pancreatic cancer and history of pancreatic insufficiency, a causal association between octreotide and the event cannot be ruled out.									
PHHY2013DE055598/58/F/ Germany	Idiopathic non-insulinoma pancreatogenous hypoglycemia/ NA/NA	Pancreatic failure	NA/NA/NA	NA	NA	NA/NA	Hypoglycemia uncontrolled with medications requiring surgical intervention/Diazoxide	Subtotal pancreatectomy	Non-serious event of PEI post subtotal pancreatectomy for uncontrolled hypoglycemia, hence not related to octreotide therapy.
Clinical reviewer's comment: While the case is confounded by patient's subtotal pancreatectomy, a causal association between octreotide and the event cannot be ruled out.									
NVSC2021CH213044/70/M/ Switzerland	NET/10-30 mg frequency not specified/intramuscular	Pancreatic failure/Weight loss, diarrhea, abdominal pain	5 months/ Discontinued/Deteriorated	PERT	NA	No/NA	Ileus, small intestinal segment resection, advanced NET with abdominal metastases and peritoneal carcinomatosis/NA	Advanced NET	Given the presence of major confounders (history of small intestinal segment resection, advanced NET with abdominal metastases and peritoneal carcinomatosis) and the lack of improvement following octreotide discontinuation and PERT (pancreatin) initiation, a causal role of octreotide therapy is considered unlikely in this case.
Clinical reviewer's comment: A causal association between octreotide and the event cannot be ruled out given temporal relationship, however, the case is confounded by patient's underlying advanced NET, while lack of symptomatic improvement with octreotide discontinuation does not support a causal association.									

Abbreviations: F, female; M, male; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TTO, time to onset; NA, not available; NET, neuroendocrine tumor; PERT, pancreatic enzyme replacement therapy.

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/s/

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04/04/2024 03:18:27 PM

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

Pharmacovigilance and Drug Utilization Review

Date: July 26, 2023

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Product Names/Applications/Applicants:

Drug name	Active ingredient	Application	Applicant
Mycapssa	Octreotide acetate	NDA 208232	Amryt
Sandostatin	Octreotide acetate	NDA 019667	Novartis
Sandostatin LAR	Octreotide acetate	NDA 021008	Novartis
Somatuline Depot	Lanreotide acetate	NDA 022074	Ipsen Pharma
Lanreotide	Lanreotide acetate	NDA 215395	Invagen Pharms
Signifor	Pasireotide diaspartate	NDA 200677	Recordati Rare Diseases
Signifor LAR Kit	Pasireotide diaspartate	NDA 203255	Recordati Rare Diseases

Subject: Pancreatic exocrine insufficiency (PEI)

SS ID #: 1004917

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TABLE OF CONTENT

EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance and Drug Utilization Review is for the Division of Pharmacovigilance (DPV) and Division of Epidemiology II (DEPI-II) to provide to the Division of General Endocrinology (DGE) an evaluation of pancreatic exocrine insufficiency (PEI) associated with the use of somatostatin analogs (SAs) from the FDA Adverse Event Reporting System (FAERS) and medical literature. This signal was identified by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). PEI is not labeled for SAs in the United States Prescribing Information (USPI); however, it is labeled in the EU Summary of Product Characteristics (SmPC) for octreotide. Accordingly, a review was undertaken to assess the need to update the USPI for SAs regarding the risk of PEI. The information and recommendations in this review will assist DGE to determine if PEI should be added to labeling for the SA drug class.

This review identified 27 cases in FAERS of PEI associated with the use of SAs, including 14 cases of octreotide and 13 cases of lanreotide. DPV finds an association between octreotide and lanreotide and PEI based on temporal relationship, positive dechallenge, and plausible biologic mechanism. No postmarketing cases of PEI have been identified at this time that are considered causally related to pasireotide.

DEPI-II examined U.S. sales distribution and patient utilization of SAs to provide context for the FAERS cases and medical literature. Analysis of sales distribution data showed an increase in total sales of SAs between 2012 and 2021. Octreotide accounted for the majority ((b) (4)%) of the SA market, while sales of lanreotide ((b) (4)) and pasireotide ((b) (4)%) represented a smaller proportion of the examined market in 2021. Additionally, patient data from both U.S. outpatient pharmacies and non-federal hospitals showed that octreotide accounted for the majority of use among the drug class, representing (b) (4)% and (b) (4)% in 2021, respectively.

We do not agree with the octreotide Applicant that inclusion of PEI in the octreotide labeling would "neither appear warranted nor provide clinically relevant information." Although octreotide is prescribed to treat diarrhea associated with carcinoid tumor, paradoxically, as shown in this review, it may cause steatorrhea secondary to PEI. This may lead to dose escalation of octreotide, resulting in worsening of steatorrhea. The inclusion of PEI in product labeling alerts the clinician to the potential for this adverse event for proper work up, thereby improving patient care and reducing healthcare costs.

(b) (4)

Based on this review, OSE recommends the following:

- Add or modify to the WARNINGS AND PRECAUTIONS section of the octreotide and lanreotide USPI to inform health care professionals that if new or worsening steatorrhea, weight loss, or malnutrition is reported, evaluate patients for pancreatic exocrine insufficiency and manage accordingly.
- Update the *Postmarketing Experience* section of the octreotide and lanreotide USPI to include pancreatic exocrine insufficiency.

Although no postmarketing cases of PEI have been identified at this time that are considered causally related to pasireotide, we encourage DGE to use other data sources to determine if somatostatin class labeling is warranted to include pasireotide.

1 INTRODUCTION

The purpose of this Pharmacovigilance and Drug Utilization Review is for the Division of Pharmacovigilance (DPV) and the Division of Epidemiology II (DEPI-II) to provide to the Division of General Endocrinology (DGE) an evaluation of pancreatic exocrine insufficiency (PEI) associated with the use of somatostatin analogs (SAs) from the FDA Adverse Event Reporting System (FAERS) and medical literature. This signal was identified by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) and is labeled in the Summary of Product Characteristics (SmPC) for octreotide in the European Union. PEI is not labeled for SAs in the United States Prescribing Information (USPI). The information and recommendations in this review will assist DGE to determine if PEI should be added to labeling for the SA drug class.

1.1 BACKGROUND

1.1.1 Octreotide EMA Assessment of PEI

In November 2020, the Rapporteur of the EMA PRAC identified a potential safety signal concerning PEI with the use of octreotide.[1] The signal was triggered by a medical literature report describing a seven-month and three-week-old male who developed PEI, vitamin K deficiency and cutaneous hemorrhagic syndrome after receiving octreotide.[2] In addition, a review of the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) database identified 21 spontaneous cases of PEI occurring after octreotide treatment.[1] Five relevant observational studies (two retrospective, two prospective, and one cross-sectional study) in patients with gastroenteropancreatic (GEP) neuroendocrine tumors (NET) also reported the occurrence of PEI during treatment with octreotide.[3,4,5,6,7] Given the number of literature publications as well as the cases in EudraVigilance, on March 11, 2021, the PRAC requested the marketing authorization holder of octreotide-containing medicinal products, Novartis, conduct a cumulative review of all cases suggestive of PEI with the use of octreotide, including a review of the published literature, post-marketing experience, and clinical trials.

A comprehensive review was conducted by Novartis.[1] They concluded the absence of evidence of a causal relationship against a high background incidence of PEI in the patient population receiving octreotide. They concluded an update of the SmPC to include PEI "would appear neither warranted nor provide clinically relevant information." PRAC agreed there was limited information to establish a causal association between octreotide and PEI, and highlighted that the symptoms of PEI overlapped with the known symptoms of both NET-associated carcinoid syndrome and labeled adverse reactions to octreotide.[1,8] They also indicated that lack of awareness of PEI as a possible etiology in symptomatic patients with NET treated with octreotide could lead to unnecessary alterations in octreotide dose if the prescriber suspects the symptoms are due to a lack of efficacy or increase in serotonin production caused by the tumor. This could result in a delay in the diagnosis of PEI and appropriate treatment with pancreatic enzymes. As such, PRAC requested an update to the octreotide SmPC Section 4.4 "Special warnings and precautions for use" and concurrently Package Leaflet Section 2 to alert prescribers about the risk of PEI in patients with GEP-NETs.

1.1.2 Neuroendocrine tumors

The term "carcinoid" has been generally applied to well-differentiated neuroendocrine tumors (Wd-NETs) originating in the digestive tract, lungs, or rare primary sites, such as the kidneys or ovaries.[9] Currently, the term carcinoid is used to refer to Wd-NETs arising in the lung, but within the gastrointestinal tract, the term carcinoid has fallen out of favor, and the World Health Organization (WHO) recommendation is to use the term "NET."[10] Regardless of anatomic site, the term "neuroendocrine carcinoma" is usually assigned to high-grade or poorly differentiated NETs. Carcinoid syndrome may be the initial manifestation of NET. Chronic flushing and or diarrhea are the typical manifestations of carcinoid syndrome, which is the result of secretion of serotonin and other vasoactive substances into the systemic circulation. The diagnosis of carcinoid syndrome requires these symptoms and corresponding elevations in lab tests. Carcinoid syndrome is primarily associated with metastatic tumors originating in the midgut (i.e., distal small intestine and proximal colon). In contrast, hindgut (i.e., distal colorectal) and foregut (i.e., gastroduodenal, lung) NETs are uncommonly associated with carcinoid syndrome. Treatment options for NETs and carcinoid syndrome include surgery and medical management with SAs. In addition to Wd-NETs of the gastrointestinal tract, other Wd-NETs arising in the pancreas may cause severe diarrhea, including gastrinomas and vasoactive intestinal peptide tumors (VIPomas). In such cases, serum levels of gastrin and vasoactive intestinal polypeptide (VIP) may be elevated, and aid in the differential diagnosis.

1.1.3 Somatostatin and SAs

Somatostatin, a cyclic polypeptide, is one of the main inhibitors of endocrine and exocrine hormone secretion in humans.[11] Native somatostatin is not useful in clinical practice because it has an extremely short half-life of 1–3 minutes, rapidly degraded by ubiquitously distributed peptidases in plasma and tissues.[12] After the characterization of somatostatin, several synthetic SAs with a longer half-life were developed. To date, three of them have been approved in clinical practice: lanreotide and octreotide are considered first-generation SAs, and pasireotide is considered a second-generation SA.

Somatostatin is distributed throughout the entire body, although it is particularly abundant in nervous tissue of the cortex, hypothalamus, brainstem, spinal cord, gastrointestinal tract, and pancreas. Both somatostatin-14 and somatostatin-28 are expressed throughout regions of the gastrointestinal tract.[13] The physiological effects of somatostatin are largely inhibitory (Table 1). Common adverse effects with SAs (e.g., nausea, abdominal cramps, diarrhea, malabsorption of fat, and flatulence) are a consequence of the physiologic actions of somatostatin on the gastrointestinal tract and exocrine pancreas.[14]

Table 1. Somatostatin physiology[13]

CNS	Inhibits growth hormone release from pituitary
	Antinociception
Liver	Decreases blood flow
	Inhibits bile duct secretion
	Inhibits gallbladder contraction
Pancreas	Inhibits endocrine secretion

	Inhibits exocrine secretion
Gastrointestinal	Inhibits salivary amylase release
	Inhibits gastric acid secretion and gastric emptying
	Inhibits gastrointestinal hormone secretion
	Slows gastrointestinal motility
	Inhibits absorption (primarily carbohydrates)
	Reduces intestinal fluid volume
	Decreases splanchnic blood flow

SAs can slow the growth (antiproliferative effects) of some gastrointestinal cancers, particularly NETs. This antitumor activity appears to be related to both direct and indirect effects. Directly, activation of somatostatin receptors in tumor cells induces cell cycle arrest or apoptosis primarily through regulation of MAP kinase and phosphotyrosine phosphatase activities. Somatostatin receptors are also expressed on some tumor blood vessels, providing an indirect mechanism for inhibiting tumor angiogenesis and secretion of growth factors.[15,16]

1.1.4 PEI

PEI is a condition caused by reduced or inappropriately low secretion or activity of pancreatic juice and its digestive enzymes, pancreatic lipase in particular.[17] PEI can result in clinical manifestations such as steatorrhea, weight loss and biochemical alterations related to lipid and liposoluble micronutrient malabsorption and maldigestion.[18] Overt maldigestion is associated with easily detectable symptoms, impaired quality of life, and risk of significant complications due to malnutrition.[17] Risk factors associated with PEI include acute and chronic pancreatitis, pancreatic resection and surgery, pancreatic cancer, cystic fibrosis, and diabetes.[19] PEI has been reported to be common in patients with diabetes mellitus with a prevalence widely ranging, in different studies, in both type I (25–74%) and type II (28–54%).[20]

Symptoms of PEI include mild abdominal discomfort, bloating, cramping, and increased flatulence. Patients with severe insufficiency have steatorrhea and weight loss. Steatorrhea and weight loss develop late in the disease process after there is loss of 90% of pancreatic enzyme secretion. Less severe degrees of PEI cause subclinical consequences that may result in untoward repercussions for the nutritional status of patients. Therefore, PEI should be suspected, diagnosed, and treated early in subjects with symptoms such as bloating, abdominal discomfort, and otherwise unexplained nutritional deficiencies.

Normally, the exocrine pancreas secretes digestive enzymes, including lipase, elastase, amylase, trypsin and chymotrypsin, into the second portion of the duodenum via the pancreatic duct.[21] Stimulation of pancreatic enzyme secretion is mediated by hormonal and neuronal control. When gastric contents (chyme) empty into the duodenum, secretin and cholecystokinin (CCK) are secreted. In response to acid, secretin stimulates pancreatic release of bicarbonate and water. In response to fat and protein, CCK stimulates release of pancreatic enzymes.[22] Adequate mixing of chyme and these secretions is critical and can be disrupted by altered surgical anatomy or gastric acid. Mechanisms of PEI include inadequate synthesis and secretion of pancreatic enzymes, decreased stimulation, pancreatic ductal obstruction and decreased pancreatic enzyme activity in the small bowel. Some of the common causes of PEI are chronic pancreatitis,

pancreatic adenocarcinoma, and cystic fibrosis. Many of the causes of PEI (Table 2) share a common pathophysiologic mechanism that results in inadequate pancreatic enzyme digestion.

Table 2. Causes of PEI and Mechanisms[21]

Cause	Mechanism
Chronic pancreatitis	Permanent structural damage of ducts and parenchyma
Cystic fibrosis	Dysfunctional pancreatic secretion secondary to CFTR mutations
Main pancreatic duct obstruction	Decreased secretions of pancreatic enzymes
Pancreatic resection	Decreased secretions of pancreatic enzymes
Gastric resection	Decreased hormonal stimulation, rapid transit, inadequate mixing of chyme with pancreatic enzymes
Short bowel syndrome	Decreased hormonal stimulation, rapid transit, inadequate mixing of chyme with pancreatic enzymes
Hereditary hemochromatosis	Iron deposition in the pancreas
Celiac disease	Small bowel mucosal disease leads to decreased CCK mediated pancreatic stimulation
Zollinger-Ellison syndrome	Gastrinoma causes inactivation of pancreatic enzymes via increased gastric acid
Abbreviations: CCK=cholecystokinin, CFTR=Cystic fibrosis transmembrane conductance regulator	

The differential diagnosis of PEI includes other causes of chronic diarrhea such as celiac disease, small intestinal bacterial overgrowth, giardiasis, Crohn's disease, microscopic colitis, and irritable bowel syndrome.[21] PEI should be considered in patients with risk factors for pancreatic disease or chronic unexplained diarrhea.

The diagnosis of PEI is best made by a combination of history, exclusion of other causes of malabsorption, and diagnostic laboratory and imaging studies, including cross-sectional imaging of the pancreas. The most practical diagnostic approach involves testing that is noninvasive, inexpensive, and readily available. Such laboratory tests that provide indirect measures of pancreatic function include fecal elastase-1 (FE-1), fecal fat, and levels of fat-soluble vitamins. An FE-1 level less than 200 μg/g is abnormal and commonly used as a threshold for the diagnosis of PEI, and levels <100 μg/g indicate severe PEI.[21] Chymotrypsin is another enzymatic product of pancreatic secretion used in the diagnosis of PEI. The specificity of fecal chymotrypsin for mild to moderate and advanced PEI is lower as compared with FE-1. Serum trypsinogen levels are associated with pancreatic acinar cell mass. Serum trypsinogen is not specific for PEI and has a low sensitivity for mild insufficiency but has a high sensitivity for advanced PEI when levels are less than 20 ng/mL.[23] Patients with severe PEI have elevated levels of fecal fat or steatorrhea (>7 grams of fat per 100 grams of stool per day; >14 grams of fat per 100 grams of stool per day are indicative of severe fat malabsorption).[21] Cross-sectional imaging should be obtained in adult patients with steatorrhea to rule out pancreatic cancer and to evaluate for structural changes of the pancreas.[21]

The mainstay of management in patients with symptoms of maldigestion and steatorrhea due to PEI is administration of exogenous pancreatic enzymes, which relieve symptoms and long-term sequelae of PEI, enable normal dietary fat intake, and allow for weight gain.

1.2 REGULATORY HISTORY

There are seven FDA-approved SAs currently marketed in the U.S. The first SA, octreotide acetate (Sandostatin®) was approved by the FDA on October 21, 1988. Table 3 lists the currently available SAs in the U.S. for the indications listed.

Table 3. SAs Approved by FDA in the U.S.

Active ingredient	**Octreotide acetate**			**Lanreotide acetate**		**Pasireotide diaspartate**	
Trade name	Mycapssa	Sandostatin	Sandostatin LAR	Somatuline Depot	Lanreotide	Signifor	Signifor LAR Kit
Application NDA	208232	019667	021008	022074	215395	200677	203255
Approval date	6/26/20	10/21/88	11/25/98	8/30/07	12/17/21	12/14/12	12/15/14
Dosage form	PO capsule	SQ or IV injection	SQ injection	SQ injection	SQ injection	SQ injection	IM injection
Indication (dose)	Acromegaly (20 mg BID)	Acromegaly (50 µg TID) Carcinoid tumor (1500 µg QD) VIPoma (450 µg QD)	Acromegaly (50 µg TID) Carcinoid tumor, VIPoma (600 µg QD)	Acromegaly (90 mg Q 4WK) GEP-NET* (120 mg Q 4WK) Carcinoid syndrome (120 mg Q 4WK)	Acromegaly (90 mg Q 4WK) GEP-NET (120 mg Q 4WK)	Cushing's disease (0.3-0.9 mg BID)	Acromegaly (40 mg Q 4WK) Cushing's disease (10 mg Q 4WK)

Abbreviations: BID=twice daily, GEP-NET=gastroenteropancreatic neuroendocrine tumor; IM=intramuscular, IV=intravenous, LAR=long-acting release, PO=by mouth, Q=every, QD=daily, SQ=subcutaneous, TID=three times daily, VIPoma=vasoactive intestinal peptide tumor, WK=week

On December 4, 2019, the Division of Metabolism and Endocrinology Products requested an oncology consult under NDA 213224.[a] This consult requested the Division of Oncology-II (DO2) review and comment on the information in the proposed product labeling that pertained to the indications of metastatic carcinoid tumors and VIPomas. The consult response from DO2 states, "Octreotide also reduces splanchnic blood flow, gastric acid secretion, gastrointestinal motility, and *pancreatic exocrine function.*"[24] This reduction in pancreatic exocrine function may explain the possible biologic mechanism of PEI with SAs.

On August 2, 2022, DGE requested DPV assess whether a newly identified safety signal (NISS) should be opened for PEI and the SA drug class based on the EMA PRAC report and labeling in the SmPC for octreotide. On August 3, 2022, DPV opened NISS ID #1004917, and moved it to the evaluation phase after conferring with DGE, which is the basis for this review.

(b) (4)

[redacted]

[a] The Applicant submitted a new NDA for a concentrated formulation of Octreotide Acetate Injection (2.5 mg/mL), provided as a pen injector 2.8 mL device, via the 505(b)(2) pathway with reliance on the FDA's prior findings of safety and efficacy for Sandostatin injection (NDA 019667). The Agency issued a Complete Response for this NDA, dated May 19, 2021.

1.3 RELEVANT PRODUCT LABELING

1.3.1 SA United States Prescribing Information[26,27,28,29,30,31,32]

SAs are not currently labeled for PEI, however the USPIs contain language related to other gastrointestinal adverse reactions. Table 4 provides a summary of gastrointestinal-related adverse reactions listed in the USPI for each SA.

Table 4. Labeled Gastrointestinal-Related Adverse Reactions in the USPI for SAs

Adverse Event	Bynfezia Pen (octreotide acetate)	Mycapssa (octreotide acetate)	Sandostatin (octreotide acetate)	Sandostatin LAR (octreotide acetate)	Somatuline Depot (lanreotide acetate)	Signifor (pasireotide diaspartate)	Signifor LAR (pasireotide diaspartate)
May alter absorption of dietary fats			WP	WP			
Steatorrhea			**AR**	**AR**	**PM**		
Diarrhea	AR, OD	AR, OD, PCI	AR, OD	AR	AR, PCI	AR, OD	AR, PCI

Definitions: WP=Warnings and Precautions, AR=Adverse Reactions, PM=Postmarketing Experience, OD=Overdosage, PCI=Patient Counseling Information

1.3.2 Octreotide SmPC[33]

Octreotide received central marketing authorization from the EMA on February 16, 2012. The SmPC for octreotide injection contains the following information related to PEI:

4. Clinical particulars

4.4 Special warnings and precautions for use

Pancreatic function
Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving octreotide therapy for gastroenteropancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating, and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION AND CASE SELECTION CRITERIA

Case Definition
The case definition of PEI requires the following in this review:

Category I

- Chronic diarrhea or steatorrhea

AND

- FE-1 of <200 mcg/g or terminology synonymous with significantly 'abnormal fecal elastase test'
  OR
- Fecal chymotrypsin consistent with PEI[b]
  OR
- Serum trypsinogen levels less than 20 ng/mL
  OR
- Positive direct pancreatic function test [e.g., CCK stimulation test, secretin stimulation test]

Category II

- Clinician diagnosis of PEI

Case Selection Criteria[c]
In this review, case selection criteria included the following:

- Inclusion Criteria
  - Meets case definition of PEI in association with exposure to SA
- Exclusion Criteria
  - Other more likely causes of steatorrhea (e.g., inflammatory bowel disease, sprue-like enteropathy, short bowel syndromes, small bowel overgrowth,

[b] 2.3-51.4 U/g is a reference range (available at www.mayocliniclabs.com/test notifications/attachment.php?id=32474)
[c] A causality assessment tool was not used. Instead, inclusion and exclusion criteria were used.

acute or chronic pancreatitis, cystic fibrosis, common bile duct, or pancreatic duct obstruction)
- Insufficient information to assess causality
- Unlikely causal association
- Duplicate report

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 5.

