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 (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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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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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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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 (b) (4) 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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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 (b) (4) 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 (b) (4) 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) 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 clicks represent as the drug is administered.	If users do not understand what the clicks are for during drug administration, it may cause confusion.	Consider specifying in Step 5B what the clicks 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 (b) (4) 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: (b) (4)
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 opening __/__/__". 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.	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 opening __/__/__. Discard unused portion 28 days after first opening." in bold font under storage information. The "__/__/__" in the statement will alert the users to write a complete date (month, day, and year) on the carton labeling.
6.	Only the strength per milliliter (b) (4) 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: (b) (4)

[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	(b) (4) 2.8 mL (2.5 mg/mL)
Dose and Frequency	50 mcg to 2 (b) (4) 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)

[redacted]

[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 (b) (4) Limitations of Use
In patients with carcinoid syndrome and VIPomas, the effect of octreotide (b) (4) on size, rate of growth and development of metastases, has not been determined.

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 mcg/ (b) (4) to 600 mcg/ (b) (4) 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. (b) (4) experience with doses above 750 mcg/day is limited.

2.3 VIPomas
Daily dosages (b) (4) 200 mcg to 300 mcg in 2-4 divided doses (b) (4) 150 mcg to 750 mcg (b) (4) but usually doses above 450 mcg/(b) (4) 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
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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

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy (8.3)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with octreotide acetate use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. 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 *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received intravenous doses of octreotide up to 1 mg/kg/day during the period of organogenesis. A slight reduction in body weight gain was noted in pregnant rats at 0.1 and 1 mg/kg/day. There were no maternal effects in rabbits or embryo-fetal effects in either species up to the maximum dose tested. At 1 mg/kg/day in rats and rabbits, the dose multiple was approximately 7 and 13 times, respectively, at the highest recommended human dose of 1500 mcg/day based on body surface area.

In a pre- and post-natal development rat study at intravenous doses of 0.02–1 mg/kg/day, a transient growth retardation of the offspring was observed at all doses which was possibly a consequence of growth hormone inhibition by octreotide. The doses attributed to the delayed growth are below the human dose of 1500 mcg/day, based on body surface area.

8.2 Lactation

Risk Summary

There is no information available on the presence of octreotide in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Studies show that octreotide administered subcutaneously passes into the milk of lactating rats *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Bynfezia Pen, and any potential adverse effects on the breastfed child from Bynfezia Pen or from the underlying maternal condition.

Data

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).

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as the therapeutic benefits of a reduction in GH levels and normalization of insulin-like growth factor 1 (IGF-1) concentration in acromegalic females treated with octreotide may lead to improved fertility.

17 PATIENT COUNSELING INFORMATION

Females and Males of Reproductive Potential

Inform female patients that treatment with Bynfezia Pen may result in unintended pregnancy *[see Use in Specific Populations (8.3)]*.

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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

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 September 2018, which falls within the surveillance interval. The inspections were conducted under the following submissions: (b) (4).

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	Sun Pharmaceutical Industries, Ltd.	Pharmacokinetics Department, Tandalja, Vadodara, Gujarat, India

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/s/

FOLAREMI ADEYEMO
06/11/2019 10:59:16 AM