Table 5. FAERS Search Strategy*	
Date of search	August 23, 2022[d]
Time period of search	October 21, 1988[†] to August 22, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product active ingredient: octreotide, octreotide acetate, octreotide hydrochloride, octreotide pamoate, lanreotide, lanreotide acetate, pasireotide, pasireotide diaspartate, pasireotide pamoate
MedDRA search terms (Version 25.0)	*Pancreatic disorder* (PT), *Endocrine pancreatic disorder* (PT), *Pancreatic failure* (PT), *Steatorrhoea* (PT), *Faecal elastase concentration abnormal* (PT), *Faecal elastase concentration decreased* (PT), *Malabsorption* (PT), *Lipase decreased* (PT), *Lipase abnormal* (PT), *Pancreatic enzyme abnormality* (PT), *Pancreatic enzymes decreased* (PT), *Faecal elastase test* (PT), Pancreatic enzymes abnormal (PT), Exocrine pancreatic function test abnormal (PT), Blood elastase decreased (PT), Amylase abnormal (PT), Amylase decreased (PT), Stool chymotrypsin abnormal (PT), Stool chymotrypsin decreased (PT), Stool trypsin (PT), Immunoreactive trypsinogen abnormal (PT), Immunoreactive trypsinogen decreased (PT), Secretin test increased (PT)
* See Appendix A for a description of the FAERS database. † Earliest SA approval: Sandostatin (octreotide acetate) injection (NDA 019667) Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

2.3 DATA MINING SEARCH STRATEGY

DPV used the Empirica Signal software with the strategy described in Table 6 to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., "potential signals"). If a drug-event combination has a score (EB05) of ≥ 2, this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Disproportionality analyses were used to assess the potential association of drugs and events in the SA drug class using data in the FAERS database.

[d] An updated search for pasireotide using the criteria in Table 5 from August 22, 2022, to May 31, 2023, retrieved no reports of pasireotide and PEI.

Table 6. Data Mining Search Strategy*	
Data refresh date	May 28, 2023
Product terms	octreotide, lanreotide, pasireotide
Empirica Signal run name	PAM (S)
MedDRA search strategy	PT *Pancreatic failure* , PT *Pancreatic disorder*, PT *Endocrine pancreatic disorder*, PT *Steatorrhoea*, PT *Faecal elastase concentration abnormal*, PT *Faecal elastase concentration decreased*, PT *Malabsorption*, PT *Lipase decreased*, PT *Lipase abnormal*, PT *Pancreatic enzyme abnormality*, PT *Pancreatic enzymes decreased*, PT *Faecal elastase test*, PT *Pancreatic enzymes abnormal*, PT, *Exocrine pancreatic function test abnormal*, PT *Blood elastase decreased*, PT, *Amylase abnormal*, PT *Amylase decreased*, PT *Stool chymotrypsin abnormal*, PT *Stool chymotrypsin decreased*, PT *Stool trypsin*, PT *Immunoreactive trypsinogen abnormal*, PT *Immunoreactive trypsinogen decreased*, PT *Secretin test increased*
Limits	EB05 ≥ 0.0
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAM=product active moiety, PT=Preferred Term	

2.4 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategies described in Table 7 and 8.

Table 7. Literature Search Strategy	
Date of search	August 23, 2022
Database	PubMed
Search terms	((somatostatin analogs) or (somatostatin analogues) or (octreotide) or (pasireotide) or (lanreotide)) and ((pancreatic exocrine insufficiency) or (exocrine pancreatic insufficiency) or (pancreatic insufficiency) or (pancreatic failure))
Years included in search	1988[†]-2022
[†]Earliest SA approval: Sandostatin (octreotide acetate) injection (NDA 019667)	

Table 8. Literature Search Strategy	
Date of search	June 1, 2023
Database	Embase

Table 8. Literature Search Strategy	
Search terms	('somatostatin analog'/exp OR 'somatostatin analog' OR (('somatostatin'/exp OR somatostatin) AND analog)) AND ('pancreatic exocrine insufficiency'/exp OR 'pancreatic exocrine insufficiency' OR (pancreatic AND ('exocrine'/exp OR exocrine) AND insufficiency))
Years included in search	1988[†]-2022
[†]Earliest SA approval: Sandostatin (octreotide acetate) injection (NDA 019667)	

2.5 APPLICANT INFORMATION REQUEST

On May 31, 2022, DGE sent Information Requests (IRs) to applicant holders of octreotide, lanreotide, and pasireotide products for a comprehensive assessment of PEI associated with the use of SAs from clinical trials, postmarketing experience, and medical literature.[34,35,36,37,38,39,40]

2.6 DRUG UTILIZATION

The Drug Utilization Team within DEPI-II used proprietary databases available to FDA to conduct these analyses. See **Appendix B** for detailed descriptions and limitations of the databases. Time periods for different analyses varied based on data availability.

2.6.1 Data Sources

2.6.1.1 Sales Distribution Data

DEPI-II used the (b) (4) database to determine the primary settings of care where SAs (octreotide, lanreotide, and pasireotide) were sold from manufacturers to all U.S. channels of distribution in 2021.

In addition, we used (b) (4) database to obtain the annual estimated number of packages[e] (vials, syringes, or ampules) sold for SAs from manufacturers to all U.S. settings of care[f], stratified by drug molecule, from 2012 through 2021.

The sales distribution data represent the amount of product sold from manufacturers to various channels of distribution and does not reflect what is being sold to or administered to patients directly.

2.6.1.2 Patient-Level Data
Non-Federal Hospital Data

We used the (b) (4) database to obtain the annual estimated number of patients with a hospital billing for SAs from U.S. non-federal hospitals, stratified by

(b) (4)

drug molecule, from 2016 through 2021. National estimates are captured from inpatient or outpatient hospital discharge billing records. An outpatient visit includes emergency room, same-day surgeries, rehabilitation of all types, reoccurring outpatient visits, and other outpatient visits that do not involve the emergency room. They do not include stand-alone outpatient clinics or pediatric hospitals.

Outpatient Pharmacy Data

We used the [redacted] (b) (4) database to obtain the annual estimated number of patients who received a dispensed prescription for SAs from U.S. outpatient pharmacies, stratified by drug molecule, from 2012 through 2021. Outpatient pharmacies include retail, mail-order, and long-term care pharmacies. Of note, Metys does not capture patients dispensed prescription from or drugs administered in non-retail settings, such as clinics, doctors' offices, and other settings.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 276 reports. After applying the case definition and case selection criteria in Section 2.1, 27 cases were included in the case series of PEI reported with SA use (see Figure 1).

Figure 1. FAERS Case Selection

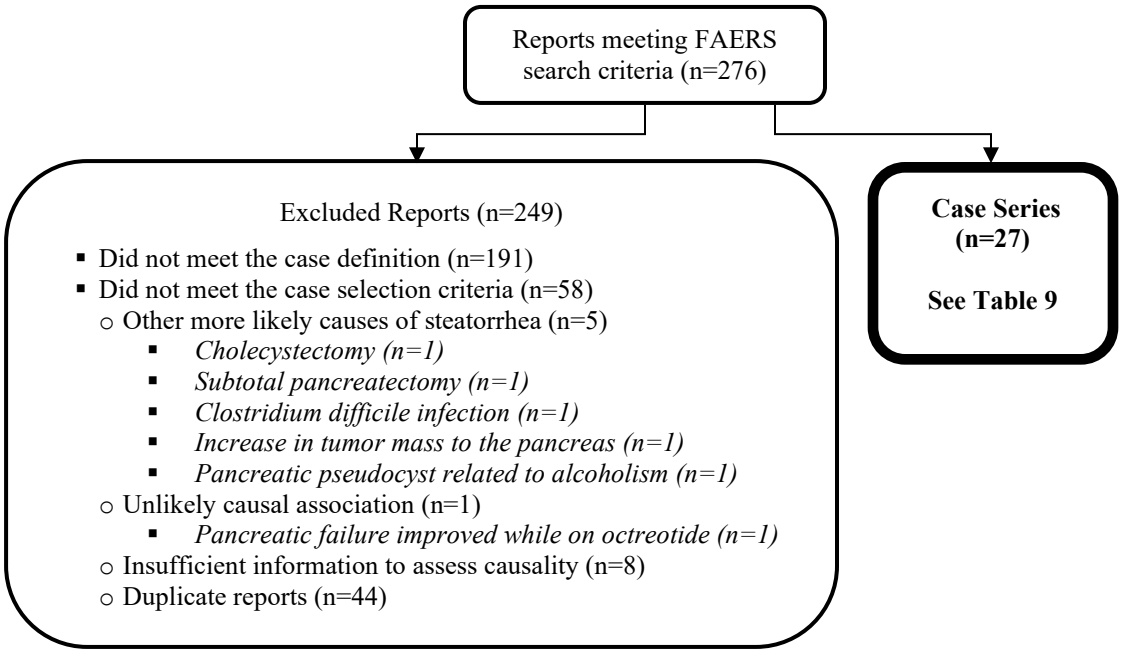

Table 9 summarizes our case series consisting of 27 FAERS cases of PEI reported with SAs. Notably, no cases of PEI with pasireotide products were included in our case series (see Drug Utilization Section 3.5 regarding pasireotide drug utilization compared to octreotide and lanreotide).

Appendix C contains a line listing of the 27 cases in this case series.

Table 9. Descriptive Characteristics of Cases Reporting PEI with SAs in this FAERS Case Series, Received by FDA From October 21, 1988[*]- August 22, 2022 (n=27)			
Characteristic	**Octreotide (n=14)**	**Lanreotide (n=13)**	**Total (n=27)**
Report type			
Expedited	7	8	15
Periodic	-	2	2
Literature	7[†]	3[‡]	10
Patient sex	N=13	N=12	N=25
Female	7	5	12
Male	6	7	13
Age (years)	N=12	N=12	N=24
Median	62	63	63
Range	31-82	47-77	31-82
Country			
U.S.	8	4	12
Foreign	6[§]	9[‖]	15
Case Definition Category			
Category I	2	1	3
Category II	12	12	24
Year received by FDA			
2000-2010	2	1	3
2011-2020	10	11	21
2021	2	1	3
Indication	N=14	N=13	N=27
NET	3	2	5
Pancreatic NET	2	1	3
Carcinoid syndrome	2	1	3
GEP-NET	-	3	3
Ileal NET	2	-	2
Carcinoid tumor	1	-	1
Metastatic carcinoid tumor	1	-	1
Pulmonary carcinoid	1	-	1
Polycystic liver ADPKD	1	-	1
Congenital hyperinsulinism	1	-	1
Refractory diarrhea	-	1	1
Acromegaly	-	1	1
Metastatic pancreatic NET	-	1	1
Neuroendocrine carcinoma	-	1	1
Metastases to liver	-	1	1
NET lung	-	1	1
Serious outcome[¶]	N=14	N=11	N=25
Death	1	1	2
Hospitalization	2	3	5
Other serious	11	7	18
Reporter Type			
Physician	5	8	13
HCP, NOS	9	5	14
Time to onset[**]	N=7	N=6	N=14
Median (months)	15	5	8
Range	"few hours" to 50 months	"same day" to 60 months	"few hours" to 60 months

Table 9. Descriptive Characteristics of Cases Reporting PEI with SAs in this FAERS Case Series, Received by FDA From October 21, 1988[*]- August 22, 2022 (n=27)

Characteristic	Octreotide (n=14)	Lanreotide (n=13)	Total (n=27)
Reported AE of interest (non-mutually exclusive)[††]	N=11 Diarrhea (4) Weight loss (4) Bloating (3) Gas (3) Abdominal pain (2) Bruising (1) Coagulopathy (1) Nausea (1) Vomiting (1) Steatorrhea (1) Night blindness (1) Abdominal distension (1)	N=13 Diarrhea (9) Steatorrhea (5) Weight loss (4) Abdominal pain (3) Abdominal cramping (3) Nausea (3) Gas (3) Bowel obstruction (1) Malabsorption (1) Bloating (1) Pale feces (1)	N=24 Diarrhea (13) Weight loss (8) Steatorrhea (6) Gas (6) Abdominal pain (5) Bloating (4) Nausea (4) Abdominal cramping (3) Bruising (1) Coagulopathy (1) Vomiting (1) Night blindness (1) Abdominal distension (1) Bowel obstruction (1) Malabsorption (1) Pale feces (1)
FE-1 (µg/g)	N=2	N=1	N=3
Median	129	74	120
Range	120-137	NA	74-137
Treatment[‡‡]	N=13	N=8	N=21
PERT	11	7	18
Oral Iron	1	0	1
Vitamins (A,D,E,K)	1	0	1
Low fat diet	0	1	1
SA therapy modification	N=14	N=13	N=27
Dose decreased	2	0	2
Drug discontinued	2	4	6
No change	10	9	19
Patient disposition	N=9	N=4	N=12
Resolved[§§]	6	2	7
Resolving	2	0	2
Not resolved	1	2	3

[*] Earliest SA approval: Sandostatin (octreotide acetate) injection (NDA 019667)

[†] One octreotide literature report was captured in FAERS but not identified in the literature search.[41]

[‡] One lanreotide literature report was captured in FAERS but not identified the literature search[42]

[§] Six foreign cases from Great Britain (1), Belgium (1), Canada (1), Finland (1), Switzerland (1), Spain (1).

[‖] Nine foreign cases from Great Britain (2), Australia (1), Belgium (1), Canada (1), Spain (1), Japan (1), Israel (1), Netherlands (1).

[¶] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case may contain more than one serious outcome. One case with a death with octreotide (FAERS 9247639) reported a patient who developed malabsorption syndrome after receiving octreotide to treat metastatic carcinoid tumor; the cause of death was reported as metastatic carcinoid cancer causing liver failure.

[**] Time to onset calculated from the initiation of SA to the diagnosis of PEI.

[††] A case may contain more than one AE of interest. Night blindness is an initial sign of Vitamin A deficiency.

[‡‡] A case may contain more than one treatment.

[§§] Of the eight octreotide patients who reported resolution, seven patients did not discontinue octreotide, but PEI resolved with the addition of PERT, and one patient discontinued octreotide without the addition of PERT. Of the two lanreotide patients who reported resolution, both patients discontinued lanreotide, one of which was also treated with PERT.

Abbreviations: ADPKD=autosomal dominant polycystic kidney disease, AE=adverse event, FE-1=fecal elastase-1, GEP-NET=Gastroenteropancreatic neuroendocrine tumor, HCP=healthcare provider, NET=neuroendocrine tumor, NOS=not otherwise specified, PEI=pancreatic exocrine insufficiency, PERT=pancreatic enzyme replacement therapy, SA=somatostatin analog

REPRESENTATIVE CASES (N=7)

FAERS 7602892 (Belgium, 2010-2883, 2010):
This clinical study case was received from a physician investigator and concerned a 77-year-old male patient enrolled in a phase III, multi-center, prospective, exploratory, open label study to assess the efficacy and safety of lanreotide acetate 120 mg in the symptomatic treatment of patients with refractory diarrhea. The patient did not have any relevant medical history. Concomitant medications included mebeverine, tamsulosin, and olanzapine. One day after receiving treatment with study drug, the patient experienced "severe" steatorrhea. It was reported the patient felt nauseous and had to stay in bed. The following day he was hospitalized due to the steatorrhea. Treatment for the event included Creon 150 mg three times a day and a low-fat diet. Treatment with study drug was discontinued due to the adverse event. Four days later, the event severity changed to mild and three weeks later the event "completely" resolved. The reporter suspected a causal relationship between study drug and the event.

Reviewer comment: This patient experienced "severe" steatorrhea requiring hospitalization one day after receiving lanreotide to treat refractory diarrhea. The close temporal relationship between the onset of steatorrhea and initiation of lanreotide supports a causal relationship between steatorrhea and lanreotide. Resolution of the event upon discontinuation of the lanreotide also supports a drug-event relationship, although it is confounded by treatment with pancreatic enzyme replacement therapy (PERT). However, resolution of the steatorrhea with the administration of PERT suggests a pancreatic etiology. Notably the absence of an underlying carcinoid or NET to explain the occurrence of PEI supports a causal role of lanreotide with PEI.

FAERS 8222206 (US, PHHY2011US95004, 2011)
FAERS 8222216 (US, PHHY2011US95871, 2011)
FAERS 8222210 (US, PHHY2011US95882, 2011)
FAERS 8222205 (US, PHHY2011US95887, 2011)
FAERS 8222224 (US, PHHY2011US95888, 2011):
The following five cases consist of a cohort of patients reported by Saif and Larson et al. who developed PEI after receiving chronic octreotide to treat NET.[3] The corresponding cases were also submitted to FAERS. The publication provided additional details not reported in the FAERS cases. A summary of the publication is provided below.

The charts of 43 patients with histological diagnosis of NET were retrospectively reviewed and followed up at the Yale Cancer Center from July 2005 to May 2010.[3] An observation of worsening diarrhea in two patients who were stable in their symptoms and biochemical profile (e.g. serum chromogranin, 5-HT) at a constant dose of octreotide analogs led investigators to examine other etiologies for worsening diarrhea, including PEI.

The observation started with two patients who were treated for NET. The patients' diarrhea was controlled on a stable dose of octreotide. After a mean of two years of octreotide treatment, diarrhea recurred and was thought to be related to uncontrolled disease secondary to the NET. The octreotide LAR dose was escalated, with no improvement in diarrhea. Stool testing revealed a high fat content consistent with a diagnosis of fat malabsorption. PEI was diagnosed based on no previous history of pancreatitis, hemochromatosis, cystic fibrosis, or pancreatic surgeries.

After consultation with gastroenterologists, who concurred with the clinical diagnosis, these two patients were prescribed PERT. Both patients had improvement in their symptoms, including steatorrhea, after a median duration of replacement enzymes for 4 weeks.

After the authors noted this finding, three additional patients were identified with similar clinical presentations (i.e., no improvement, in fact worsening of diarrhea with escalation of octreotide dose). After consultation with gastroenterology, stool studies for fat quantification confirmed the diagnosis of PEI. The symptoms and diarrhea improved after a median duration of 3 weeks of PERT. In addition, the dose of octreotide LAR was reduced from 80 to 60 mg in two patients.

Overall, in this cohort of 43 patients, 11.6% of patients with NET on chronic octreotide analog therapy developed PEI.

Table 3. Cohort of patients treated with pancreatic enzyme replacement who were on chronic octreotide LAR therapy for neuroendocrine tumors.

Age/sex	Location of primary	Stage	Sandostatin dose (mg)	Duration	Cumulative dose (mg/m^2)	Symptoms	Diagnostic test	Treatment	Outcome
67/M	Pancreas	IV	30	18 months	540	Weight loss, gas problems and bloating	Fecal stool	Creon	Improved
64/F	Ileum	IV	80	36 months	2590	Diarrhea	Fecal stool	Creon	Improved
53/F	Pancreas	IV	30	50 months	1500	Weight loss, gas problems and bloating	Fecal stool	Creon	Improved
51/M	Ileum	IV	80	38 months	670	Bloating	Fecal stool	Creon	Improved
48/M	Unknown primary	IV	30	12 months	360	Weight loss and gas problems	Fecal stool	Creon	Improved

Saif MW, Larson H, Kaley K, Shaib W. Chronic octreotide therapy can induce pancreatic insufficiency: a common but under-recognized adverse effect. Expert Opinion on Drug Safety 2010; 9:6, 867-873

<u>Reviewer comment:</u> This cohort of five patients was stable in their symptoms and dose of octreotide to treat NET prior to experiencing worsening of diarrhea. The median duration of therapy was 36 months. Nevertheless, worsening diarrhea was treated by dose escalation of octreotide as it was thought to be related to underlying disease. In all cases, diarrhea did not improve (or worsened) with dose escalation of octreotide. Stool studies for fat quantification confirmed the diagnosis of PEI, while excluding alternative etiologies. All patients reported symptomatic improvement with PERT despite continuation of octreotide therapy (octreotide dose was decreased in two patients). This suggests that PEI was the underlying cause of diarrhea and steatorrhea in all five patients.

In the Saif and Larson report, all five patients had metastatic disease and in the opinion of the DPV oncologist, worsening carcinoid syndrome would not be unexpected from progressive NET. However, PEI would be an unusual manifestation related to a primary NET localized to the pancreas (without carcinoid syndrome) unless there is obstruction of the pancreatic duct or a history of substantial resection of the primary pancreatic tumor. Although subtle, the authors of the paper have told us that these patients did not have progression of their underlying NET: "failed in improvement of diarrhea and weight loss following dose escalation of octreotide as initially it was thought to be related to progressive disease." Although the authors convey that PEI was not due to progressive disease, we assume the omission of imaging documentation may have been related to publication restrictions, such as word limits. In conclusion, all five patients

were treated with PERT, and therefore symptom improvement is difficult to ascribe to any factor other than PERT therapy.

FAERS 18056692 (Spain, ES-SUN PHARMACEUTICAL INDUSTRIES LTD-2020R1-253615, 2020):[2]
The patient is a seven month and three-week-old male with diazoxide unresponsive congenital hyperinsulinism, caused by a heterozygous pathogenic paternally inherited mutation in the ABCC8 gene. He was found to have bruising of legs, back and forearms after two months of octreotide treatment (8.9 µg/kg/day divided into four daily doses). Laboratory findings identified abnormal clotting values related to a decrease in all vitamin K-dependent proteins, consistent with deficiency of vitamin K (a fat-soluble vitamin) as the cause of the cutaneous hemorrhagic syndrome. Platelet and full blood counts were normal except for hypochromic microcytic anemia [hemoglobin 9.9 g/dL (11–14.5 g/ dL), red cell count 5×10^6 (4×10^6–5.3×10^6), MCV 61.5 fl (72–89 "fT")]. Bruising disappeared and coagulopathy resolved with a three-day course of vitamin K treatment. Levels of the other fat-soluble vitamins (A, D, E) were within the normal range. The patient was discharged without incident.

Further investigation at an unspecified date revealed steatorrhea and a decrease in FE-1(125 µg/g)] in repeated measurements. Other causes of PEI, such as cystic fibrosis and pancreatic hypoplasia were excluded, the latter based on PET scan findings. The child also developed cholelithiasis requiring ursodeoxycholic acid therapy, with favorable outcome. At 12 months of age, the patient required up to 12.7 mcg/kg/day of octreotide to maintain capillary blood glucose levels above 65–70 mg/dL. He has also needed PERT, oral iron supplementation, and dietary supplements with fat-soluble vitamins (vitamins A, D, E, K). He had normal growth and weight patterns, as well as adequate neurodevelopment at the time of report submission.

Reviewer comment: This patient developed PEI with a cutaneous hemorrhagic syndrome two months after starting octreotide to treat congenital hyperinsulinemic hypoglycemia (off label indication). Steatorrhea and low levels of FE-1 were diagnostic of PEI in this patient. Vitamin K deficiency likely occurred due to fat malabsorption secondary to PEI, thereby leading to bruising and coagulopathy in this patient. The temporal relationship between the onset of PEI and initiation of octreotide supports a possible association between PEI and octreotide. The patient's steatorrhea improved with PERT which supports a pancreatic etiology for the event.

3.2 DATA MINING

Table 10 summarizes the results of the data mining analysis using Empirica Signal for pancreatic failure reported with SA use with an EB05 score > 0.0.

Table 10. Data Mining Results Using Empirica Signal for Pancreatic Failure Reported With SA Use, Sorted by EB05 ≥ 0*

Product active moieties	PT or Narrow_Alg SMQ	N	EB05	EBGM	EB95
Lanreotide	Steatorrhoea	36	42.393	56.295	73.579
Lanreotide	Pancreatic failure	17	15.312	26.602	40.467
Octreotide	Steatorrhoea	60	14.335	18.52	23.228
Octreotide	Pancreatic failure	26	7.432	10.698	15.84

Octreotide	Pancreatic enzymes decreased	5	2.81	8.116	43.336
Lanreotide	Malabsorption	11	2.736	4.582	7.304
Octreotide	Malabsorption	27	2.446	3.387	4.593
Pasireotide	Steatorrhoea	5	2.332	5.155	10.544
Lanreotide	Pancreatic enzymes decreased	3	1.469	4.633	34.005
Lanreotide	Faecal elastase concentration decreased	2	0.847	3.229	11.639
Octreotide	Amylase decreased	2	0.687	2.306	6.129
Octreotide	Endocrine pancreatic disorder	1	0.287	1.496	5.249
Pasireotide	Pancreatic failure	1	0.256	1.331	4.66
** A score (EB05) of ≥ 2 indicates 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected."*					

Reviewer comment: Steatorrhoea, malabsorption, and pancreatic failure were disproportionally reported for both lanreotide and octreotide. Only steatorrhoea was disproportionally reported for pasireotide (see Drug Utilization Section 3.5 regarding pasireotide drug utilization compared to octreotide and lanreotide).

3.3 LITERATURE

DPV retrieved 231 literature citations from PubMed (n=108) and Embase (n=123), of which 18 were duplicates.

PubMed

DPV retrieved 108 literature citations in PubMed for SAs and PEI using the search criteria in Table 7. The titles and abstracts of the citations were reviewed to identify relevant articles reporting safety information. Of the 108 citations, 105 were excluded for the following reasons:

- 56 were research articles evaluating efficacy of SAs for multiple therapeutic indications (i.e., GEP-NET, pancreatitis, hyperinsulinism, diarrhea, prevention of post-operative complications after major pancreatic surgery)
- 14 were research articles evaluating efficacy of radiolabeled SA for the treatment of NET
- 12 were research articles evaluating the effectiveness of surgical management to treat pancreatic disease
- 20 articles did not pertain to the topic of this review
- 2 articles were duplicates of those previously identified in the FAERS case series[2,3]
- 1 letter to the editor[43] which commented on an article by Panzuto et al.[g] but provided no new information related to SA-associated PEI

Embase

DPV retrieved 123 literature citations in Embase for SAs and PEI using the search criteria in Table 8, of which 18 of were also retrieved in our PubMed search. Of the 105 unique citations, 104 were excluded for the following reasons:

[g] Panzuto et al.[46] was a review article that summarized four articles (Saif and Larson et al.[3], Saif and Romano et al.[7] Lamarca et al.[5], and Rinzivillo et al.[6]) that are additionally discussed below or in Section 3.1.

- 62 were review articles evaluating pancreatic disease
- 21 articles did not pertain to the topic of this review
- 12 were review articles evaluating NET
- 9 were review articles evaluating congenital hyperinsulinism and or hyperinsulinemic hypoglycemia

See below for a summary of the four articles of interest retrieved from our literature search, as well as two articles[h] identified from the Applicants' IR responses in Section 3.4.

Literature articles identified from Applicant IR responses (n=2)

Caplin et al.[44] conducted a randomized, double-blind, placebo-controlled, multinational study of lanreotide in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive NETs of grade 1 or 2[i], and documented disease-progression status. Patients were randomly assigned to receive lanreotide at a dose of 120 mg (101 patients) or placebo (103 patients) once every 28 days for 96 weeks. The primary end point was progression-free survival, defined as the time to disease progression or death. Secondary end points included overall survival, quality of life, and safety. Half of the patients in the lanreotide group had adverse events related to the study drug (vs. 28% in the placebo group), most commonly diarrhea (26% vs. 9%). Eight events were considered to be related to the study drug. Seven events including hyperglycemia, diabetes mellitus, nausea, vomiting, abdominal pain, biliary fistula, and cholelithiasis occurred in the lanreotide group and bile duct stenosis occurred in the placebo group. Notably, five participants (5%) of the patients receiving lanreotide experienced decreased pancreatic enzyme levels versus none (0%) in the placebo group.

Reviewer comment: This prospective randomized, double-blind, placebo-controlled trial examined the antiproliferative effects of lanreotide to control disease progression in metastatic enteropancreatic NET. The study drug-related adverse events seen in half of the patients in the lanreotide group versus placebo included GI-related events. The five patients who experienced decreased pancreatic enzymes versus none in the placebo group supports an association between decreased pancreatic enzymes and lanreotide.

Khan et al.[45] published a single center nine-year retrospective cohort study in the United Kingdom, which examined the long-term results of lanreotide in 69 patients with malignant carcinoid syndrome, assessing clinical and objective response and tolerance. Minimal data regarding treatment tolerability were reported in this study. However, the study noted that 35 patients (51%) experienced steatorrhea controllable by PERT. Additionally, patients developed asymptomatic cholelithiasis (n=3, 4%), increased diarrhea with no evidence of steatorrhea which resolved spontaneously (n=3, 4%), and abdominal pain which also resolved spontaneously (n=4, 6%).

[h] Caplin et al. and Khan et al. publications were not captured in the literature search as these were clinical studies evaluating the efficacy of lanreotide to treat metastatic enteropancreatic NET and malignant carcinoid syndrome, respectively.

[i] A tumor proliferation index (on staining for the Ki-67 antigen) of <10%.

Reviewer comment: This retrospective study aimed to present long-term results of lanreotide in a cohort of patients with malignant carcinoid syndrome. The most common adverse event was steatorrhea. FE-1 testing was not reported, although steatorrhea controllable by PERT is consistent with PEI as the cause of the steatorrhea.

Literature articles identified from the literature search (n=4)

Lamarca and McCallum et al. published a prospective, observational study investigating the frequency of SA-induced PEI in 50 sequential patients with advanced Wd-NETs treated with SAs.[5] PEI was diagnosed based on results of stool FE-1 quantification (below normal level or a reduction of ≥ 21% from baseline), which was performed at baseline and every three months thereafter. Symptom-based diagnosis of PEI was also accepted if FE-1 could not be performed. Patients who had PEI at study entry were also included and classified as SA-related PEI if PEI worsened after the start of SAs or if PERT initiation was required after initiation of SAs. Patients received 4-weekly long-acting octreotide (60%) or lanreotide (40%). PEI developed in 12 (24%) of the patients after a median of 2.9 months from SA initiation. Of the 12 patients, 8 (67%) were based on FE-1 levels; the remaining 4 (33%) were based on clinical symptoms (2 had PEI at study entry). Most (11 of 12) required PERT.

Reviewer comment: This relatively small prospective non-randomized, non-blinded case series supports findings that PEI occurs during SA therapy. However, there is no comparator group of similar patients who were not treated with SAs. PEI developed in 12 patients after a median of 2.9 months from SA initiation. The publication does not explicitly state if patients improved with PERT, although PERT was used "for symptom management." Study interpretation is limited by inclusion of patients who had PEI at the time of study entry, prior to SA initiation, and a somewhat non-specific categorization of PEI outcomes, noting that 33% of patients did not have a confirmatory FE-1 to determine development of SA-associated PEI. The authors also did not specify if either octreotide or lanreotide was associated with a greater proportion of these SA-related PEI outcomes. The authors concluded that, based on these results, PEI occurs at a higher rate than previously reported (one in four patients with Wd-NETS treated with SAs), and that clinicians need to diagnose and treat this SA-related adverse-event.

Rinzivillo et al.[6] published results of a prospective single-center study evaluating 35 patients treated with SAs for >12 months due to unresectable/advanced nonpancreatic Wd-NETs. Biochemical parameters and FE-1 were assessed to diagnose PEI. Seven patients (20%) had PEI, given the presence of abdominal symptoms and a median FE-1 value of 180 mcg/g of stool. No patient had severe PEI, defined as FE-1 < 100 mcg/g of stool. Elevated glycated hemoglobin levels were a significant predictor for developing PEI (odds ratio 4.81, p=0.01).

Reviewer comment: Similar to Lamarca et al. this is a small prospective non-randomized, non-blinded case series. Although development of SA-associated PEI occurring in 20% of these patients is of interest, this percentage reflects only long-term users because at least 12 months of SA treatment was required prior to study entry. Otherwise, study entry criteria and outcome determination of PEI was more rigorously defined than similar parameters in the Lamarca et al. study. Notably, this patient population had additional risk factors for PEI, including higher

glycated hemoglobin levels at baseline, suggesting that patients who developed PEI in this study were predisposed to this outcome.

The study by Saif and Romano[7] was identified as one of the four studies described within a review article by Panzuto et al.[46] Saif and Romano retrospectively reviewed medical charts and pharmacy records of 110 Wd-NET patients who received SAs (104 octreotide long-acting preparation and 6 lanreotide). PEI was defined by an FE-1 level below normal (or a reduction of ≥ 21.2%) or steatorrhea on quantitative fecal fat test. Nineteen patients (17%) were diagnosed with PEI. These patients were treated with PERT; only 14 patients had improvement in diarrhea within 8 weeks of initiating PERT.

Reviewer comment: An abnormal FE-1 level was not required for patients to be categorized as SA-associated PEI, and these published results do not report how many patients had abnormal FE-1 levels. Five patients categorized with PEI did not improve with PERT, which leads us to suspect that some patients may have been misclassified as having SA-associated PEI.

Hall et al.[47] conducted a clinical study assessing pancreatic exocrine function in octreotide- or lanreotide-treated patients with NETs using the 13C-mixed triglyceride breath test.[48] Exocrine function was reduced in all patients (n=10) following SA therapy; median reduction from baseline was −23.4% (range:−42.1–0.5%,p=0.005).

Reviewer comment: This small clinical study provides evidence that octreotide and lanreotide decrease pancreatic function in patients with NETs, using a clinically sensitive diagnostic test.[48] Therefore, the Hall et al. study provides supportive evidence that octreotide and lanreotide could contribute to PEI in patients with NETs. Although this study reported a reduction in exocrine function, the authors assert the impact on pancreatic function occurs early in treatment where the relationship to dysfunction and outcome is significant.

3.4 APPLICANT IR RESPONSES

The following are Applicants' evaluations of PEI associated with the use of SA from clinical trials, postmarketing experience, and the medical literature. See **Appendix D** for additional details.

Novartis: Sandostatin/Sandostatin LAR (octreotide) injection[49]

Clinical Trials

The Applicant identified 4 cases of PEI out of 1723 patients treated with octreotide within 16 clinical trials and 1 compassionate use program, including patients with acromegaly and carcinoid tumors. All four cases reported confounding factors.

Postmarketing

The Applicant identified 25 cases of pancreatic failure identified in the Novartis global safety database coded with the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) *Pancreatic failure*. None of the cases were deemed possibly related.

Scientific Literature

Novartis also included publications by Lamarca and McCallum et al.[5], Rinzivillo et al.[6], Saif and Romano[7] noted in Section 3.3 of the review.

Novartis conclusion
Given the absence of evidence of a causal relationship and against a high background incidence of PEI in the patient population receiving octreotide, the Applicant concluded an update to the USPI to include PEI would "neither appear warranted nor provide clinically relevant information."

Ipsen Bioscience: Somatuline Depot (lanreotide) injection[50]

Clinical Trials
Out of 378 patients in the GEP-NET pool treated with lanreotide within two clinical trials, the Applicant identified 5 cases of pancreatic enzymes decreased, 6 cases of steatorrhea, 16 cases of flatulence, 6 cases of abdominal distension, 4 cases of weight decreased, and 3 cases of pancreatic insufficiency. No causality assessments were provided for these events. Out of the 170 patients in the acromegaly pool treated with lanreotide within two clinical trials, the Applicant did not identify any cases of pancreatic insufficiency, steatorrhea, or decreased pancreatic enzymes.

Postmarketing
The Applicant identified 52 cases of PEI identified in the Ipsen global safety database coded with the MedDRA PT *Pancreatic failure* and by key word search (i.e., pancreatic exocrine insufficiency, exocrine pancreatic insufficiency, and pancreatic insufficiency). The Applicant assessed 20 cases as possibly related to lanreotide; the other cases reported confounding factors or had insufficient information to assess causality.

Scientific Literature
Ipsen Bioscience also included publications by Caplin et al.,[44] and Khan MS et al.[45] noted in Section 3.3 of the review.

Ipsen Bioscience conclusion
The Applicant validated PEI as a signal for lanreotide and the evaluation is currently ongoing.

Recordati Rare Diseases (RRD) Signifor LAR (pasireotide) injection[51]

Clinical Trials
No cases of PEI associated with the use of pasireotide were identified from clinical trials in the RRD global safety database.

Postmarketing
The Applicant identified 5 cases of PEI associated with Signifor LAR in the RRD global safety database coded with the MedDRA PT *Pancreatic failure*, PTs related to signs and symptoms of PEI, and by key word search (i.e., pancreatic exocrine insufficiency, exocrine pancreatic insufficiency, pancreatic insufficiency). The Applicant assessed two

of these cases as unrelated to Signifor LAR, and the Applicant used contradictory language referring to the remaining three cases. Although the Applicant states "three cases were considered as related to Signifor LAR" they conclude "our investigation did not retrieve any cases of PEI related to the use of pasireotide." Nonetheless, case specific information is reported in the IR response regarding three of these cases, which are noteworthy for positive temporality and recovery from steatorrhea with PERT.

Scientific Literature
RRD also included a publication by Muhammad et al.[52] evaluating pancreatic insufficiency in an open-label, conversion study; however, no diagnostic evaluation was performed to confirm PEI in the study.

RRD conclusion
The Applicant did not identify any relevant cases of PEI causally related to the use of Signifor LAR. They concluded there is no clinical evidence PEI may be associated with pasireotide use.

Amryt Pharma: Mycapssa (octreotide) oral capsule[49]
The Applicant did not identify any relevant cases from clinical trials, post-marketing experience, or the medical literature were identified from the Amryt global safety database.

Invagen Pharmaceuticals: Lanreotide injection[50]
The Applicant did not identify any relevant cases of PEI from clinical trials or post-marketing experience were identified from the Invagen global safety database.

RRD: Signifor (pasireotide) injection[51]
The Applicant did not identify any relevant cases of PEI with Signifor from clinical trials, post-marketing experience, or the medical literature were identified from the RRD global safety database

3.5 DRUG UTILIZATION

3.5.1 Settings of Care

In 2021, U.S. manufacturer sales data showed that approximately (b) (4)% of SAs were distributed to non-retail settings (primarily non-federal hospitals), (b) (4)% to mail-order, and (b) (4)% to retail settings of care[j]. Our analyses focused on sales of SAs to all U.S. settings of care and patient utilization from both outpatient and non-federal hospital settings.

3.5.2 Sales Distribution Data

Table 1 in **Appendix E** displays the annual estimated number of packages (vials, syringes or ampules) sold for SAs from manufacturers to all U.S. settings of care, stratified by drug molecule, from 2012 through 2021.

[j] Source: (b) (4) National Sales Perspectives. Year 2021. Data Extracted November 2022. File: NSP 2022-724 SA by sup ch 11-14-2022. Sales data for the somatostatin analogs (octreotide, lanreotide, and pasireotide were combined to determine the settings of care for these products.

Total sales of SAs increased [redacted]% from an estimated [redacted] packages between 2012 and 2021, with a peak in sales observed in 2020 ([redacted] packages). Octreotide accounted for [redacted]% ([redacted] packages) while lanreotide represented [redacted] ([redacted] packages) in 2021. Sales of pasireotide represented [redacted]% of the SA market.

As illustrated in **Figure 2** below, sales of octreotide increased from an estimated [redacted] to [redacted] packages between 2012 and 2021, with a peak in sales in 2020 ([redacted] packages). Sales of lanreotide also increased from [redacted] to [redacted] packages during the study period. Meanwhile pasireotide sales increased to a peak of [redacted] packages in 2015, then decreased to [redacted] packages in 2021. Over the ten-year time frame, sales of lanreotide and pasireotide remained low compared to octreotide.

Figure 2. Annual estimated number of packages sold for somatostatin analogs from manufacturers to all U.S. settings of care, stratified by drug molecule, 2012-2021

3.5.3 Outpatient Utilization Data

Table 2 in **Appendix E** provides the annual estimated number of patients who received a dispensed prescription for SAs from U.S. outpatient pharmacies, stratified by drug molecule, from 2012 through 2021.

The total number of patients with a dispensed prescription for SAs decreased from an estimated (b) (4) to (b) (4) patients between 2012 and 2021. Octreotide accounted for the highest proportion of outpatient use at (b) (4)% ((b) (4) patients), while lanreotide accounted for (b) (4)% ((b) (4) patients) in 2021. A negligible amount of pasireotide use was captured from U.S. outpatient pharmacies during the study period (single-digit estimates).

As illustrated in **Figure 3** below, patients with a dispensed prescription for octreotide decreased from an estimated (b) (4) to (b) (4) patients between 2012 and 2021, while lanreotide increased from (b) (4) to (b) (4) patients.

Figure 3. Annual estimated number of patients who received dispensed prescriptions for somatostatin analogs from U.S. outpatient pharmacies, stratified by drug molecule, 2012-2021

3.5.4 Non-Federal Hospital Patient Data

Table 3 in **Appendix E** provides the annual estimated number of patients with an inpatient or outpatient hospital discharge billing for SAs from U.S. non-federal hospitals, stratified by drug molecule, from 2016 through 2021.

The total number of patients with a hospital billing for SAs increased from an estimated (b) (4) to (b) (4) patients between 2016 and 2021. Octreotide accounted for (b) (4)% ((b) (4) patients), while lanreotide accounted for (b) (4) ((b) (4) patients) in 2021. Pasireotide use represented (b) (4)% of the SA market from U.S. non-federal hospitals during the examined study period.

As illustrated in **Figure 4** below, patients with a hospital billing for octreotide increased from an estimated (b) (4) to (b) (4) patients between 2016 and 2021. Patient utilization of lanreotide also increased from (b) (4) to (b) (4) patients during the study period. Meanwhile pasireotide use increased to a peak of about (b) (4) patients in 2020, then decreased to (b) (4) patients in 2021.

Figure 4. Annual estimated number of patients with a hospital billing for somatostatin analogs from U.S. non-federal hospitals, stratified by drug molecule, 2016-2021

4 DISCUSSION

This review identified 27 cases in FAERS of PEI associated with the use of SAs, including 14 cases of octreotide and 13 cases of lanreotide. Notably, we did not identify any FAERS cases related to pasireotide. We also identified six articles from the medical literature that included clinical trial evidence that pancreatic exocrine function is decreased by octreotide and lanreotide. Although the published observational studies demonstrate a high incidence of PEI with SA use in patients with NET/GEP-NETs, the interpretation of these studies is limited by study design issues (e.g., lack of baseline pancreatic function, lack of comparator group, no confirmatory FE-1 levels) to assess the development of SA-induced PEI.

Octreotide

DPV identified 14 cases in FAERS of PEI associated with octreotide. All 14 cases reported a serious outcome including death and hospitalization, although the single case reporting death was not attributable to octreotide. Two of 14 cases reported a temporal relationship to octreotide, with one reporting a positive dechallenge. In seven cases the patient recovered with PERT despite continuation of octreotide. Continuing therapy may be related to the fact SAs are used to treat chronic conditions where discontinuation of therapy may cause withdrawal symptoms. Notwithstanding, resolution with PERT suggests underlying PEI was the cause of the diarrhea and steatorrhea. One case describing a patient experiencing night blindness from vitamin A deficiency, related to malabsorption from chronic steatorrhea, reported resolution of symptoms with discontinuation of octreotide. Although this patient did not receive PERT, the authors assert that "pancreatic enzyme supplementation could be a therapeutic option to attenuate

steatorrhea in this setting" which suggests a PEI etiology for the event. The six remaining cases were confounded by underlying pathology (e.g., advanced NETs, cancers of the mid-gut, pancreas) and other medical conditions (e.g., gastric and small bowel resection, pancreatic atrophy.

A published retrospective chart review of patients diagnosed with NET noted 5 of 14 cases reported no improvement or worsening diarrhea with dose escalation of octreotide.[3] The temporal relationship between worsening diarrhea and dose escalation of octreotide supports a potential causal association between octreotide and PEI.

The clinical study by Hall et al.[47] provides evidence that octreotide and lanreotide decrease pancreatic function in patients with NETs, using a clinically sensitive diagnostic test and provides supportive evidence that octreotide and lanreotide could contribute to PEI in patients with NETs.

Lanreotide

DPV identified 13 cases in FAERS of PEI associated with lanreotide. Most (11 of 13) cases reported serious outcomes including death and hospitalizations, although the single case reporting death was not attributable to lanreotide. Two cases reported PEI temporal to the initiation of lanreotide, of which one reported a positive dechallenge. The other reported hospitalization for steatorrhea two days after starting lanreotide, which improved upon discontinuation and treatment with PERT. In both cases, the absence of underlying NET to explain the incidence of PEI supports a causal association between PEI and lanreotide. The 11 remaining cases were confounded by underlying pathology (e.g., biological progression of underlying NET, neoplasm progression).

In addition to the Hall et al.[47] study noted above, the clinical study by Caplin[44] provides evidence that lanreotide decreases pancreatic enzyme levels.

Pasireotide

DPV did not identify any cases in FAERS of PEI associated with pasireotide. The lack of PEI cases may be related to low drug utilization of pasireotide relative to the other SAs ((b) (4)% versus (b) (4)% and (b) (4) for octreotide and lanreotide, respectively). Based on the following quotations, the number of patients with an indication for pasireotide is less than the number of patients with GEP-NET indication(s) for other SAs. "About 10 to 15 new cases per million people are diagnosed [with Cushing's disease] in the US each year" where most are treated surgically and do not need pasireotide[53] compared to "more than 12,000 people in the United States are diagnosed with a [GEP-NET] each year, and approximately 171,000 people are living with this diagnosis."[54]

Pasireotide, which is a second generation SA, differs from octreotide and lanreotide, which are first generation SAs. This relates to the mechanism of action of SAs, which are mediated by their interaction with human somatostatin receptors (SSTRs).[55] Five isoforms of SSTRs have been described (SSTR 1–5). The binding affinity is different for pasireotide than for first generation SAs. Pasireotide has a reduced binding affinity for SSTR 2 and SSTR 5,[31] while octreotide and lanreotide have a high-affinity binding to SSTR 2 and SSTR 5.[29,30] This difference in binding

affinity accounts for some of the efficacy advantage of pasireotide in treating Cushing's disease, as compared with first generation SAs,[56] although it is unclear if this also accounts for a possible difference in safety as regards to risk of PEI.

Drug Utilization

Analysis of U.S. sales distribution data showed that octreotide accounted for the majority of the SA market between 2012 and 2021, while sales for lanreotide and pasireotide represented a smaller proportion. Over the past ten years, sales for octreotide increased from an estimated (b) (4) (b) (4) to (b) (4) packages. Additionally, analyses of U.S. outpatient pharmacy and U.S. non-federal hospital data showed that octreotide accounted for the majority of use in both settings of care. In 2021, an estimated (b) (4) patients received a dispensed prescription for octreotide and (b) (4) patients had a hospital discharge billing for octreotide. Of note, because these data sources are discrete from each other, patients may be double counted if they received the drug in both settings of care in the same year.

Limitations

There are several limitations to our review. First, the postmarketing cases are confounded by indication and treatment with SAs; symptoms of PEI overlap with those of carcinoid syndrome and SA-related adverse events, limiting attribution of symptoms. Additionally, the majority of these cases contain significant confounding factors such as underlying advanced or metastatic NET, pancreatic atrophy, pre-existing PEI, and onset of PEI symptoms prior to the start of SA. Underlying advanced or metastatic NET may involve obstruction of the pancreatic duct which can lead to decreased secretion of pancreatic enzymes. Notably, cases reporting onset of PEI symptoms prior to SA initiation were not excluded as an association cannot be ruled out due to worsening of symptoms after SA initiation.

Some FAERS cases have limited information making a causality assessment challenging, including a lack of diagnostic laboratory results (e.g., FE-1) and dechallenge information. Only 3 of 27 cases in our series reported FE-1 levels, however the majority of cases reported steatorrhea where patients (8/27, 30%) responded to PERT. Dechallenge is complicated because of the risk of withdrawal symptoms with SAs; additionally, assessment following dechallenge would be complicated by treatment with PERT. Finally, potential underreporting of PEI may occur as overt steatorrhea does not occur until 90% of glandular function has been lost;[57] however, it is still possible that complications of PEI including steatorrhea may occur with moderate impairment of exocrine function. Furthermore, it is plausible to consider that there may be substantial underreporting to FAERS (i.e., more than usual) because PEI may have a prolonged time to onset, and cases are less frequently recognized as being due to a drug that was started years before the event. Attribution of symptoms to underlying disease may also contribute to underreporting to FAERS.

Biological Plausibility

SAs are known to cause inhibition of exocrine pancreatic secretion, through inhibition of principal regulatory hormones (e.g., CCK), and therefore it is biologically plausible they may cause PEI.[13] Given the plausibility of this mechanism, a casual association between SA and the development of PEI cannot be excluded.

Considerations for Labeling

We do not agree with the octreotide Applicant that inclusion of PEI in the octreotide labeling would "neither appear warranted nor provide clinically relevant information." Although octreotide is prescribed to treat diarrhea associated with carcinoid tumor, paradoxically, as shown in this review, it may cause steatorrhea secondary to PEI (or at the very least, development of steatorrhea due to other causes may be mistaken for uncontrolled underlying disease). This may lead to dose escalation of octreotide, resulting in worsening of steatorrhea. The inclusion of PEI in product labeling alerts the clinician to the potential for this adverse event for proper work up and treatment, thereby improving patient care and reducing healthcare costs.

(b) (4)

Discussions with DGE and Participating Divisions within the Office of New Drugs

DPV presented our findings to DGE on March 10, 2023. Representation from DGE (Theresa Kehoe and Marina Zemskova), DO (Amy Barone), and DPV Oncology (Graça Dores) were in attendance. There was general consensus to convey the risk of 'Pancreatic Exocrine Insufficiency' associated with lanreotide and octreotide in Postmarketing Experience. DGE also indicated their plans to arrange for gastroenterology consultation within the Office of New Drugs. There was general consensus to harmonize labeling using terminology 'Pancreatic Exocrine Insufficiency' in Postmarketing Experience. A follow-up meeting was held with DGE, including the Division of Gastroenterology on June 8, 2023. Both divisions agreed with DPV that the octreotide and lanreotide USPIs should 1) include information in ADVERSE REACTIONS *Postmarketing Experience* regarding the risk of PEI, and 2) include (or update) a WARNINGS AND PRECAUTIONS (related to malabsorption) to recommend that if new or worsening steatorrhea, weight loss, or malnutrition occurs, to evaluate patients for 'pancreatic exocrine insufficiency' and manage accordingly.[k] The participants acknowledged that no postmarketing cases of PEI have been identified at this time that are considered causally related to pasireotide, and DGE continues to assess the possible merits of revising the pasireotide USPI regarding PEI, noting sales of pasireotide represented (b) (4) % of the SA market drug utilization in 2021.

5 CONCLUSION

In conclusion, we find an association between octreotide and lanreotide and PEI based on temporal relationship, positive dechallenge, and plausible biologic mechanism. No postmarketing cases of PEI have been identified at this time that are considered causally related to pasireotide, although this may be related to sales of pasireotide representing (b) (4) % of the SA market drug utilization in 2021 or possibly differing binding affinity.

6 RECOMMENDATIONS

Based on this review, OSE recommends the following:

[k] The following labels contain WARNINGS AND PRECAUTIONS regarding dietary fat malabsorption including Mycapssa, Sandostatin, and Sandostatin LAR

- Add or modify to the WARNINGS AND PRECAUTIONS section of the octreotide and lanreotide USPI to inform health care professionals that if new or worsening steatorrhea, weight loss, or malnutrition is reported, evaluate patients for pancreatic exocrine insufficiency and manage accordingly.
- Update the *Postmarketing Experience* section of the octreotide and lanreotide USPI to include pancreatic exocrine insufficiency.

Although no postmarketing cases of PEI have been identified at this time that are considered causally related to pasireotide, we encourage DGE to use other data sources to determine if somatostatin class labeling is warranted to include pasireotide.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

IQVIA National Sales Perspectives™

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~89% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

IQVIA U.S. Launch Edition

Launch provides a complete repository on the U.S. marketplace from 1992 to present, capturing both prescription (NPA) and sales data (NSP). Data are available in IQVIA's business intelligence tool SMART and are updated quarterly.

Symphony Health Metys™

Powered by IDV® Metys™ is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions, 73% of all U.S. mail order prescriptions, 75% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level. Metys™ Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.

IQVIA Hospital Visit Analyzer

Hospital Visit Analyzer (HVA) provides un-matched insights into patient visits and treatments that occur in Short-Term, General Non-Federal Hospitals (STGNFs). With history back to 2005, HVA is an accounting system specific to each hospital that tracks all billable events that take

place during a visit, including drugs administered, devices used, all patient diagnoses. and procedures/tests performed. The greatest advantage of HVA is the ability to see drug and device use within the hospital, which is often not captured by UB-04 forms.

IQVIA has the largest panel of hospitals, with approximately 350-400 facilities contributing patient visit records to HVA per year. Data are collected on approximately 18M+ patients across 60M+ hospital visits per year. Both Inpatient and Outpatient, as well as all pay types are captured for 100% of visits within each hospital on the panel. These data are then projected to national estimates. Data are updated monthly, with a lag of 75 days after the end of hospital discharge (inpatient) or encounter (outpatient).

Limitations of SA Utilization Data

The drug utilization findings should be interpreted within the context of the limitations of the data sources used. The sales distribution data represents the quantity of SAs sold from manufacturers to the various U.S. channels of distribution; these data do not reflect what is directly sold or administered to patients. The sales data are provided in this review as a possible surrogate for nationwide estimates of drug exposure to assist in the evaluation of the market share of these drug products. Patient-level data for SAs were also provided to inform on the extent of outpatient and hospital use. Collectively, these data provide insight into the distribution and utilization of SAs in the United States. In addition, the drug utilization data provided are national estimates, no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate.

8.3 APPENDIX C. FAERS LINE LISTING OF PEI IN PATIENTS WITH SA CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Lanreotide									
1	11-DEC-2018	15707779	1	US-IPSEN BIOPHARMACEUTICALS, INC.-2018-18912	Periodic	47	Male	USA	OT
2	30-DEC-2016	13076511	2	JP-IPSEN BIOPHARMACEUTICALS, INC.-2016-11484	Expedited (15-Day)	60	Female	JPN	OT
3	25-SEP-2017	14009190	3	GB-IPSEN BIOPHARMACEUTICALS, INC.-2017-10891	Expedited (15-Day)	63	Female	GBR	OT, DE, HO
4	27-FEB-2018	14575872	2	ES-IPSEN BIOPHARMACEUTICALS, INC.-2018-02749	Expedited (15-Day)	61	Male	ESP	OT
5	21-MAY-2018	14919210	2	CA-IPSEN BIOPHARMACEUTICALS, INC.-2018-02183	Expedited (15-Day)	47.	Male	CAN	OT
6	16-JUL-2018	15149405	2	NL-IPSEN BIOPHARMACEUTICALS, INC.-2018-10311	Expedited (15-Day)	77	Male	NLD	HO, OT
7	11-DEC-2018	15708473	1	US-IPSEN BIOPHARMACEUTICALS, INC.-2018-18907	Periodic	72	Female	USA	
8	28-JAN-2019	15879852	4	GB-IPSEN BIOPHARMACEUTICALS, INC.-2019-00074	Expedited (15-Day)	66	Female	GBR	OT
9	21-MAY-2020	17810326	1	US-IPSEN BIOPHARMACEUTICALS, INC.-2020-08975	Expedited (15-Day)			USA	OT
10	24-AUG-2021	19734117	2	AU-IPSEN BIOPHARMACEUTICALS, INC.-2021-20369	Expedited (15-Day)	76	Female	AUS	OT
11	10-SEP-2010	7602892	2	2010-2883	Expedited (15-Day)	77	Male	BEL	HO
12	01-AUG-2011	8063287	1	US-ABBOTT-11P-163-0734355-00	Periodic	62	Male	USA	
13	23-OCT-2012	8861103	1	2012-3952	Expedited (15-Day)	49	Male	ISR	HO
Octreotide									
14	23-JUL-2020	18056692	3	ES-SUN PHARMACEUTICAL INDUSTRIES LTD-2020R1-253615	Expedited (15-Day)	0.6	Male	ESP	OT
15	26-OCT-2020	18427310	4	NVSC2020GB255711	Expedited (15-Day)	82	Female	GBR	HO, OT
16	19-OCT-2021	19970871	3	NVSC2021CH213044	Expedited (15-Day)		Male	CHE	LT, DS, HO, OT
17	02-NOV-2021	20024903	1	NVSC2021CA249183	Expedited (15-Day)		Female	CAN	OT
18	03-DEC-2003	4037201	1	PHBS2003FI13210	Expedited (15-Day)	61	Female	FIN	OT
19	10-AUG-2006	6103133	2	PHEH2006US09680	Expedited (15-Day)	59	Female	USA	OT
20	02-NOV-2011	8222205	1	PHHY2011US95887	Expedited (15-Day)	51	Male	USA	OT
21	02-NOV-2011	8222206	1	PHHY2011US95004	Expedited (15-Day)	67	Male	USA	OT

22	02-NOV-2011	8222210	1	PHHY2011US95882	Expedited (15-Day)	53	Female	USA	OT
23	02-NOV-2011	8222216	1	PHHY2011US95871	Expedited (15-Day)	64	Female	USA	OT
24	02-NOV-2011	8222224	1	PHHY2011US95888	Expedited (15-Day)	48	Male	USA	OT
25	28-DEC-2012	9011934	1	FK201204173	Expedited (15-Day)	62	Female	BEL	OT
26	23-APR-2013	9247639	2	PHEH2013US008897	Expedited (15-Day)	63	Male	USA	DE, OT
27	30-SEP-2013	9564852	1	PHEH2013US020222	Expedited (15-Day)			USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, HO=hospitalization, LT= life-threatening, DS= disability, OT=other medically significant, AUS=Australia, BEL=Belgium, CAN=Canada, CHE=Switzerland, ESP=Spain, FIN=Finland, GBR=Great Britain, ISR=Israel, JPN=Japan, NLD=Netherlands

8.4 APPENDIX D: APPLICANT IR RESPONSES

Novartis Sandostatin/Sandostatin LAR (octreotide) injection[49]

Clinical Trials

Of the 1723 patients treated with octreotide within 16 clinical trials and 1 compassionate use program, including patients with acromegaly and carcinoid tumors, 4 cases with PEI were identified. The Applicant noted the following:

- 1 case reported study treatment with everolimus and octreotide
- 1 case reported ileum resection, bile duct obstruction, cholestasis, and pancreatitis at baseline
- 1 case reported underlying diabetes
- 1 case reported history of ileum surgery and concomitant medications potentially causing pancreatitis (i.e., lisinopril/HCT and clopidogrel)

Postmarketing

Of the 25 cases identified in the Novartis global safety database coded with a Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) *Pancreatic failure*, the Applicant noted the following:

- 13 of 25 cases had an unlikely causality due to confounding factors:
  - 5 cases reported advanced NET Stage IV of the pancreas (n=2), ileum (n=2), and unknown primary origin (n=1) (described in the publication by Saif and Larson et al.)[3] a significant risk factor for PEI.
  - 2 cases reported subtotal pancreatectomy
  - 3 cases reported progression of underlying malignancy including metastases to the pancreas (n=1), abdomen (n=1), and progression of hepatocellular carcinoma causing hepato-pancreatic insufficiency (n=1)
  - 1 case reported pancreatic atrophy
  - 1 case reporting preexisting PEI and non-compliance to PERT
  - 1 case was confounded by prior gastrointestinal surgery
- 11 cases contained limited information (e.g., time to onset, medical history, concomitant medications, laboratory investigations, action take with octreotide, event outcome). In one of these cases the Applicant notes that additional information is needed for a full medical assessment (described in the publication by Ros-Perez).[2]
- 1 case did not report a diagnosis of PEI (multi-organ failure following infections not related to octreotide).

Scientific Literature

Novartis also included publications by Lamarca and McCallum et al.,[5] Rinzivillo et al.,[6] Saif and Romano et al. [7] noted in Section 3.3 of the review.

Ipsen Bioscience Somatuline Depot (lanreotide) injection[50]

Clinical Trials

Of the 378 patients treated with lanreotide within two clinical trials[l,m] the Applicant noted the following drug related treatment emergent adverse events (TEAE) in the GEP-NET/NET pool:

- 5 patients reported pancreatic enzymes decreased (1.3%)
- 6 patients reported steatorrhea (1.6%),
- 16 patients reported flatulence (4.2%)
- 6 patients reported abdominal distension (1.6%),
- 4 patients reported weight decreased (1.1%) and
- 3 patients reported pancreatic insufficiency (0.8%)

Of the 170 patients treated with lanreotide within two clinical trials[n,o] the Applicant noted the following drug related TEAE in the acromegaly pool:

- 16 patients reported loose stools (9.4%)
- 12 patients reported flatulence (7.1%)
- 2 patients reported abdominal distension (1.2%)
- 9 patients reported weight decreased (5.3%)
- 0 patients reported pancreatic insufficiency, steatorrhea, and pancreatic enzymes decreased

Postmarketing

Of the 52 cases identified in the Ipsen global safety database coded with MedDRA PT *Pancreatic failure* and by narrative search using the terms pancreatic exocrine insufficiency, exocrine pancreatic insufficiency, or pancreatic insufficiency, the Applicant noted the following:

- 23 cases were excluded from further analysis due to pre-existing PEI that did not worsen with lanreotide (n=22) or did not report confirmation of PEI (n=1)
- 15 cases contained limited information (e.g., time to onset, medical history, concomitant medications, outcome)
  - company causality was related in 9 of 15 cases
- 14 cases reported a temporal association with lanreotide. The Applicant reported confounders in all cases (non-mutually exclusive):
  - 6 cases reported concomitant or past use of octreotide
  - 5 cases reported concurrent diabetes mellitus
  - 5 cases reported pancreatic NET
  - 3 cases reported pancreaticoduodenectomy
  - 3 cases reported pre-existing diarrhea

[l] ELECT 2-55-52030-730, a double blind, randomized, placebo controlled clinical trial investigating the efficacy and safety of Somatuline depot (lanreotide) 120 mg injection in the treatment of carcinoid syndrome.

[m] CLARINET 2-55-52030-726, a phase III, randomized, double blind, stratified comparative, placebo controlled, parallel group, multicenter study to assess the effect of deep subcutaneous injections of lanreotide Autogel 120 mg administered every 28 days on tumor progression free survival in patients with nonfunctioning pancreatic endocrine tumour.

[n] E-28-52030-717, a phase II, multi-center, randomized, double-blind study, in patients with acromegaly evaluating the efficacy and safety of a single deep subcutaneous administration of lanreotide Autogel (60, 90, or 120 mg) versus placebo, followed by a single-blind fixed dose phase evaluating the pharmacokinetic, pharmacodynamic, efficacy and safety profile of multiple deep subcutaneous administrations of lanreotide Autogel (60, 90 and 120 mg) ending in open label dose titration phase, (n=107).

[o] E-54-52030-081, a phase III, multicenter, open study to assess the efficacy and safety of lanreotide Autogel (60, 90 or 120 mg) in patients with acromegaly previously treated or not by SAs (n= 63).

- 2 cases reported disease progression
- 1 case reported left pancreatectomy
- 1 case reported pancreatic gastrinoma

- a causal association to lanreotide could not be excluded in 11 of the 14 cases

Scientific Literature

Ipsen Bioscience also included publications by Caplin et al.[44]and Khan MS et al.[45] noted in Section 3.3 of the review.

Ipsen Bioscience conclusion

The Applicant has validated PEI as a signal for lanreotide and the evaluation is currently ongoing.

Recordati Rare Diseases (RRD) Signifor LAR (pasireotide) injection[51]

Clinical Trials

No cases of PEI associated with the use of pasireotide were identified from the RRD global safety database.

Postmarketing

Of the 31 cases identified in the RRD global safety database coded with MedDRA PT *Pancreatic failure*, PTs related to the signs and symptoms of PEI,[p] and by narrative search using the terms pancreatic exocrine insufficiency, exocrine pancreatic insufficiency, or pancreatic insufficiency, the Applicant noted the following:

- 26 cases reported gastrointestinal disturbances that were not relevant to pancreatic insufficiency and did not suggest PEI
- 5 cases reported PEI (n=1) and signs and symptoms suggestive of pancreatic insufficiency (n=4)
  - 1 case was not related to pasireotide due to multiple risk factors (e.g., pancreatic pseudocyst, biliary cysts, "steatostatic" liver, ketoacidosis decompensation, smoking, alcoholism, chronic calcifying pancreatitis, diabetes, addiction to drugs)
  - 1 case was not related due to the presence of multiple gastrointestinal disorders
  - 3 cases reporting signs and symptoms suggestive of pancreatic insufficiency were related to pasireotide
  - 3 cases related to pasireotide reported improvement of steatorrhea with administration of PERT

Scientific Literature

[p] SOC Gastrointestinal disorders: Pancreatic disorder, Abdominal pain, Abdominal discomfort, Diarrhoea, Abdominal distension, Flatulence, Abnormal faeces, Faeces soft, Faeces discoloured, Steatorrhoea, Faecal elastase concentration decreased
SOC Metabolism: Malabsorption, Malnutrition, Abnormal loss of weight
SOC Investigation: Weight decreased, Lipase decreased, Lipase abnormal, Pancreatic enzyme abnormality, Pancreatic enzymes decreased, Faecal elastase concentration abnormal, Faecal elastase test, Faecal elastase concentration decreased
SOC General disorders: Fatigue

RRD also included a publication by Muhammad et al.[52] regarding the occurrence of steatorrhea that was considered a symptom of pancreatic insufficiency in an open-label, investigator initiated, conversion study (PAPE study), but the diagnosis of pancreatic insufficiency was not provided as no diagnostic evaluation was performed to confirm PEI in the study.

RRD conclusion
The Applicant did not identify any cases of PEI related to the use of pasireotide. There is no clinical evidence PEI may be associated with pasireotide use.

Amryt Pharma Mycapssa (octreotide) oral capsule[49]
No relevant cases from clinical trials, post-marketing experience, or the medical literature were identified from the Amryt global safety database.

Invagen Pharmaceuticals Lanreotide injection[50]
No relevant cases of PEI from clinical trials or post-marketing experience were identified from the Invagen global safety database.

RRD Signifor (pasireotide) injection[51]
No relevant cases of PEI from clinical trials, post-marketing experience, or the medical literature were identified from the RRD global safety database.

8.5 APPENDIX E. DRUG UTILIZATION TABLES

Table 1. Annual estimated number of packages sold for somatostatin analogs from manufacturers to all U.S. settings of care, stratified by drug molecule, 2012-2021

	2012		2013		2014		2015		2016	
	Packages (n)	Share (%)	Packages (n)	Share (%)	Packages (n)	Share (%)	Packages (n)	Share (%)	Packages (n)	Share (%)
Total Packages*									(b) (4)	
octreotide										
lanreotide										
pasireotide										

	2017		2018		2019		2020		2021	
	Packages (n)	Share (%)	Packages (n)	Share (%)	Packages (n)	Share (%)	Packages (n)	Share (%)	Packages (n)	Share (%)
Total Packages*									(b) (4)	
octreotide										
lanreotide										
pasireotide										

Source: IQVIA US Launch. Years 2012-2021. Data extracted November 2022. File: US Launch 2022-724 SA molecule by eaches 11-14-2022

***Packages in NSP was measured in eaches, which represents the number of single items such as vials, syringes, or ampules contained in a unit or shipping package and purchased by providers and pharmacies in a specific time period.**

Table 2. Annual estimated number of patients who received a dispensed prescription for somatostatin analogs from U.S. outpatient pharmacies, stratified by drug molecule, 2012-2021

	2012		2013		2014		2015		2016	
	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)
Total Patients*	(b) (4)									
octreotide										
lanreotide										
pasireotide										

	2017		2018		2019		2020		2021	
	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)
Total Patients*	(b) (4)									
octreotide										
lanreotide										
pasireotide										

Source: Symphony Health Metys. Years 2012-2021. Data extracted November 2022. Files: Metys 2022-724 SAs patients 11-14-2022, Metys 2022-724 octreotide patients 11-14-2022, Metys 2022-724 lanreotide patients 11-14-2022, Metys 2022-724 pasireotide patients 11-14-2022

***Unique patients may not sum exactly due to patients receiving more than one therapy during the study period and may be counted more than once. Therefore, summing across drug therapy is not advisable and will result in overestimates of patient counts.**

Table 3. Annual estimated number of patients with a hospital billing for somatostatin analogs from U.S. non-federal hospitals, stratified by drug molecule, 2016-2021

	2016		2017		2018		2019		2020		2021	
	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)	Patients (n)	Share (%)
Total Patients*	(b) (4)											
octreotide												
lanreotide												
pasireotide												

Source: IQVIA Hospital Visit Analyzer (HVA). Years 2016-2021. Data extracted November 2022. File: 1.04 HVA 2021-724 SA by molecule Y2016-2021 11-22-2022

***Unique patients may not sum exactly due to patients receiving more than one therapy during the study period and may be counted more than once. Therefore, summing across drug therapy is not advisable and will result in overestimates of patient counts.**

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/s/

AMY I CHEN
07/26/2023 09:50:40 AM

GRACA M DORES
07/26/2023 10:05:35 AM

KUSUM S MISTRY
07/26/2023 12:03:05 PM
Drug use data cleared by the database vendors (May 1, 2023).

DANIEL I WORONOW
07/26/2023 12:14:07 PM

JENNIE Z WONG
07/26/2023 12:38:05 PM

MONICA MUNOZ
07/26/2023 12:41:53 PM

JAMIE L KLUCKEN
07/26/2023 12:59:54 PM

RAJDEEP K GILL
07/27/2023 09:53:31 PM

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/s/

AMY I CHEN
08/01/2023 01:25:19 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 27, 2020

To: Geanina Roman-Popoveniuc, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Meghna Jairath, Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for octreotide acetate injection, for subcutaneous use

NDA: 213224

In response to DMEP's consult request dated April 12, 2019, OPDP has reviewed the proposed product labeling (PI), and Instructions for Use (IFU) for octreotide acetate injection, for subcutaneous use**.** This application is a 505(b)(2) relying on NDA 019667 for Sandostatin.

PI, IFU: OPDP's comments on the proposed PI are based on the draft materials in SharePoint on January 16, 2020 and are provided below.

Please note that comments on the IFU will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
01/27/2020 12:21:54 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 27, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213224
Product Name and Strength:	Bynfezia Pen (octreotide acetate injection) 2,500 mcg/mL (2.8 mL)
Applicant/Sponsor Name:	Sun Pharmaceuticals
OSE RCM #:	2019-693 and 2019-694-2
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, carton labeling, and Instructions for Use (IFU) received on January 27, 2020 for Bynfezia Pen. The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised information (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations made by the Office of Policy for Pharmaceutical Quality (OPPQ) on January 24, 2020 (See Appendix B for the recommendations). DMEPA previously completed a memorandum for the container label, carton labeling, and Instructions for Use (IFU) on January 20, 2020.[a]

2 CONCLUSION

The Applicant implemented all the recommendations and we have no additional recommendations at this time.

[a] Schlick J. Label and Labeling Review Memo for Bynfezia (NDA 213224). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 16. RCM No.: 2019-693 and 2019-694-1.

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/s/

JAMES H SCHLICK
01/27/2020 02:07:29 PM

MILLIE B SHAH
01/27/2020 02:21:10 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	January 23, 2020
To:	Meghna M. Jairath, PharmD Senior Regulatory Health Project Manager **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	TRADENAME (octreotide acetate)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 213224
Applicant:	Sun Pharmaceutical Industries Limited

1 INTRODUCTION

On March 26, 2019 Sun Pharmaceutical Industries Limited submitted for the Agency's review an original New Drug Application (NDA) 213224 for TRADENAME (octreotide acetate) injection, for subcutaneous use. The proposed indication for TRADENAME (octreotide acetate) injection, for subcutaneous use is for:

- Reduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [somatomedin C] in adult patients with acromegaly who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses.
- Treatment of severe diarrhea/flushing episodes associated with metastatic carcinoid tumors in adult patients.
- Treatment of profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors in adult patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on April 12, 2019, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for TRADENAME (octreotide acetate) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft TRADENAME (octreotide acetate) injection, for subcutaneous use IFU received on March 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 16, 2020.
- Draft TRADENAME (octreotide acetate) injection, for subcutaneous use Prescribing Information (PI) received on March 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 17, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
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CHARUNI P SHAH
01/23/2020 09:57:08 AM

MARCIA B WILLIAMS
01/23/2020 10:00:27 AM

LASHAWN M GRIFFITHS
01/23/2020 10:10:36 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING AND INSTRUCTIONS FOR USE
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 16, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213224
Product Name and Strength:	Octreotide Acetate Injection 7 mg/2.8 mL (2.5 mg/mL)
Applicant/Sponsor Name:	Sun Pharmaceuticals
OSE RCM #:	2019-693 and 2019-694-1
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, carton labeling, and Instructions for Use (IFU) received on January 15, 2020. The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label, carton labeling, and Instructions for Use (IFU) for Octreotide Acetate Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Schlick J. Human Factors Results, Label and Labeling Review for Octreotide Acetate Injection (NDA 213224). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 09. RCM No.: 2019-693 and 2019-694.

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/s/

JAMES H SCHLICK
01/16/2020 09:38:25 AM

MILLIE B SHAH
01/16/2020 11:14:27 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	12/16/2019		
To:	Meghna Jairath		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	DMEP
From	Peter Petrochenko OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	NDA 213224, Octreotide Acetate Injection ICC 1900319 ICCR2019-04781		
Recommendation	**Filing Recommendation Date: 6/7/2019** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 8/26/2019 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 1/14/2020 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 213224
Sponsor	Sun Pharmaceutical Industries Limited
Drug/Biologic	Octreotide Acetate Injection
Indications for Use	For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors
Device Constituent	Pen-Injector
Related Files	n/a

Review Team	
Lead Device Reviewer	*Peter Petrochenko*

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			Injection force of the final finished device after stability/shipping was provided interactively. Previously the Sponsor wanted to leverage break loose and glide force of the plunger/cartridge only (which includes one out of specification result in the 18-months study) in place of injection force of the completely assembled device. Sponsor agreed to add injection force of the final finished device at release, investigation any failures and reject batches per their sampling plan.

				Injection time was not provided; however, the justification is acceptable since this is a manually driven injector with different doses.
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	Reviewed by CDER/OND/DMEPA
Facilities & Quality Systems			X	Reviewed by CDRH/OC

2.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

Comment #1:
While the sponsor addressed the cartridge glide force failures observed over stability, we recommend CDER OPQ to assess if this impacts their review of the (b) (4) processes of the cartridge since the root cause of the observed high forces was due to (b) (4) the cartridge. CDRH ultimately accepted the response and observed failures since their process detected the failures, their follow-up quality activities were adequate (root cause investigation, sampling plan/batch rejection) and they added injection force testing of the final finished device to their release testing program.

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Sun Pharmaceutical Industries Limited is requesting approval of Octreotide Acetate Injection. The device constituent of the combination product is a Pen-Injector.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

please review the new NDA

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device Performance
- Biocompatibility
- Risk Assessment
- Labeling pertaining to the device
- Design controls

This review will not cover the following review areas:

- Human Factors (deferred to DMEPA)
- Facilities and Compliance (Separate CDRH OC Consult)
- Fluid path extractables leachables
- Drug compatibility

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

None

3.2.1. Related Files

N/A

3.3. Indications for Use

Combination Product	Indications for Use
Octreotide Acetate Injection	For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed
All files in 3.2.P.5 and 3.2.P.7
Response to IRs

4. DEVICE DESCRIPTION

4.1. Device Description

Octreotide Acetate Injection, 2.5 mg/mL, is filled in 3 mL colorless USP glass cartridges with 10 mm rubber plunger stopper and seal ( ). One filled and sealed cartridge of Octreotide Acetate Injection, 2.5 mg/mL, packed in one transparent cartridge holder and assembled with the help of blue body subassembly (dark blue button and white dose set knob) and blue cap for pen injector.

Table 3.2.P.1:4

	Components	Description for Sun's Product
Primary	Cartridge	3 mL colorless USP glass cartridge
	Plunger Stopper	10 mm stopper plunger
	Seal	seal for 3mL cartridge
Secondary	Pen	Disposable pen, Blue body subassembly with dark blue button and white dose set knob
	Cap	blue cap for disposable liquid pen
	Cartridge Holder	Transparent cartridge holder for disposable liquid pen

Changes from Wave 1 to Wave 2, in outer appearance of the fully assembled device are provided below in image 1.0:

(b) (4)

Table 3.0 Summarizes general characteristics of the injector:

Table 3.0

Device Characteristics	Applicable (Yes /No)	Details	Document reference
Injector/Platform Name	Yes	(b) (4)	ERD 18-035, Section 1. Scope
Specifications	Yes	Customer Specifications and Design Input Specifications	ERD 18-035 ERD 18-106
Injection tissue	Yes	Subcutaneous injection	ERD 18-106, Section 4.1
Depth of Injection	Yes	Subcutaneous injection	ERD 18-106, Section 4.1
Audible / visual feedback	Yes	Dose increment indication is audible and dose set knob is visual, end of dose is also visible.	ERD 18-035, Section 5.2.1 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements, SID 12
Cap Removal Force	Yes	Its normal end user action. It comes under ergonomics/ comfortable to use.	ERD 18-035, Section 5.2.3 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements SID 10, product functions ID 142-02, 142-03
Dose Accuracy	Yes	Volumetric Accuracy per ISO 11608-1	ERD 18-035, Section 5.2.1 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements SID 3
Activation Force	No	Not Applicable	Not Applicable
Visibility of medication / container dose	Yes	Cartridge holder is transparent so that user can see medication inside glass cartridge	ERD 18-035, Section 3.1.4 ERD 18-106, Section 6.3.1 functional

			requirements SID 14
Last dose specifications	Yes	It is as per ISO 11608-1:2014	ERD 18-106, Section 6.3.1 functional requirements SID 3, Input/Cust. Req. ID 251
Safety Features	Yes	Ergonomics and comfortable to use	ERD 18-106, Section 6.3.1 functional requirements SID 10
Needle specifications, length and gauge	Yes	Needle 31 G x 5mm	ERD 18-035, Section 1. Scope ERD 18-106, Section 1.3.1
Connection type	Yes	User replaceable needles	ERD 18-106, Section 1.0 Description
Conformance to applicable standards	Yes	All applicable regulations, standards and guidance are mentioned	ERD 18-106, Section 5.0
Type of use (Single use, disposable, reusable)	Yes	Multi use, disposable	ERD 18-106, Section 1.0 Description
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Yes	Self-administration or administered by Health Care Provider	ERD 18-106, Section 4.1 Intended Use
Injection mechanism (e.g., manual piston, spring, gas, etc.)	Yes	Manual piston	ERD 18-035, Section 3.1.5.1 ERD 18-106, Section 1.0 ERD 18-106, Section 2.1.2
Method of actuation, any Automated Functions	No	No automated function	Not Applicable
Residual Medication	Yes	Total deliverable volume is minimum 2.8mL. However Cartridge would be filled with (b) (4)	ERD 18-106, Section 1.3.2
Delivered Volume (for single dose or selectable volume range for multi-dose pens)	Yes	It is multi-use, variable dose, disposable pen where four doses would be delivered viz. i) 20 µL (b) (4) ii) 40 µL iii) 60 µ iv) 80 µ	ERD 18-106, Section 1.3.2 and 1.3.3
Drug Container Type	Yes	3.0mL standard glass cartridge	ERD 18-035, Section 1. Scope, ERD 18-106, Section 1.3.1
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Yes	Dose marking is in mcg however delivery would be in corresponding µL as concentration of drug is 2500 µg/mL.	ERD 18-035, Section 3.1.3 System markings, ERD 18-106, Section 1.3.3
		It can be administered at home or in	

Environments of use, Storage conditions and expiry	Yes	clinical environment. (b) (4)	ERD 18-106, Section 4.1.1.1 ERD 18-106, Section 4.1.1.2
Graduation marks / fill lines	Yes	Cartridge holder has dark colored markings to show the position of inside rubber stopper.	ERD 18-106, Section 1.3.3 system markings
Preparation and administration	Yes	The fully assembled drug device combination product would be supplied to the end user. During first use, user will detach the cap, attach the needle, prime the pen, set the dose and insert the needle at injection site and deliver the dose as per instructions given in Instructions For Use (IFU).	ERD 18-035, Section 1. Scope ERD 18-106, Section 2.0
Complete Material composition of injector	Yes	Fully assembled pen injector device is composed of several components, sub-components and sub-assemblies.	ERD 18-035, Section 1.0 scope, 3.1.1 Materials

4.2. Steps for Using the Device

1. Pull off the pen cap.
2. Take a new needle and tear off the paper tab. Push the needle straight onto the pen and turn clockwise until it is tight. Pull off the outer needle cover and keep it for later.
3. Prime the pen (if it is new). - Turn the dose set knob and set it to ‘’(b) (4)’’. With the needle pointing up push in the injection button all the way until it stops. Repeat this procedure until you see a stream.
4. Routine use (for every dose) - Attach a new needle. Turn the dose set knob to select the correct dose you need to inject. - Insert the needle into selected injection site. Push and hold the injection button for 10 seconds. Then pull the needle from skin.
5. Put outer needle cover on needle. Unscrew and pull off needle and throw it away.
6. Replace the pen cap.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Device description and steps for use is acceptable. Additionally, the Sponsor has provided a direct side by side comparison of their device to the RLD device.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

4.4. Facilities Information

NOTE: A separate consult is being done for compliance by OC.

4.5. Quality System Documentation Triage Checklist

NOTE: A separate consult is being done for compliance by OC.

5. LABELING

5.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
Labeling is adequate.

(b) (4)

[redacted]

5.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Labelled volume (Dose Markings)	X		

5.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by
- ☐ Insert Consultant Name ; The full memo is located in Appendix B.
- ☑ The Lead Reviewer

Below is a summary of the review & recommendation:

Clinical Labeling is reviewed by CDER Clinical team and Instructions for Use are reviewed by DMEPA. A cursory review was done by the Lead Reviewer and no issues were identified regarding device labeling specifically.

5.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

☑ **No Additional Information Requests – Finalize Labeling Review Section**

6. DESIGN CONTROL SUMMARY

6.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	**X**		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	**X**		
Mitigations are adequate to reduce risk to health	**X**		
Version history demonstrates risk management throughout design / development activities	**X**		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	**X**		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device		X (IR resolved)	
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

6.2. Design Controls Information Requests and Responses

(b) (4)

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Drug Container Type	Yes	3.0mL standard glass cartridge	ERD 18-035, Section 1. Scope, ERD 18-106, Section 1.3.1
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Yes	Dose marking is in mcg however delivery would be in corresponding µL as concentration of drug is 2500 µg/mL.	ERD 18-035, Section 3.1.3 System markings, ERD 18-106, Section 1.3.3

Device Characteristics	**Applicable (Yes /No)**	**Details**	**Document reference**
Environments of use, Storage conditions and expiry	Yes	It can be administered at home or in clinical environment. (b) (4)	ERD 18-106, Section 4.1.1.1 ERD 18-106, Section 4.1.1.2
Graduation marks / fill lines	Yes	Cartridge holder has dark coloured markings to show the position of inside rubber stopper.	ERD 18-106, Section 1.3.3 system markings
Preparation and administration	Yes	The fully assembled drug device combination product would be supplied to the end user. During first use, user will detach the cap, attach the needle, prime the pen, set the dose and insert the needle at injection site and deliver the dose as per instructions given in Instructions For Use (IFU).	ERD 18-035, Section 1. Scope ERD 18-106, Section 2.0
Complete Material composition of injector	Yes	Fully assembled pen injector device is composed of several components, sub-components and sub-assemblies.	ERD 18-035, Section 1.0 scope, 3.1.1 Materials

Reviewer Comments:

The deficiency requested the Sponsor to: clarify whether their design change affected any internal and/or mechanical components, clarify which version(s) were used for all applicable device testing, and provide a justification for each modification and whether it affected device performance. The Sponsor has replied that they used a 'Wave 1' version for exhibit batch pen components and 'Wave 2' for pen components for commercial batches. The Sponsor argues that changes in Wave 2 make the delivery device "more robust" and "better in look and feel" and do not affect performance. Table 1.0 in the response above shows that Wave 1 was used for the clinical BE study, stability testing, verification, and formative HF testing; while Wave 2 was also used for verification testing and summative HF. Table 2.0 shows that the verification test requirements are the same for both versions and that both versions had the same acceptance criteria. This bridges the Wave

1 to the Wave 2 device acceptably. The modifications are minor and do not appear to affect performance (main changes are pen cap shape, markings, etc.). The Sponsor additionally provided a more complete device description. This is acceptable.

The response above also mentions that activation force is not applicable. In this case it is not activation force, but injection force that is an essential performance requirement (discussed below)

Reviewer Comments

The following IRs were sent and resolved as part of the review.

1. In your Summary of Container Closure System, you provided a comparison between the "existing" and "commercial" versions of the pen injector and stated that "*there is some minor changes to the secondary packaging components between the exhibit and propose commercial pen injector.*" Please clarify whether the design change affected any internal and/or mechanical components and which version(s) were used for all applicable device testing including the provided batch analyses, stability, and all clinical studies. If the testing you have performed used different versions, please provide a complete justification for each modification and whether it is expected to affect device performance, specifically, whether essential performance requirements (Dose Accuracy, Activation/Break loose/Glide Forces, Needle Length/Gauge) and other performance requirements (Ex. cap removal force) are affected.

    a. Additionally, your device description is only provided in the Summary of Container Closure System and is missing information on several device characteristics. This information is required to ensure the device functions safely and effectively in the intended environment of use. Please provide a complete device description of the final finished device you intend to market. In your description, be sure to include pictures and/or diagrams of internal device components. A complete device description should also include (following aspects should be selected only if they apply to your device): the Injector/Platform Name, Specifications, Injection tissue and depth of injection, Audible / visual feedback, Cap Removal Force, Dose Accuracy, Activation Force, Visibility of medication container/Dose, Last Dose Specifications and Safety Features, Needle Specifications (Length(s), Gauge(s)), Connection type, Conformance to applicable standards, Type of Use (e.g. single use, disposable, reusable, other), Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use), Injection mechanism (e.g., manual piston, spring, gas, etc.), Method of actuation, any Automated Functions, Residual Medication, Delivered Volume (for single dose or selectable volume range for multidose pens), Drug Container Type, Dose Units of Measure (e.g., mL, Units, mg, increments, etc.), Environments of use, Storage conditions and expiry, Graduation marks / fill lines, Preparation and administration (describe all that are applicable), Safety Features, Complete Material composition of injector, and other characteristics which may be applicable to your device. Please note if this information is provided elsewhere in the submission you may simply reference it.

2. Risk Analysis Documentation – Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.). Refer to recognized consensus standard ISO 14971 "Medical devices - Application of risk management to medical devices" or device specific Guidance for more details.

3. We acknowledge you have provided verification testing of your device in your submission. You did not provide a specification for Injection Time, although your labeling indicates a specific injection

time. Please provide a justification why you have not included injection time in your verification testing or release/stability/shipping testing. Alternatively provide Design Verification Documentation traced to the design inputs of the device constituent which applies to injection time. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use and justify a statistically significant sample size for this verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

a. Additionally, you have not clarified whether your verification testing was performed with the final to-be-marketed version of the device. As part of design verification, you should verify the EPRs with the to-be-marketed version of the device constituent and the intended biologic/drug product. However, if you plan to rely on verification testing conducted with a surrogate (or different device design) be sure to provide a scientific rationale for the acceptability of the surrogate for the intended biologic/drug product (i.e. fluid characteristics, viscosity, etc.). If available, results of stability / shelf-life testing may be provided if the to-be-marketed version of the device constituent and intended drug/biologic product are used.

6.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	Y
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	NA – OC consult
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	NA
Applying Human Factors and Usability Engineering to Medical Devices	NA – DMEPA consult

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products	**NA**	**Y**
ISO 11608- 1:2014. Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems.	**Y**	**Y**

6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

ICC 1900319
NDA 213224, Octreotide Acetate Injection
Sun Pharmaceutical Industries Limited

Reviewer Comments
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #	(b) (4)	

	(b) (4)
Sponsor Response	Addressed in Design verification section
Reviewer Comments	See section below
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

7. RISK ANALYSIS

7.1. Risk Management Plan

(b) (4)

Reviewer Comments
The approach is acceptable and covers the requirements outlined in the initial IR to the Sponsor.

7.2. Hazard Analysis and Risk Summary Report

Sponsor's uFMEA (AFMEA):

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(b) (4)

Reviewer Comments
The Sponsor's risk management process leverages the design FMEA from the supplier, (b) (4) has a complete risk management plan, which is continuously applied during the (b) (4) Disposable Pen life cycle and additional risks, if identified, are reviewed and documented following the process described in the document submitted in the NDA by the Sponsor. In addition, the Sponsor has a risk management process for use risks and final assembly processes.

7.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☑ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The risk analysis provided is sufficient.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
	Click or tap to enter a date.	Click or tap to enter a date.
Information Request #	(b) (4)	

	(b) (4)
Sponsor Response	

	(b) (4)
Reviewer Comments	The deficiency requested the Sponsor to provide a risk analysis for the device constituent. The Sponsor stated that as part of human factor studies, Application Failure Modes and Effects Analysis (AFMEA) or User FMEA have been conducted which included risks associated with the device constituent part per ISO 14971. Design Failure Modes and Effects Analysis (dFMEA) had also been conducted for the Disposable Liquid Pen (DLP) platform by device supplier, (b) (4) . The platform is used for this pen injector. The Sponsor has also provided Letter of Authorization (LOA) for (b) (4) (b) (4) (b) (4) which contains the dFMEA. As part of their response, the Sponsor has also provided a Process Failure Modes and Effects Analysis (pFMEA) for the pen assembly and the final packaging. The pFMEA identified potential failure modes, unwanted events, root causes and mitigations during assembly, filling, labelling and packaging. The response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Delivered Dose Accuracy	Dose(mcg)=50 Dose volume=0.02mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4). Dose(mcg)=100 Dose volume=0.04mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4). Dose(mcg)=200 Dose volume=0.08mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4).	Y Finished Product -Analytical Test Procedure, pg. 44/50	Y (HF Validation for dose selector)	Y	Y
Glide force	Not more than (b) (4) N	Y	Y	Y- See IR 12.2.1-12.2.2	Y
Break-loose force	Not more than (b) (4) N	Y	Y	Y – See IR 12.2.1-12.2.2	Y
Injection Time	Not Provided	Y (leveraged by break loose and glide force testing above)	N/A	N/A	N/A
Injection Force	(b) (4) N	Y	Y	Y	Y

Reviewer Comment

Injection time not provided – a justification or complete testing was required and requested with an IR. The Sponsor responded with a justification that injection time is not relevant since it is variable and since they additionally instruct the user to hold the injector for 10 seconds after visual/audio feedback that the injection is complete.

The Sponsor has not directly addressed dial torque of the dose selector or injection force of the button itself. Dial torque measurement, however, is independent from the drug/cartridge, therefore, it can be leveraged from (b) (4) (b) (4) (b) (4), shown below, where the requirement is (b) (4) N.

The Sponsor makes the argument that injection force (pushing the button) is manual and is a direct push. The risk is present, however, of poorly manufactured components creating friction between the button and container (breakloose and glide forces were tested on the internal container only). However, BL/GF are very low ((b) (4) N) and the interference from components or internal friction is not likely to raise the force much higher than (b) (4) N, which would need further testing.

To note, the (b) (4) from (b) (4) had data on the component alone (likely without aging or shipping) in the current version of (b) (4) (b) (4), which has an UL of (b) (4) which is acceptable:

(b) (4)

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Therefore, the device is showing possibility for out of spec glide force and injection force is not reported in the submission. The following IR was issued and resolved (See IR section 12.2.1 and 12.2.2)

8.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Delivered Dose Accuracy	Dose(mcg)=50 Dose volume=0.02mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4)	32 nos. of pens are taken. For a particular dose volume, 96 values of delivered dose need to be taken. Dose Delivered from Prefilled pen in mL = Weight of sample (g) delivered from Pen injector / Density of the sample Calculate mean, standard deviation of dose delivered for 96 values of 32 pen injector for each dose setting (0.02mL, 0.04mL and 0.08mL). Calculate the K_{Actual} for each dose volume. Where "K" is tolerance limit factor as per ISO 11608-1:2014. Pass if $K_{Actual} \geq$ (b) (4) for each dose setting	K value: 8.167 K value: 9.800 K value: 8.727	Y	Y	Y
	Dose(mcg)=100 Dose volume=0.04mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4).		K value: 7.538 K value: 8.083 K value: 7.231			
	Dose(mcg)=200 Dose volume=0.08mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4).		K value: 10.667 K value: 8.167 K value: 5.529			
Glide force	Not more than (b) (4) N	Disassemble the pen and take out cartridge for testing. • Take 32 nos. of filled, crimped, stoppered cartridges	Mean: 4.943 N Mean: 4.941 N Mean: 5.287 N	Y	Y	Y

		• Calculate the travel distance "X" in mm using scale from end of stopper touching the • Solution to bottom part of syringe as shown in picture & Set the parameter in machine…				
Break-loose force	Not more than (b) (4) N	Disassemble the pen and take out cartridge for testing. • Take 32 nos. of filled, crimped, stoppered cartridges • Calculate the travel distance "X" in mm using scale from end of stopper touching the • Solution to bottom part of syringe as shown in picture & Set the parameter in machine…	Mean: 6.607 N Mean: 6.375 N Mean: 6.936 N	Y	Y	Y
Injection Time	Variable, based on dose; also variable depending on force exerted by user.	N/A	N/A	N – N/A	Y	Y

Reviewer Comment

Injection time is not provided, which was an initial IR. The Sponsor has responded saying that injection time is not a necessary EPR for this device since the injection is manually driven and has different dose selections. This response was discussed above and is acceptable, primarily because the sponsor controls for break loose and glide forces.

8.1.3. Evaluation of Test Methods

(b) (4)

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Results:	(b) (4) **Table 4: Break loose force and Glide force test data** **Octreotide Acetate Injection, 2.5mg/mL, Pen Injector, 2.8mL** **Sr. No.** / **Break loose force (N)** / **Glide force (N)** (b) (4) **Mean** 9.2221 8.0968 **Std. Dev.** 0.7396 0.7644 **COV** 8.0199 9.4408
Conclusions/ Reviewer Comments:	The Shipping testing and protocol are not acceptable as they do not cover injection force. Also, the stability testing checked on 9/9/19 (manufactured in 2017). **The follow-up IR above addresses the verification testing absence for injection force.**
Acceptable:	☒**Yes** ☐**No**

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The verification testing is acceptable and covers ass EPRs, except for injection time, which is not covered, since it is variable.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
Information Request #3	Click or tap to enter a date.	Click or tap to enter a date.

(b) (4)

[redacted]

	(b) (4)
Sponsor Response	

	[redacted] (b) (4)
Reviewer Comments	The Sponsor provided a justification for not using injection time as an EPR. The Sponsor claims that injection time is not a relevant parameter, since it is variable with each dose setting and the amount of force applied by the user. This is acceptable since the injection time parameter is also indirectly controlled through dose accuracy testing (and partially through B/L and glide force release testing). The response is acceptable. Biocompatibility was leveraged from [redacted] (b) (4) has stated that they comply with ISO 10993 and a summary report of all in vitro and chemistry studies was provided. This is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

8.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review
☐ There are clinical studies for review

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

11.FACILITIES & QUALITY SYSTEMS (Deferred to CDRH/OC)

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐

CDRH Facilities Inspection Review was not conducted	☑

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☑

11.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	Release testing - Volume in container Not less than 3.1 ml. Delivered Dose Accuracy – for dose of 50, 100, and 200 mcg	Y
BL Force	Release testing	Y
Glide Force	Release testing	Y
Injection Time	Not Provided – Justification provided – acceptable due to BL and glide forces	N/A
Injection Force	Release testing	Y

Reviewer Comments

Th Sponsor's approach is sufficient except for injection time, for which the Sponsor provided a justification interactively. Sample batch release specification and results for dose accuracy:

15	**Delivered Dose Accuracy**	Dose(mcg)=50 Dose volume=0.02mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4).	In-house	K value: 8.167	K value: 9.800	K value: 8.727
		Dose(mcg)=100 Dose volume=0.04mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4).		K value: 7.538	K value: 8.083	K value: 7.231
		Dose(mcg)=200 Dose volume=0.08mL ± (b) (4) ml, K value = Pass if K greater than equal to (b) (4).		K value: 10.667	K value: 8.167	K value: 5.529

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion (Deferred to OC)

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

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MEGHNA M JAIRATH
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HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	January 9, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213224
Product Name and Strength:	Octreotide Acetate injection 7 mg/2.8 mL (2.5 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sun Pharmaceuticals
FDA Received Date:	March 28, 2019, July 12, 2019, August 29, 2019, September 13, 2019
OSE RCM #:	2019-693 and 2019-694
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh-Nhu Nguyen, MS

1. REASON FOR REVIEW

This review was conducted to evaluate a human factors (HF) validation study report and labels and labeling submitted under NDA 213224 for octreotide acetate injection. This is a combination product with a proposed pen injector device constituent part.

1.1 PRODUCT DESCRIPTION

The Sponsor proposes a disposable single-patient use pen injector containing 7 mg/2.8 mL (2.5 mg/mL) octreotide acetate for subcutaneous administration capable of delivering doses of 50 mcg, 100 mcg, 150 mcg and 200 mcg. The product is intended for the treatment of the following:

- Acromegaly
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors.
- Profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

The Sponsor conducted their human factors (HF) validation study without seeking Agency feedback prior to conducting the study. The Sponsor submitted their HF validation study results in a meeting package, and we provided comments to the Sponsor that we disagreed with their rationale to group patients and caregivers into one user group.[a] The Sponsor submitted their revised HF validation study results on March 28, 2019 to include a separate patient and caregiver user group. The revised results are the subject of this review.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information	B
Human Factors Validation Study Report	C
Information Requests	D
Labels and Labeling	E

[a] Johnson, J. IND Information Request or Advice. Written Responses for IND 141456. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2019 FEB 07. Available in DARRTS: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d9cb3&_afrRedirect=1787586094213177

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the HF validation study design, errors/close calls/use difficulties observed with critical and essential tasks (Table 2), and our analysis to determine if the HF study results support the safe and effective use of the proposed product. We also provide our assessment of the labels and labeling and device (e.g. pen-injector).

The Sponsor did not submit their HF validation study protocol for Agency review prior to conducting their HF validation study. Thus, we could not provide comments on the protocol methodology. During our review of the HF validation study results, we identified methodological concerns that the moderator script included leading language when describing the use scenarios. However, despite the leading language, we are able to evaluate the HF study results.

The pen-injector is capable of delivering a maximum dose of 200 mcg per injection, but the prescribing information indicates that doses up to 500 mcg have been used. The Instructions for Use (IFU) submitted in the original submission on March 28, 2019 did not include instructions on how to give multiple injections to complete a dose greater than 200 mcg using the same pen. Thus, we sent an information request to seek clarification. The Sponsor responded by providing the instructions on administering doses greater than 200 mcg (See Appendix D for further details), which will require users to perform more than one injection, and indicated that the IFU has been revised accordingly. Additionally, we requested the Sponsor provide information on similar products used by intended users with similar physical and cognitive characteristics that can require multiple injections to complete a dose. Based on our evaluation of the available data for performing two injections (see Table 2 below) and our regulatory experience across similar products that require multiple injections, we determined that no additional human factors data should be submitted for review for the revisions made to the IFU for doses great than 200mcg. We will monitor post marketing cases for any signals that the instructions to complete a dose greater than 200 mcg with multiple injections are leading to use errors.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study included 15 caregiver, 15 patients, and 15 HCP participants. All participants were untrained and use of the IFU was optional and self-directed by the participants.

Each study participant attempted 2 injections: (1) a first-time use scenario, followed by (2) a second-time use scenario.

3.2 RESULTS AND ANALYSES

Table 2: Summary and analyses of errors/close calls/use difficulties observed with critical and essential tasks

Table 2 describes the errors/close calls/use difficulties observed with critical and essential tasks in the HF study, the Sponsor's analyses and proposed mitigation strategies, and DMEPA's analyses and recommendations.

Table 2					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Prime the new pen (C) Session 1	3 use errors P(b)(6) and P(b)(6) (HCP) and P(b)(6) Caregiver (CG) did not prime the pen before giving the injection. After their debriefs, the Moderator had each participant complete Step 3 (priming). All three participants successfully primed while following the IFU and demonstrated the knowledge to only	P(b)(6) stated that she skipped steps 3C and D (pressing the injection button, which causes a stream of medication to come out of the needle) because she did not want to push medication out. P(b)(6) stated that he skipped Steps 3C and D because he felt it was a waste of medication and did not understand the purpose of priming the pen. When the Moderator asked P(b)(6) the purpose of priming other injection devices, P(b)(6) correctly stated that he primes a syringe to get the air out	These errors were partially attributed to users being untrained. P(b)(6) and P(b)(6) thought that the priming step was for the dose and did not fully understand what priming meant. P(b)(6) thought priming was unnecessary for the pen. Additionally, P(b)(6) did not read the decision tree above Step 3. We feel the participants did not	The study demonstrated that participants can perform the intended priming procedure when they take their time to follow and use the instructions. Those who do not follow the instructions and make their own assumptions will likely not prime the pen the first time. However, given the course of injecting multiple times a day this would likely result in a small underdose. Failing to prime multi-dose pens is a common occurrence for untrained	Based on the Applicant's URRA, the harm associated with failing to prime the new pen is a partial underdose. The root cause for the error was due to participants thinking the priming step was for the dose and did not fully understand what priming meant, and thinking priming was unnecessary for the pen. We reviewed the IFU section that instructs users to prime the new pen and we find the residual risk acceptable for these errors. We have no recommendations at this time.

	prime a new pen.	to ensure the patient receives their full dose. P(b)(6) stated that he thought that the 100 was the dose value for the pen. When asked to read over Step 3, P(b)(6) was able to understand the procedure and noted that he did not know what priming meant. All 3 participants stated that after reading Step 3 in its entirety, it made sense and they understood what the instructions were communicating. Additionally, both HCPs stated that they would never use a new injection device on a patient without first receiving some type of training or procedural overview from a colleague.	pay enough attention when looking at the instructions and made their own assumptions, which lead to not priming the pen.	users. Had they been trained and in- serviced, as is expected to occur in the real world, this use error would have occurred. The residual risk associated with this error is acceptable as it would result in a small underdose the first day. This residual risk cannot be further minimized.	
Dial the correct dose (C) Session 1 and 2	2 use errors	P(b)(6) stated in the debrief that he thought the 100 was the dose for the first time, that he did not	Both errors were partially attributed to users being untrained.	The study demonstrated that participants can safely and correctly dial their dose when they	Based on the Applicant's URRA, the harm associated with failing to dial the correct dose is underdose.

	P(b)(6) (Patient) dialed to 100 (the priming value) and immediately injected as they did not prime (as mentioned above) and did not dial the prescribed dose (200 mcg). P(b)(6) (Patient) primed the pen with 100 mcg and then forgot to dial the dose before injecting for the second unaided injection.	understand what priming meant and that he skipped from the step of dialing to 100 (step 3A) and went right to the injection step (step 5) but offered no reason why he did not continue with steps 3B-D or steps 4A-4C. P(b)(6) stated they were trying to recall the procedure based on their memory and focused more on the priming and not the need to dial the dose. Additionally, P(b)(6) stated that the IFU steps regarding the dial going back to zero after priming (Step 3C) and dialing your dose (Step 4C) were clear and no changes were necessary to the IFU as he attributed the error to his mistake to not dial the dose.	P(b)(6) was quick to rush and skip steps, which lead to not injecting the intended dose. P(b)(6) was asked to repeat the full process for the first injection again and demonstrated that he could safely and effectively perform the intended dosing procedure for the assigned dose. P(b)(6) was trying to go off of his memory since he had already injected once with this device in the study, which influenced the participant to not dial the dose.	follow the IFU. An IFU cannot mitigate against someone trying to recall the procedure from their memory. Nor can it mitigate from someone who intentionally skips a number of steps in the process, which is attributed to the user not the design of the IFU. Our analysis would conclude that no changes are necessary to the pen design or IFU given the nature of the errors observed, which were both attributed to the user and not the pen or IFU.	We reviewed the Sponsor's root cause analysis and agree with their assessment. We contacted the clinical team to determine the severity of harm if an underdose was given in the proposed patient population. The clinical team stated that the clinical harm of a single underdose is clinically nonsignificant. We also reviewed the IFU section that instructs users to prime the new pen and dial the dose, and we find the residual risk acceptable for these errors. We have no recommendations at this time.
Remove the	3 use errors – 1st	P(b)(6) stated that she did not	Both errors were	P(b)(6) and P(b)(6) were both	Based on the Applicant's URRA,

needle from device and discard before placing the pen cap back on. (C) Session 1 and 2	injection P(b)(6) (Patient) recapped the pen with the needle still attached and thought they had removed it with the outer needle cap when they demonstrated the need to remove the needle. The needle did not come off and P(b)(6) did not notice when recapping the pen. P(b)(6) (Patient) was physically unable to remove the needle from the pen after multiple attempts and support from the moderator to follow the instructed procedure. P(b)(6) stated they would have called someone for help. The Sponsor noted in a footnote that P(b)(6) (Caregiver) did not reach the step of removing the needle	realize the needle was still attached, but the next time she used the pen she would have noticed it and removed the needle before giving another injection. P(b)(6) suggested that Step 6B's header be changed to "Remove used needle by…". P(b)(6) did not offer any suggestions for improving the IFU. With a different needle P(b)(6) was successful in removing the needle stating, "I did it! Well, that was easy. I think I could successfully use it."	partially attributed to users being untrained. P(b)(6) rushed when attempting to remove the needle, did not turn the covered needle several times, and did not check the pen to ensure the needle had been removed. P(b)(6)s difficulty in removing the needle was a result of the participant not turning the covered needle enough time to release it. P(b)(6) demonstrated on their second injection their ability to remove the needle.	successful in removing the needle for their second injection, demonstrating that the process of removing the needle is acceptable. The residual risk associated with not removing the needle is acceptable as both participants were aware a needle should not be re-used and would have noticed it later or gotten support to remove the needle before their next injection. The study demonstrated that participants can safely and correctly remove the needle when following the instructions step-by-step.	the harm associated with failing to remove the needle is chance of infection. We reviewed the Sponsor's root cause analysis and agree with their assessment. We also reviewed the IFU section that instructs users to remove the needle using the outer cover and we determined the residual risk is acceptable for these errors. We have no recommendations at this time.

	(after injection) since he skipped most of the procedure. The moderator stopped the process and debriefed P(b)(6) that they did not perform the needle removal steps. The N values have been adjusted to reflect the total number of participants who were given the opportunity to complete this sub-task. P(b)(6) demonstrated that they could successfully remove the needle on their second attempt after the debrief, as well as for the second unaided injection.				
	2nd injection – 2 use difficulties Two HCPs (P(b)(6) and P(b)(6)) stated they had a little difficulty taking off the needle after the injection.	2nd injection Both participants stated that they would be able to do the procedure in the future.	2nd injection - The Sponsor stated that it was likely the user overtightened the needle when attaching the needle to the pen.	2nd injection – The pen needle and pen design are the same as many multi-use pens on the market. Therefore, the residual risk with this difficulty is acceptable.	

Perform the Injection with a pen that has already been primed (E) Session 2	Two Patients and 1 HCP primed the pen on the second injection.	The Sponsor did not provide a description of this error.	No root cause was conducted by the Sponsor	On page 91 of the HF results document, the Sponsor indicated that priming the pen after the first prime is not a failure, but at user's discretion to prime the needle if desired.	Based on the Applicant's URRA, the potential risk with this error is loss of drug as users are wasting drug from the pen during each priming. Thus, we find the residual risk for these errors acceptable and have no recommendations at this time.
Knowledge Probe – Discard pen after 28 days from first use (C)	2 use errors P(b)(6) (Patient) and P(b)(6) (Patient) did not correctly answer the knowledge probe, "According to the instructions, how long can you use a pen before you must dispose of it?" P(b)(6) and P(b)(6) stated that the pen must be disposed of when the expiration date has passed, if the pen appears broken or damaged, or if the medication is cloudy or contains particles. P(b)(6) and P(b)(6)	P(b)(6) stated that he started with step 1 and missed the important section. When asked to read the section, P(b)(6) stated that it is clearly presented. P(b)(6) stated that she felt like she read the instructions thoroughly but could not find the answer. When asked to read the section, P(b)(6) stated that the information was not clearly presented. P(b)(6) and P(b)(6) both suggested making the	Both participants were confused by the question and could not understand what the question was asking for or why their answers were incorrect. The analysis concluded that this was a study artifact, as the question was not clear, given that the participant's responses were accurate as to when the pen must be disposed.	The study demonstrated that most participants know how long they could use the pen even after first use, even if the expiration date has not passed and if the pen still contains medication. The residual risk associated with this error is acceptable as most pens are used before 28 days after use. These errors cannot be further minimized as the information is presented in the IFU multiple times. Healthcare providers and pharmacists will likely review this information	Based on the Applicant's URRA, the potential risk associated with failure to discard after 28 days from first use is compromised drug efficacy. We reviewed the IFU and the information to discard after 28 days is the first item in the 'Important Information' section. We find the residual risk for these errors acceptable, and we have no further recommendations at this time.

	were unable to answer that the pen must be discarded after 28 days from first use.	section in the IFU more noticeable.		with patients, which participants in the study were deprived of having in the untrained scenario.	

3.3 LABELS AND LABELING

We identified concerns with the label and labeling from a medication error perspective. See the table in Section 4.1 for the Division and the table in Section 4.2 for the Applicant that include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation. At this time, we have determined that these recommendations do not require additional human factors validation study data to be submitted for review.

4 CONCLUSION & RECOMMENDATIONS

The results of the HF validation study identified failures, close calls, and use difficulties with critical and essential tasks. Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. In Section 4.1 (Division) and Section 4.2 (Applicant), we have provided recommendations and we recommend that the revisions be implemented prior to approval of the NDA. In this particular instance, we have determined that that these changes can be implemented without additional validation testing to be submitted for review.

4.1 RECOMMENDATIONS FOR THE DIVISION

Table 3: Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information			
1.	We note that the package type term is presented as (b) (4) (b) (4) throughout the PI, which is inconsistent with *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.*[b]	The package type term is used to identify how the medication should be safely handled and used.	We defer to Office of Pharmaceutical Quality to determine the correct package type term for this product and convey this to the Applicant.

[b] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. October 2018. Available from https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf

4.2 RECOMMENDATIONS FOR SUN PHARMACEUTICALS

Table 4: Identified Issues and Recommendations for Sun Pharmaceuticals (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	In Step 2, under Section "How should I give a dose larger than 200 mcg (More than 1 Injection)?" you use the term "(b) (4)" in the second sentence; however, you use the term "remaining dose" in the first sentence of that step.	Inconsistent terminology may cause confusion	Revise the step from (b) (4) to "(b) (4) your remaining dose."
2.	In Step 3, under Section "How should I give a dose larger than 200 mcg (More than 1 Injection)?" you use the term "(b) (4)" in the first sentence; however, you use the term "remaining dose" in Step 2 of the same section.	Inconsistent terminology could cause confusion.	Revise the phrase "(b) (4)" to "remaining dose" in Step 3.
3.	In the Section "How should I give a dose larger than 200 mcg (More than 1 Injection)?" you do not include an example to help users understand the calculations needed to give the correct amount for the second injection.	Without an example calculation, patients may not understand the steps to calculate the remaining amount leading to wrong doses.	Include an example calculation. We recommend the following or something similar: *For example, if your dose is 300 mcg, turn the dose set knob to 200 mcg for your first injection. Your remainder dose is 100 mcg. For the second injection, turn your dose set knob to 100 mcg to give the remaining dose.*

4.	In the Section "How should I give a dose larger than 200 mcg (More than 1 Injection)?" you do not include directions in the event a third injection is needed (e.g. 450 mcg or 500 mcg dose).	No directions on how to give a 450 mcg or 500 mcg dose (i.e. 3 injections) could cause confusion and lead to a wrong dose given.	Include a table to explain the steps to give a 450 mcg or 500 mcg dose (3 injections) to improve clarity. We recommend a table to make the steps easier to follow rather than text only, which could be difficult to follow with multiple steps.
5.	Step 5B in your IFU does not indicate what the (b) (4) represent as the drug is administered.	If users do not understand what the (b) (4) are for during drug administration, it may cause confusion.	Consider specifying in Step 5B what the (b) (4) signify during drug administration.
6.	Step 6A and Figure V do not instruct users to use the "scoop method" of recapping the needle.	Recapping the needle without using the "scoop method" can lead to an increase risk of accidental exposure.	Revise the graphic in step 6 A to show the "scoop method" of recapping the needle. This method is the preferred method when you are required to recap the needle.[c] Additionally, revise your instructions to reflect the revised method of recapping the needle.

[c] https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=20294&p_table=INTERPRETATIONS Accessed on March 28, 2019.

Container Labels			
1.	The container label does not include the dosage form 'Injection' on the principal display panel	This important information should be included on labels and labeling.	Include the dosage form 'Injection' on the principal display panel.[d]
2.	Only the strength per milliliter (2.5 mg/mL) is listed. The total strength per total volume is not included on the principal display panel.	Omission of the product's total strength may lead to preparation and administration errors.	Add the product strength expressed as total strength per total volume above the concentration per mL.[e] Display strength prominently, but in such a way so that it is not competing with the trade name. Example: 7 mg/2.8 mL (2.5 mg/mL)
3.	There is no statement to record the date of first opening.	A statement to record the date of first opening can assist users to throw out medication at the expiration date.	Include the statement "Date of first (b) (4) __/__/__". The "__/__/__" in the statement will alert the users to write a complete date (month, day, and year) on the container label.

[d] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[e] United States Pharmacopoeia (USP) General Chapter <1> Injections.

Carton Labeling			
1.	The carton labeling does not include the dosage form 'Injection' on the principal display panel	This important information should be included on labels and labeling.	Include the dosage form 'Injection' on the principal display panel.[f]
2.	The route of administration is on the side panel and not the principal display panel.	The route of administration may be overlooked if not displayed on the principal display panel.	Per *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*[g], we recommend including the route of administration on the principal display panel.
3.	The usual dosage statement is not consistent with the Prescribing Information (PI)	Inconsistency may result in confusion.	To ensure consistency with the Prescribing Information, revise the statement, "(b) (4) " to read "Recommended Dosage: See prescribing information."

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[g] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

4.	The net quantity statement for each carton configuration does not have enough prominence to adequately distinguish between the 1 pen and 2 pen carton configuration	This could cause the pharmacy to dispense the wrong quantity and possibly lead to dose delay or dose omission if the user receives the one pen configuration rather than the two-pen configuration.	Consider increasing the prominence of the "One" or "Two" in the net quantity statement on the principal display panel or consider adding a picture of two pen injectors on the principal display panel of the two-carton configuration to assist with the correct net quantity selection.
5.	(b) (4)		
6.	Only the strength per milliliter (2.5 mg/mL) is listed. The total strength per total volume is not included on the principal display panel.	Omission of the product's total strength may lead to preparation and administration errors.	Add the product strength expressed as total strength per total volume above the concentration per mL.[h] Display strength prominently, but in such a way so that it is not competing with the trade name. Example: 7 mg/2.8 mL (2.5 mg/mL)

[h] United States Pharmacopoeia (USP) General Chapter <1> Injections.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Octreotide Injection received on March 28, 2019 from Sun Pharmaceuticals.

Table 2. Relevant Product Information for Octreotide Injection	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Analogue of somatostatin
Active Ingredient (Drug or Biologic)	Octreotide
Indication	Treatment of Acromegaly, Carcinoid Tumors, Vasoactive Intestinal Peptide Tumors
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	7 mg/2.8 mL (2.5 mg/mL)
Dose and Frequency	50 mcg to 250 mcg given twice daily to 4 times daily
How Supplied	2 configurations 1 and 2 disposable prefilled multiple-dose pen-injectors contained in a carton. Each pen-injector delivers the following doses: 50 mcg, 100 mcg, 150 mcg, 200 mcg
Storage	Store pens in the refrigerator between 36° to 46° F (2° to 8° C) in the carton. Protect the pen from light. After first use store pens at controlled room temperature between 68°F to 77°F (20°C to 25°C). Excursions between 59°F (15°C) and 86°F (30°C) are allowed for up to 28 days.
Container Closure/Device Constituent	Prefilled cartridge contained inside a pen-injector.
Intended Users	Administered by adults (parents/caregivers) or a healthcare provider.
Intended Use Environment	Patient's home or healthcare facility.

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HUMAN FACTORS REVIEWS

On September 13, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Octreotide and IND 141456 to identify reviews previously performed by DMEPA or CDRH. Our search did not identify any previous reviews.

B.2 PREVIOUS FSA/SPONSOR INTERACTIONS

DMEPA provided human factors related comments for the Pre-IND Meeting written responses dated December 7, 2018.[i]

[i] Pre-IND Written Responses for Octreotide Acetate IND 141456. Silver Spring (MD): FDA, CDER, ODE II, DMEP (US); 2018 DEC 7. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804c00f2&_afrRedirect=4210585635858056

APPENDIX C. HUMAN FACTORS VALIDATION STUDY REPORT

The HF study results report can be accessible in EDR via:

\\cdsesub1\evsprod\nda213224\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acromegaly\5354-other-stud-rep\human-factor-study\summativehfstudyreport_.pdf

APPENDIX D. INFORMATION REQUESTS DURING THE REVIEW

1. We issued an information request to the Sponsor requesting clarification between the doses outlined in the prescribing information and the need to give multiple injections to obtain a dose of 200 mcg or higher. The Instructions for Use (IFU) did not include task steps to follow in the event multiple injections were required to give a dose. We also requested clarification on the need to rotate injection sites if 2 injections are required to give a dose. We received the response on July 12, 2019. The response can be accessible in EDR via: \\cdsesub1\evsprod\nda213224\0006\m1\us\cover-letter-response.pdf

2. We issued a second information request for the Sponsor to provide information on other marketed products that require a second injection and includes users with similar cognitive and physical abilities with intended users of the proposed octreotide pen. We received the response on Aug 29, 2019. The response can be accessible in EDR via: \\cdsesub1\evsprod\nda213224\0009\m1\us\cover-letter-response.pdf

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Octreotide Injection labels and labeling submitted by Sun Pharmaceuticals.

- Container label received on March 28, 2019
- Carton labeling received on March 28, 2019 (2-pen carton configuration) and September 13, 2019 (1-pen carton configuration)
- Instructions for Use received on July 12, 2019
- Prescribing Information (Image not shown) received on September 13, 2019

E.2 Label and Labeling Images

Container Labels

(b) (4)

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

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

Instructions for Use:

The Instructions for Use can be accessible in EDR via:

\\cdsesub1\evsprod\nda213224\0006\m1\us\draft-ifu.docx

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES H SCHLICK
01/09/2020 02:29:16 PM

MILLIE B SHAH
01/09/2020 02:33:44 PM

QUYNHNHU T NGUYEN
01/09/2020 02:40:37 PM

M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM:	Sonia Singh, Clinical Reviewer, DO2
THROUGH:	Suzanne Demko, Team Leader, DO2
THROUGH:	Harpreet Singh, Acting Division Director, DO2
SUBMISSION #:	NDA 213224
REQUESTED BY:	CDER/DMEP
PRODUCT:	Octreotide Acetate Injection, 2.5 mg/mL (Pen Injector 2.8 mL)
SPONSOR:	Sun Pharmaceutical Industries Limited
DATE OF REQUEST:	December 4, 2019
REQUESTED COMPLETION:	January 28, 2020
DATE COMPLETED:	December 16, 2019

On December 4, 2019, the Division of Metabolism and Endocrinology Products (DMEP) requested an oncology consult under NDA 213224. The Sponsor has submitted a new NDA for a more concentrated formulation of Octreotide Acetate Injection (2.5 mg/mL), which will be provided as a pen injector 2.8 mL device, via the 505(b)(2) pathway with reliance on the FDA's prior findings of safety and efficacy for Sandostatin injection (NDA 019667). In this consult, DMEP requests DO2 to review and comment on the information in the proposed product labeling that pertains to the indications of metastatic carcinoid tumors and vasoactive intestinal peptide secreting tumors (VIPomas).

BACKGROUND

Regulatory
Sandostatin (octreotide acetate), a long acting cyclic octapeptide, is the synthetic analog of the natural hormone somatostatin. In comparison to somatostatin, octreotide is more potent in suppressing secretion of pituitary growth hormone, thyrotropin and decreases release of a variety of pancreatic islet cell hormones including insulin, glucagon and vasoactive intestinal peptide (VIP). Octreotide also reduces splanchnic blood flow, gastric acid secretion, gastrointestinal motility, and pancreatic exocrine function.

Sandostatin was approved on October 21, 1988. It is indicated for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors. Sandostatin is currently available in single dose ampules of varying concentrations (0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL) and in 5-mL multi-dose vials available as 0.2 mg/mL and 1 mg/mL.

The Sponsor's proposed Octreotide Acetate Injection (2.5 mg/mL) will be provided as a multi-dose disposable pen injector for subcutaneous delivery. The Sponsor anticipates that the new device will enhance patient compliance due to self-administration, dosing flexibility, and less discomfort due to decreased volume of administration. The planned indications, dose and route of administration are the same as for the RLD. NDA 213224 was submitted on March 28, 2019.

Label Review

Other than minor formatting changes, the proposed labeling content (shown below) relevant to the indications of metastatic carcinoid tumors and VIPomas is consistent with the Sandostatin label. Specific comments and suggested edits were included in the label and are being sent to DMEP.

Section 1: Indications and Usage

1.1 Carcinoid Tumors

TRADENAME is indicated for the (b) (4) treatment of patients with (b) (4) severe diarrhea and flushing episodes associated with (b) (4) (b) (4)

1.2 Vasoactive Intestinal Peptide Tumors (VIPomas)

TRADENAME is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

1.3 Important Limitations of Use

(b) (4)

Section 2: Dosage and Administration

2.2 Carcinoid Tumors

The (b) (4) daily dosage of TRADENAME during the first 2 weeks of therapy ranges from 100 (b) (4) (b) (4) to 600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). In the clinical studies, the **median** daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some patients with as little as 50 mcg, while others required doses up to 1,500 mcg/day. However, experience with doses above 750 mcg/day is limited.

2.3 VIPomas

Daily dosages of 200 mcg to 300 mcg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range 150 mcg to 750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg/day are not required.

Section 5: Warnings & Precautions

(b) (4)

Recommendation
DO2 recommends removal of (b) (4) The remainder of the proposed labeling submitted by the Sponsor as shown above appears acceptable for approval.

Signatures:

Primary Reviewer	Date
Team Leader	Date

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONIA SINGH
01/07/2020 09:33:59 AM

SUZANNE G DEMKO
01/07/2020 09:36:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: December 17, 2019 **Date consulted:** April 12, 2019

From: Carrie Ceresa, Pharm D., MPH, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Bynfezia Pen (octreotide acetate) injection for subcutaneous use

NDA: 213244

Applicant: Sun Pharmaceutical Industries Limited

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Proposed Indications:

1. Acromegaly
2. Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors
3. Profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors

Materials Reviewed:

- March 26, 2019, Original New Drug Application submission, NDA 213244, Octreotide acetate injection
- April 12, 2019, DPMH consult, NDA 213244, DARRTS Reference ID 4419077

- August 22, 2016, DPMH review, NDA 21008 for Sandostatin LAR (octreotide acetate long acting formulation for injectable suspension), Jane Liedtka, MD, Medical Officer, DARRTS Reference ID 3974934

Consult Question: "Please review for PLLR"

INTRODUCTION AND BACKGROUND

On March 26, 2019, Sun Pharmaceuticals Industries Limited submitted a 505b2 New Drug Application for octreotide acetate injection for the proposed indications of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors. The relied upon drug for this NDA is Sandostatin (octreotide acetate) injection NDA 019667, which was approved on October 21, 1988 and is approved for the indications stated above. The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 12, 2019, to assist with the Pregnancy and Lactation subsections of labeling.

Table 1: Octreotide Acetate Injection Drug Characteristics[1,2]

Drug Class	A somostatin analogue
Mechanism of Action	Octreotide is the acetate salt of a cyclic octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin and exerts pharmacologic actions similar to somatostatin. It is an even more potent inhibitor of growth hormone (GH), glucagon, and insulin than somatostatin. Somatostatin receptors are found in the central nervous system (CNS), hypothalamus, gastrointestinal tract (GI) tract and the pancreas.
Dose and Administration	Subcutaneous dosing schedule; dose and duration vary by indication; refer to package insert
Molecular Weight	1019.3 Daltons
Protein Binding	Mainly to lipoprotein and lesser extent to albumin
Terminal Half-Life	1.7 to 1.9 hours
Warnings and Precautions	Hyperglycemia or hypoglycemia, , thyroid function abnormalities (hypothyroidism), cardiac function abnormalities (arrhythmias) and cholelithiasis and gallbladder sludge
Adverse Reactions	In addition to the adverse reactions noted under "Warnings and Precautions," diarrhea, loose stools, nausea and abdominal discomfort were seen in 34-61% of acromegalic patients

<u>Current State of the Sandostatin (the relied upon drug for this NDA)</u>

Labeling for Sandostatin is not in the Physician Labeling Rule format.

- There is no boxed warning for embryofetotoxicity.

[1] Applicant's Proposed Octreotide Acetate Injection Product Insert

[2] August 22, 2016, DPMH review, NDA 21008 for Sandostatin LAR (octreotide acetate long acting formulation for injectable suspension), Jane Liedtka, MD, Medical Officer, DARRTS Reference ID 3974934

- There is no contraindication for pregnancy or lactation.
- Regarding human data, labeling notes the following:
  "In postmarketing data, a limited number of exposed pregnancies have been reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-300 mcg/day of Sandostatin s.c. or 20-30 mg/month of Sandostatin LAR, however some women elected to continue octreotide therapy throughout pregnancy. In cases with a known outcome, no congenital malformations were reported."
- Animal reproduction study results are provided and described further under Pregnancy- Nonclinical Experience.
- The Nursing Mother section notes the following: "It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when octreotide is administered to a nursing woman."
- There are no pregnancy testing recommendations; however, labeling notes the following about contraception:
  "Although acromegaly may lead to infertility, there are reports of pregnancy in acromegalic women. In women with active acromegaly who have been unable to become pregnant, normalization of GH and IGF-1 may restore fertility. Female patients of childbearing potential should be advised to use adequate contraception during treatment with octreotide."
- There are no known drug-drug interactions with hormonal contraceptives.

REVIEW

PREGNANCY

Acromegaly and Pregnancy

- Acromegaly is a rare disorder caused by overproduction of growth hormone (GH) which is produced by the pituitary gland. The increase in growth hormone is typically caused by a benign, noncancerous tumor of the pituitary.[3]
- The median age at diagnosis is the fourth and fifth decade of life (males ages 36 to 48 and females ages 38 to 56).[4]
- Symptoms include thick oily skin, achy joints, skin tags, enlarged lips, nose, tongue, sinuses and vocal cords, deepening of voice, fatigue or weakness, sleep apnea, headache, visual impairment, abnormal menstrual cycle or breast discharge, erectile dysfunction and decreased libido.[3]
- According to the National Institutes of Health approximately 17% of the population are affected by small pituitary tumors; however, most of those do not cause acromegaly. It is estimated that only about 3 or 4 people out of every million develop acromegaly each year and 60 out of every million suffer from acromegaly at any given time. Very rarely is acromegaly caused by a disorder other than a pituitary tumor.[3]
- Due to changes in growth hormone and insulin like growth factor-1 it is difficult to diagnosis acromegaly in pregnancy.[5]

[3] Acromegaly. National Institute of Health. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/endocrine-diseases/acromegaly. Accessed 5 December 2019.
[4] Lavrentaki, A et al. Epidemiology of acromegaly: review of population studies. Pituitary. 2017. 20(1): 4-9.
[5] Laway B, 2015, Pregnancy in acromegaly. Ther Adv Endrocrinol Metab, 6(6):267-272.

- Acromegaly does not appear to cause adverse maternal or fetal outcomes during pregnancy. It is also recommended to consider pituitary surgery during pregnancy to prohibit tumor enlargement.[5]
- Tumors that overproduce growth hormone are associated with infertility because of the effects of tumor mass on gonadotropins and hyperprolactinemia causing anovulation.[5]
- Three classes of medications are used to treat acromegaly (somatostatin analogs, dopamine agonists and growth hormone receptor ligands); however, surgical removal of the tumor is first line treatment.[5]
- There are case reports of pregnant women with acromegaly. In a review article, there were 90 pregnancies since 1997 in patients with acromegaly. Overall, there was one miscarriage (12 weeks' gestation), 4 fetal losses, 4 small-for-gestation age and one microsomia. Maternal complications included hypertension (n=9), gestational diabetes (n=8), diabetes insipidus (n=2), and preeclampsia (n=1).[6]

Metastatic Carcinoid Tumors and Pregnancy[7]

- Carcinoid Tumors are neuroendocrine tumors derived from enterochromaffin cells and typically arise in the gastrointestinal tract.
- The annual incidence of carcinoid tumors is two cases per 100,000. There are two peaks (ages 15 to 25 and 65 to 75). Under the age of 50, the incidence is twice as high in females.
- Symptoms include diarrhea and flushing leading to dehydration, hypotension and arrhythmias.
- There are several case reports of pregnant women with carcinoid tumors.
    - In a review article, the authors noted 26 reports of pregnant patient with carcinoid tumors since 1986. Of these 26 cases, there were five reports of fetal loss (three miscarriages, one ectopic pregnancy, one elective termination-reason not provided) and five reports of preterm delivery, and 16 healthy pregnancies. The authors noted that the effect of pregnancy upon carcinoid tumor progression is not clear and that overall the cases did not demonstrate significant disease progression.[8]
    - There is a report of a 36-year-old with history of pulmonary carcinoid (3-years prior to pregnancy) who became pregnant. The patient had no clinical indication of carcinoid syndrome and had normal 5-hydroxyindoleacetic acid at the time of pregnancy diagnosis. The patient had mild dyspnea at 15 weeks' gestation but follow-up testing (echocardiogram and 5-HIAA) were unremarkable for disease progression. The patient delivered a healthy female at 36 weeks' gestation. The patient remained asymptomatic and without disease progression at five-years post-pregnancy.[7]
    - There is a report of a 31-year old with history of ovarian neuroendocrine tumor with liver metastasis and carcinoid syndrome (7 years prior to pregnancy) who was found to be six weeks pregnant. The patient experienced worsening of

[6] Laway, B. Pregnancy in acromegaly. Ther Adv Endocrinol Metab. 2015; 6(6): 267-272.
[7] Zuetenhorst, J. and Taal, B. Metastatic Carcinoid Tumors: A Clinical Review. The Oncologist. 10(2): 123-131. 2005.
[8] Kevat, D et al. A case of pulmonary carcinoid in pregnancy and review of carcinoid tumours in pregnancy. Obstet Med. 2017. 10 (3): 142-149.

symptoms (recurrent flushing, abdominal cramping, diarrhea and severe orthostatic hypotension) after the onset of pregnancy. The patient had been on octreotide but stopped treatment. She was started on oxatomide and ranitidine for symptoms. The patient experienced a miscarriage at 12 weeks' gestation.[9]

- Treatment includes supportive care (avoid stress, foods that trigger symptoms, antidiarrheal medications), octreotide analogues, such as octreotide, interferon alpha, hepatic artery chemoembolization, and radiofrequency ablation.

Vasoactive Intestinal Peptide Tumors (VIPoma) and Pregnancy[10,11]

- VIPoma is a rare tumor that results in an overproduction of vasoactive intestinal peptide.
- The annual incidence is one per 10 million cases per year.
- VIPomas occur in both children (ages 2 to 4) and adults. In adults, they occur between the ages of 30 to 50 years of age and are mostly intra-pancreatic (95%).
- Patients typically present with watery diarrhea, lethargy, nausea, vomiting, muscle weakness, cramps and hypokalemia.
- The management of VIPomas involves medical management and surgery. Complete surgical resection is the treatment of choice for primary tumors. Somatostatin analogs like octreotide inhibit secretion of VIP and are used for symptomatic control.
- There are no reports of VIPoma in pregnant patients.

Nonclinical Experience

In animal reproduction studies, no-adverse developmental-effects were observed with intravenous administration of octreotide to pregnant rats and rabbits during organogenesis at doses 7 and 13-times, respectively the maximum recommended human dose (MRHD) of 1500 mcg/day based on body surface area. Transient growth retardation, with no impact on postnatal development, was observed in rat offspring from a pre- and post-natal study of octreotide at intravenous doses below the MRHD based on body surface area. The reader is referred to the current approved relied upon labeling for octreotide long-acting injection NDA 21008 .

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature with regard to octreotide exposure and pregnancy. The reader is referred to the applicant's submission for specific search parameters. The author found 22 of the articles in their search to be relevant. The relevant publications consist of 19 case reports and three review articles. There were no prospective, retrospective or observational studies located. The case reports consist of patients treated with immediate acting octreotide and octreotide long-acting injection and exposure occurred throughout all three trimesters. The reader is referred to Table 4 in the applicant's submission pages 13-25 for specifics about each case.

- One patient with familial hyperinsulinemic hypoglycemia treated with the long-acting formulation of octreotide during four different pregnancies had the following outcomes:

[9] Pistilli, et al. Pregnant with metastatic neuroendocrine tumour of the ovary: what now? Ecancermedicalscience. 2012; 6: 240.

[10] Nilubol N. Pancreatic Neuroendocrine Tumor Secreting Vasoactive Intestinal Peptide and Dopamine with Pulmonary Emboli: A Case Report. J Clin Endocrinol Metab. 2016. 101(1): 3564-3567.

[11] Sandhu, S and Jialal, I. VIPoma. StatPearls 2019.

two pregnancies she electively terminated due to a chorion villus biopsy revealing the mutation for familial hyperinsulinemic hypoglycemia, one pregnancy with fatal intrauterine growth restriction which ended at 25 weeks' gestation and one infant who died eight days after birth due to necrotizing enterocolitis (NEC). She later went on to give birth to two healthy babies; however, was not exposed to octreotide long-acting during either of those pregnancies.

- One patient taking octreotide and bromocriptine during pregnancy (unknown time) delivered at 39 weeks and 6 days, emergency cesarean due to fetal distress and neonatal asphyxia. The newborn was on mechanical ventilation for three days. Postnatal development at unknown time point was noted to be satisfactory with no malformations.
- The other case reports consist of healthy singleton deliveries and one delivery of dizygotic twins.

Data from the three review articles submitted by the applicant can be found in Table 5 of the applicant's submission, pages 26-28. The data reviewed in each article reveal no abnormal maternal or fetal outcomes.

DPMH's Review of Literature
DPMH conducted a search of published literature using PubMed and Embase regarding octreotide acetate injection exposure during pregnancy using the following search terms, "octreotide acetate injection and fetal malformations," "octreotide acetate injection and spontaneous abortion and miscarriage," "octreotide acetate injection and embryo-fetotoxicity. In addition to the applicant's review of literature, no additional relevant data were found for review. The reader is also referred to the previous octreotide review by Jane Liedtka, MD, completed on August 22, 2016 for octreotide acetate long-acting release for NDA 21008.[12]

According to Micromedex,[13]

"There are insufficient human data regarding the use of octreotide in pregnant women to determine the risk for major birth defects or miscarriage. In postmarketing evaluations, no congenital malformations were reported among pregnant women receiving octreotide for the treatment of acromegaly. Most women received doses ranging from 100 to 300 mcg/day (subQ) or 20 to 30 mg/month (IM). While most of the women were exposed during the first trimester of pregnancy, some chose to continue treatment throughout pregnancy.

A 31-year-old woman was treated with octreotide 300 mcg/day for 4 months, becoming pregnant during the last month. Her octreotide treatment was stopped but resumed at 6 month's gestation. At 8 month's gestation, a normal infant was delivered by cesarean section. Other reports describe octreotide use in women that was discontinued when their pregnancies were learned. The infants appeared normal with no evidence of congenital defects.

A 24-year-old woman with active acromegaly received continuous long-acting octreotide throughout her pregnancy and delivered a healthy girl. At the end of her first trimester of

[12] August 22, 2016, DPMH review, NDA 21008 for Sandostatin LAR (octreotide acetate long acting formulation for injectable suspension), Jane Liedtka, MD, Medical Officer, DARRTS Reference ID 3974934.
[13] Octreotide. Truven Health Analytics LLC. Micromedex.

gestation, intramuscular octreotide was increased from 10 mg per month to 20 mg per month. At 21 weeks an ultrasound showed fetal diameters around the 5th percentile, at which time fetal growth retardation was considered and subsequently octreotide was decreased to 10 mg per month. At 38 weeks a caesarean section was performed because of breech presentation. From 3 to 18 months of age, the baby's weight and length reached the 50th percentile."

According to *Drugs in Pregnancy and Lactation* by Briggs and Freeman,[14] "octreotide crosses the human placenta to the fetus." The other data summarized in Briggs is also found summarized in the tables submitted by the applicant.

Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

Octreotide administered subcutaneously passes into the milk of lactating rats. Following a subcutaneous dose (1 mg/kg) of octreotide to lactating rats, transfer of octreotide into milk was observed at a low concentration compared to plasma (milk/plasma ratio of 0.009). The reader is referred to the current approved relied upon labeling for octreotide long-acting injection NDA 21008.

Review of Literature

The applicant and DPMH conducted a search of published literature regarding octreotide exposure and breastmilk and no data were found.

According to LactMed,[15] "The excretion of octreotide into breastmilk has not been studied. However, because it has a high molecular weight of 1019 Daltons it is likely to be poorly excreted into breastmilk. It is poorly absorbed orally and has been safely administered directly to infants by injection, so it is unlikely to adversely affect the breastfed infant. One breastfed infant experienced no adverse effects during maternal use of octreotide. Until more data are available, octreotide should be used in nursing mothers with careful infant monitoring, especially if the infant is under 2 months of age. One mother was treated for acromegaly during pregnancy and postpartum with octreotide (dose not stated). She breastfed (extent not stated) her infant for 4 months with no apparent problems noted in the infant."

[14] Briggs G and R Freeman. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Wolters Kluwer/Lippincott Williams and Wilkins. http://ovidsp.dc2.ovid.com/sp-4.02.1a/ovidweb.cgi, accessed 5 December 2019.

[15] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Reviewer comment: DPMH reviewed the publications referenced in the LactMed summary above by Calao et al (1997)[16] and van der Steen et al (2018)[17] and notes that the only information provided is stated in the summary above.

According to breastfeeding expert Thomas Hale, Ph.D., in *Medication and Mothers Milk,*[18] "Octreotide is a close analog of and provides activity similar to the natural hormone somatostatin. Octreotide (Sandostatin LAR) is a long acting form consisting of microspheres containing octreotide. 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. It is used to treat acromegaly and carcinoid tumors. Due to its molecular weight, transfer to milk is probably minimal. This product, if present in milk, would not likely be absorbed to any degree." Hale rates octreotide as "L3- No Data-Probably Compatible" and also recommends that infants who are breastfed are monitored for vomiting, diarrhea and changes in feeding.

According to *Drugs in Pregnancy and Lactation* by Briggs and Freeman,[19] "It is not known whether octreotide is transferred to breast milk, but this should be expected because of the documented placental passage. No reports have been located that described the use of this agent during lactation. However, because of probable digestion following oral therapy, the risk to the nursing infant appears to be nonexistent."

Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7 x the human exposure based on body surface area. The reader is referred to the current approved relied upon labeling for octreotide long-acting injection NDA 21008.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature with regard to females and males of reproductive potential and octreotide exposure and provided a summary table of three publications that include octreotide treatment in females with polycystic ovarian syndrome (PCOS) for infertility. All three articles conclude that octreotide may reduce ovarian hyperstimulation in patients with PCOS.

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[16] Colao A et al., 1997, Extensive Personal Experience, Acromegaly, Journal of Clinical Endocrinology Metabolism, 82(9):1-5.

[17] van der Steen I et al., 2018, A Multicenter Experience with Long-Acting Somatostatin Analogues in Patients with Congenital Hyperinsulinism, Horm Res Paediat, 89:82-89.

[18] Hale, Thomas . Medications and Mother's Milk. Amarillo, Texas. Springer Publishing Company LLC. Accessed online on 12/11/2019.

[19] Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi.

DPMH's Review of Literature
DPMH conducted a review of published literature regarding octreotide exposure and females and males of reproductive potential, and no additional data were found. The reader is also referred to the previous octreotide review by Jane Liedtka, MD, completed on August 22, 2016 for octreotide acetate long-acting release for NDA 21008.[12]

Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy
In animal reproduction studies, no-adverse developmental-effects were observed with intravenous administration of octreotide to pregnant rats and rabbits during organogenesis at doses 7 and 13-times, respectively, the maximum recommended human dose. The clinical data from published literature regarding pregnancy exposure to octreotide have not identified a pattern of malformations or an increased risk of miscarriage, adverse maternal or fetal outcomes. There are no new safety concerns to communicate in pregnancy labeling.

Lactation
Octreotide administered subcutaneously passes into the milk of lactating rats. Following a subcutaneous dose (1 mg/kg) of octreotide to lactating rats, transfer of octreotide into milk was observed at a low concentration compared to plasma (milk/plasma ratio of 0.009). There are no data on the presence of octreotide in human milk; however, if octreotide was present in human milk, then it would likely be present in low amounts due to the high molecular weight. DPMH recommends the use of the benefit/risk statement in subsection 8.2 of labeling (see below).

Additionally, DPMH is recommending that divisions issue Post-Marketing Requirements (PMRs) for clinical lactation studies in drug products with little or no data on the presence of drug in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Although octreotide is indicated for multiple conditions that are rare in females of reproductive potential and during lactation, it would still be important to collect lactation information since octreotide has been found to be present in animal milk. DPMH recommends issuing a PMR for a milk-only clinical lactation study. If the drug was found to be present in maternal milk, then the applicant should see if the drug was transferred to the breastfed infant.

Females and Males of Reproductive Potential

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7 x the human exposure based on body surface area. The reader is referred to the previous DPMH review of octreotide long-acting formulation that includes the review of information regarding the improvement of fertility experience by women with acromegaly who received octreotide. During that review cycle, language regarding advising premenopausal females of the potential for unintended pregnancy. This applicant has recommended the use of the same language in subsection 8.3 and DPMH agrees.

PMR RECOMMENDATION

DPMH recommends the following:

1) The applicant should be required to conduct a lactation study (milk only) in lactating women who have received therapeutic doses of octreotide using a validated assay to assess concentrations of octreotide in breast milk and the effects on the breastfed infant. If the drug is found to be present in maternal milk, then the applicant should evaluate the infant to see if octreotide is transferred to the breastfed infant.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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

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/s/

CARRIE M CERESA
12/17/2019 03:58:19 PM

MIRIAM C DINATALE
12/18/2019 10:11:25 AM

LYNNE P YAO
12/19/2019 03:56:29 PM

ICCR Quality System Review Memo

Date:	June 13, 2019, Update September 3, 2019
To:	Teshara Bouie, OPRO/OPQ, CDER, Teshara.Bouie@fda.hhs.gov
CC:	Leeza Rahimi, Pharma D. Senior RPM, OPRO/OPQ, CDER, WO 75,Rm 4644 Leeza.Rahimi@fda.hhs.gov Office of Combination Product, Combination@fda.hhs.gov Damia Jackson, RPM, OPEQ, CDRH damia.jackson@fda.hhs.gov
Through:	Todd Courtney, Assistant Director, OPEQ/OHT1, CDRH Todd.Courtney@fda.hhs.gov
From:	Christopher J Brown, P.E., Anesthesia Device Team/DHT1C/OHT1, CDRH, WO 66, Rm 3428, Christopher.Brown@fda.hhs.gov
Applicant/Licensure:	Sun Pharmaceutical Industries Limited, Sun House Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra, India, 400063 FEI: None
Submission (Type & Number):	NDA 213224
Combination Product Name:	Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector
Combination Product Indications for Use:	For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors
Device Constituent (Type):	Auto injector or Pen

ICCR SharePoint Tracking Number:	ICC2019-04870
ICCR CTS Tracking Number:	ICC1900362
Pre-Approval Facility Inspection:	No: PAI scheduled for NDA 213225, should be reviewed prior to approval
Documentation Review (Status):	**Complete**
CDRH/OC Recommendation:	**06/13/2019: Approvable – with conditions: See Recommendation, Update 09/03/2019: Approvable**

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 213224 which will require a device inspection. Global Submit link: \\CDSESUB1\evsprod\NDA213224\213224.enx

PRODUCT DESCRIPTION

The Octreotide Acetate Pen Injector is a prefilled, variable dose, multiple dose, disposable device. The injector contains a 3.0 mL glass cartridge with a deliverable volume of 2.8 mL. The pen can deliver doses ranging from 0 µg to 200 µg with dose set markings at 50, 100, 150 and 200. The pen is used with 31-gauge 5mm (recommended size) disposable pen needles. The user attaches the needle, primes the pen (if it is a new pen), dials the dose, and then delivers the injection into a subcutaneous injection site (abdomen or thigh).

Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL contains lactic acid (b) (4), mannitol (b) (4), phenol (b) (4), water for injection (b) (4), sodium bicarbonate used for ph adjustment. Figure 1 shows the pen and components

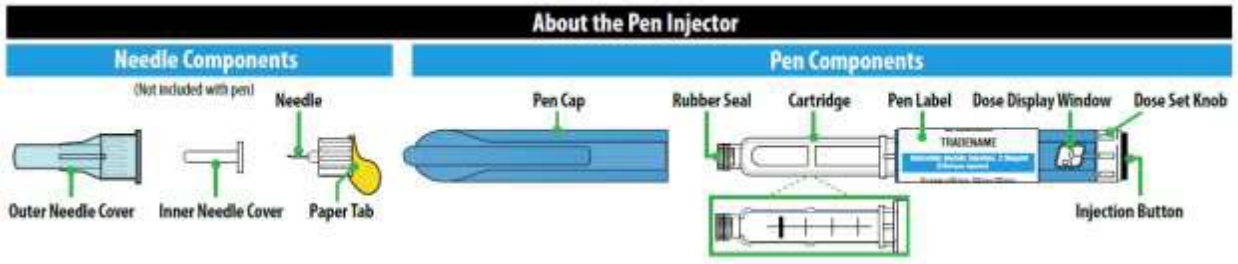

Figure 1. Pen and Components

Acromegaly

Octreotide acetate is indicated to reduce blood levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [somatomedin C] in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. (b) (4) .

Carcinoid Tumors

Octreotide acetate is indicated for the (b) (4) treatment of patients with (b) (4) severe diarrhea and flushing episodes associated with the disease.

Vasoactive Intestinal Peptide Tumors (VIPomas)

Octreotide acetate is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the combination product, Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector, in NDA 213224.

Combination Product Applicant

Firm Name: Sun Pharmaceutical Industries Limited

Address: Sun Pharmaceutical Industries Limited, Sun House Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra, India, 400063

FEI: None

Responsibility – Applicant, Parent firm of Manufacturer

An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

An inspection is not required because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent

part. It appears that Quality System documentation for the firm and combination product would likely be accessible through the manufacturing firm.

Finished Combination Product Manufacturer

(b) (4)

Responsibility – Drug product manufacture, packaging, release testing and stability testing. Drug substance release testing.

Inspectional History – (b) (4)

(b) (4)

An inspection is not required because a recent medical device inspection of the firm was acceptable. (b) (4)

Update: 09/03/2019: An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4) The inspection covered both drug CGMPs and medical device QS and was classified VAI.

Device Constituent Part Manufacturer or Specification Developer (If Applicable)

N/A

DOCUMENTATION REVIEW

Device Constituent Part Type: Auto injector or Pen

Device Constituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD

Device Constituent Part Clearance Type(Delete line if not applicable): Unknown

Combination Product NDA 213224 Proposed Indication for Use: For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors

1. Was the last inspection of the finished combination product manufacturing site, (b) (4) OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3. Is the final combination product meant for emergency use?	YES ☐	NO ☒	UNK ☐
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☒	NO ☐	UNK ☐
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☒	NO ☐	UNK ☐
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☐	NO ☒	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: ☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure,

or positive compliance history, please document your rationale below for not conducting a full ICCR review.

The device is not a life sustaining device when used with vulnerable populations and is used to manage side effects of disease. Since the one OAI classification (2016) the firm has had three acceptable inspections.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant:	Sun Pharmaceutical Limited Sun Pharmaceutical Industries Limited, Sun House Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra, India, 400063 FEI: FEI: None
Finished Combination Product Manufacturer:	(b) (4)

Applicable Sites	(b) (4)	YES ☒	NO ☐
(b) (4)		YES ☒	NO ☐

	(b) (4)
Applicable Sites	
(b) (4)	

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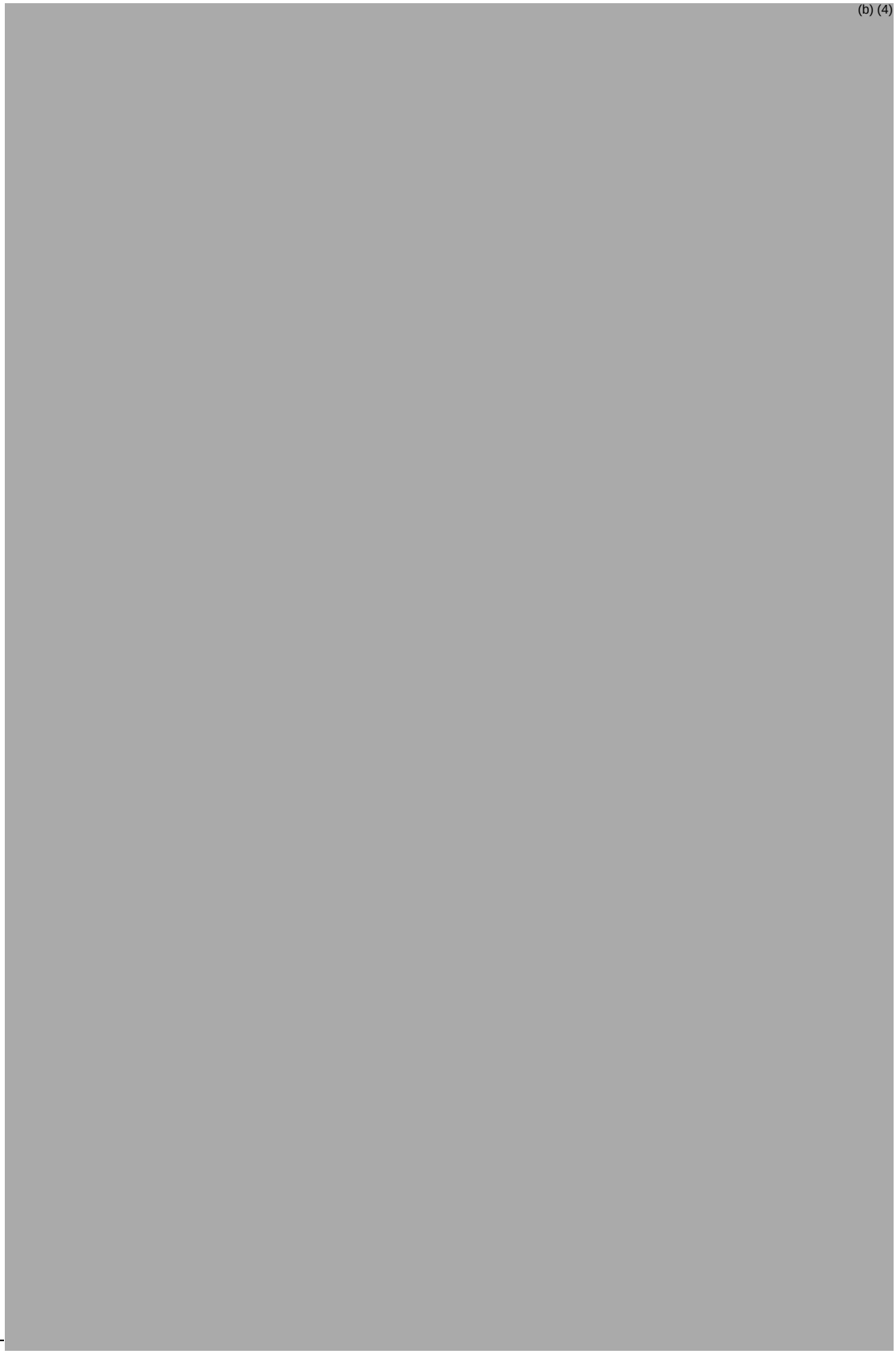
Applicable Sites	(b) (4)
(b) (4)	

(b) (4)



	(b) (4)
Applicable Sites	
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Applicable Sites	

Applicable Sites	(b) (4)
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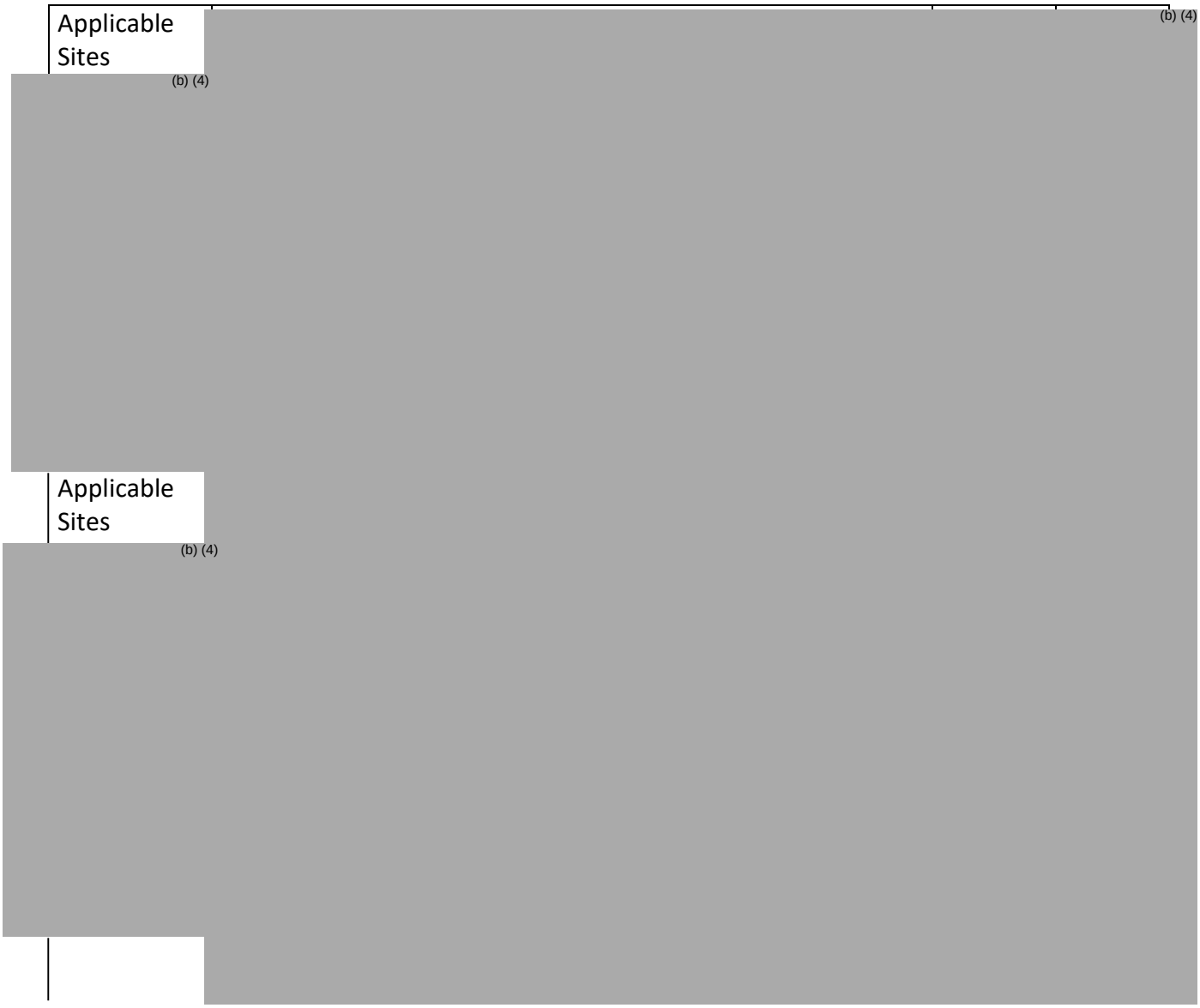
Applicable Sites	
(b) (4)	



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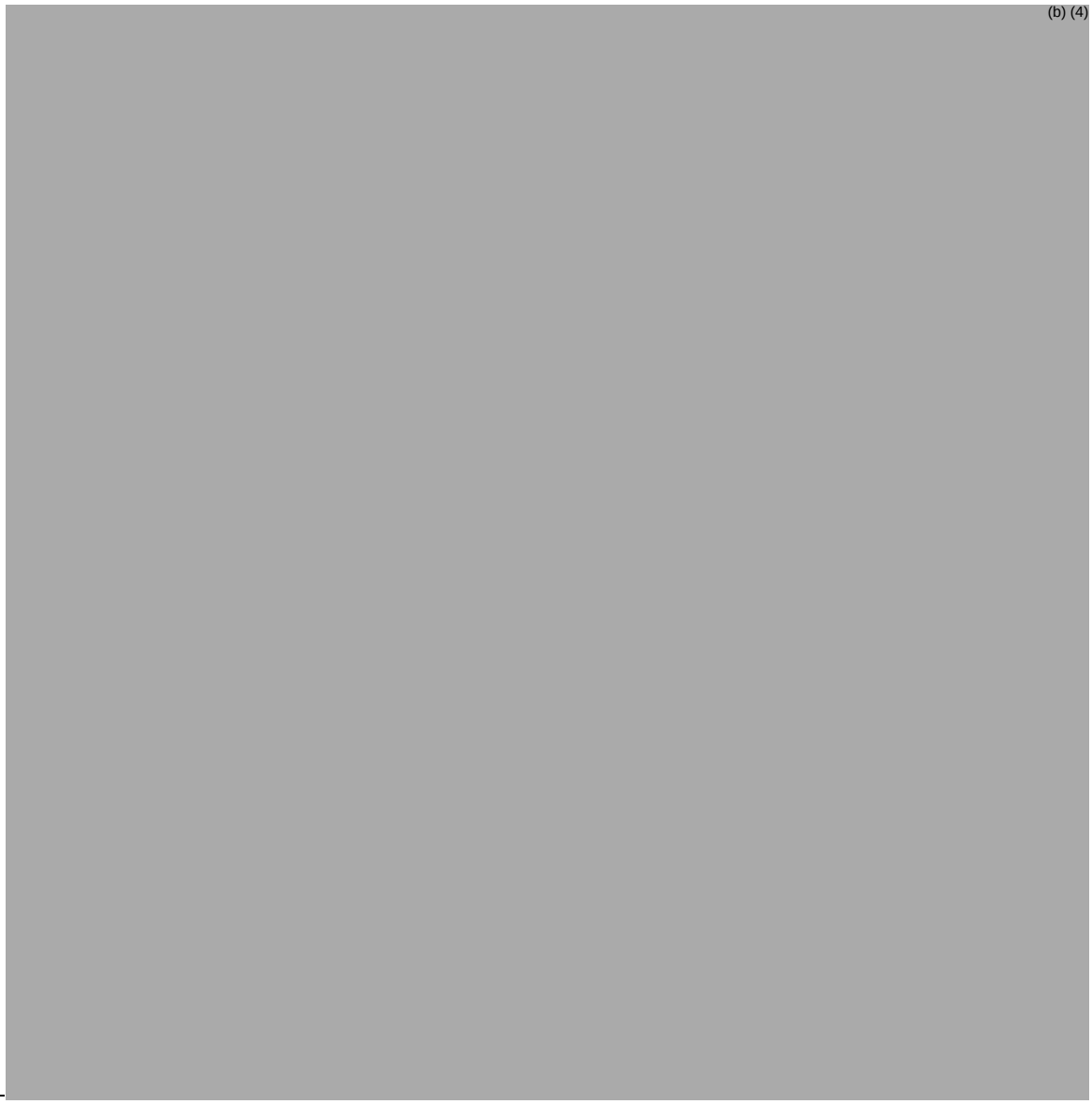

Documentation Review Recommendation:

No Deficiencies Identified. The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review.

Please note that for combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, we recommend the following FDA Guidance: 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.

RECOMMENDATION

06/13/2019: The approvability of application for NDA 213224 Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector should be delayed for the following reasons:

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. A pre-approval inspection is not recommended for the following facility:

(b) (4)

(b) (4)

Update: 09/03/2019 - The application for NDA 213224 Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector is approvable from the perspective of the applicable Quality System Requirements. The recommended inspection(s) were conducted and deemed acceptable

OC Decision: Approvable (Recommend approval to CDER) . See update above.

Reviewer: _____

Christopher Brown

Assistant Director:

Todd Courtney _____

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/s/

TESHARA G BOUIE
09/09/2019 03:54:35 PM

M E M O R A N D U M

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

DATE: 6/11/2019

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 213224

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in March 2018 and the analytical inspection was conducted in (b) (4) which falls within the surveillance interval. The inspections were conducted under the following submissions: NON-RESPONSIVE.

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Sun Pharmaceutical Industries, Ltd.	Pharmacokinetics Department, Tandalja, Vadodara, Gujarat, India
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
06/11/2019 10:59:16 AM