CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213224Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	15 Jan 2020
From	Suryanarayana Sista
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	213224
Applicant	Sun Pharmaceutical Industries Limited
Date of Submission	03/28/2019
PDUFA Goal Date	
Proprietary Name (Proposed)	Bynfezia Pen
Established or Proper Name	Octreotide Acetate
Dosage Form(s)	Injection, 2.5 mg/mL, 2.8 mL Pen Injector
Applicant Proposed Indication(s)/Population(s)	Treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide secreting tumors in adult patients
Applicant Proposed Dosing Regimen(s)	*The initial dosage is usually 50 mcg administered* (b) (4) (b) (4) *three times daily*
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors
Recommended Dosing Regimen(s) (if applicable)	*The initial dosage is 50 mcg administered* (b) (4) *three times daily. Upward dose titration is frequently required. Dosage information for patients with specific tumors are as follows:* *<u>Acromegaly</u>* *Dosage may be initiated at 50 mcg three times a day. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who will require higher doses. IGF-1 (somatomedin C) levels every 2 weeks can be used to guide titration. Alternatively, multiple growth hormone levels at 0-8 hours after octreotide acetate administration permit more rapid titration of dose. The goal is to achieve growth hormone levels less than 5 ng/mL or IGF-1 (somatomedin C) levels less than 1.9 unit/mL in males and less than 2.2 unit/mL in females. 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. IGF-1 (somatomedin C) or growth hormone levels should be reevaluated at 6-month intervals.*

	Octreotide acetate should be withdrawn yearly for approximately 4 weeks from patients who have received irradiation to assess disease activity. If growth hormone or IGF-1 (somatomedin C) levels increase and signs and symptoms recur, octreotide acetate therapy may be resumed. *<u>Carcinoid Tumors</u>* *The suggested daily dosage of* (b) (4) *during the first 2 weeks of therapy ranges from 100-600 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 1500 mcg/day. However, experience with doses above 750 mcg/day is limited.* *<u>VIPomas</u>* *Daily dosages of 200-300 mcg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range: 150-750 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.*

1. Benefit-Risk Assessment

Sun Pharmaceutical Industries Limited (SPIL) has submitted an NDA application via the 505(b)(2) pathway for octreotide acetate injection (2.5 mg/mL, 2.8 mL). Octreotide acetate is a long acting octapeptide and has been approved 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. The proposed trade name for SPIL's octreotide product is Bynfezia Pen. This application relies on FDA's finding of safety and effectiveness for the listed drug Sandostatin (octreotide acetate injection) (0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL concentration in 1 mL single-dose ampules; 0.2 mg/mL and 1 mg/mL concentration in 5 mL multiple-dose vials) (NDA 019667) for approval. In this application, SPIL has satisfactory established that such reliance is scientifically justified for the treatments indicated above. The basis for this conclusion that supports the approval of SPIL's octreotide acetate injection are briefly summarized below.

(a) The Sponsor successfully demonstrated that SPIL's octreotide acetate Pen and Sandostatin are pharmacokinetically bioequivalent in the comparative PK study PKD_17_257.
(b) Sandostatin was previously determined to be safe and effective for the same indications that the Sponsor is seeking for their octreotide product. It is expected that the benefits and risks of SPIL octreotide acetate injection used at proposed doses will be similar to the benefits and risks associated with Sandostatin 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.
(c) In clinical pharmacology study(s), the safety profile of SPIL octreotide acetate from study PKD_17_257 was consistent with the known safety profile for Sandostatin.
(d) The Sponsor submitted satisfactory CMC (drug substance, drug product and associated studies) and device related information in support of their application.

In conclusion, I concur with CMC, Clinical Pharmacology, Pharmacology/Toxicology and CDRH disciplines that recommend approval of this 505(b)(2) application; no additional data with SPIL's octreotide acetate Pen are required at this time for the approval of this application. I also agree with SPIL's octreotide acetate Pen's proposed dosing regimen of initial dosage of 50 mcg administered (b) (4) three times daily for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide secreting tumors. Refer to the complete label for additional dosing recommendations.

2. Background

On March 26, 2019, SPIL submitted a new drug application under section 505(b)(2) of the FD&C Act relying upon the Agency's finding of safety and effectiveness for Sandostatin (NDA 019667, Novartis) to support the approval.

Sandostatin is one of multiple octreotide acetate products currently approved in the US. The pharmacological actions of octreotide acetate that has a long history of clinical use are well understood. Octreotide acetate, known chemically as L-cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-Lthreonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-,cyclic (2-7)-disulfide; [R-(R*, R*)] acetate salt, is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin. Sandostatin was initially approved in 1988 to reduce blood levels of growth hormone and IGF-I (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, in an application submitted under section 505 (b)(1) of the FD&C Act (NDA 019667). Sandostatin is also approved for the following indications: acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with vasoactive intestinal peptide secreting tumors (VIPomas).

The submitted new drug application includes:

- A physicochemical assessment evaluating the octreotide acetate drug substance and the finished octreotide acetate injection, 2.5 mg/mL, pen injector, 2.8 mL drug product
- A relative bioavailability study conducted in healthy volunteers comparing SPIL octreotide acetate injection with the listed drug Sandostatin
- A biowaiver request for the lower 50, 100, and 150 µg strengths
- A nonclinical dossier which consisted of a combination of literature data and a set of toxicology studies conducted by the innovator (Literature submitted was additional information not relied upon for the approval)
- A clinical dossier which consisted of a combination of literature data and a set of safety/efficacy studies conducted by the innovator (Literature submitted was additional information not relied upon for the approval)

<u>Regulatory background</u>

A pre-IND meeting request to discuss the sponsor's development plan for octreotide acetate injection, 2.5 mg/mL, 2.8 mL Pen Injector was submitted to the Division of Metabolism and Endocrinology Products (DMEP) on October 9, 2018. In a written response issued for this meeting request, the Division noted the following:

- The submission under Section 505(b)(2) may be an appropriate regulatory pathway for the proposed product, provided that the Sponsor established a 'bridge' between their product and the listed drug that the Sponsor identified, Sandostatin (octreotide acetate) Injection (NDA 019667).
- If you intend to submit a 505(b)(2) application that relies on the FDA's previous findings of safety and/or effectiveness for one or more listed drugs or on information from the literature that pertains to a listed drug(s), you will need to establish a 'bridge' between your drug product and the listed

drug(s) you have identified to ensure that reliance on FDA's previous findings of safety and effectiveness to establish your product's safety and effectiveness is scientifically justified. Additionally, you must submit data necessary to support any aspects of the proposed drug product that differ from the listed drug(s) relied upon.

- Also, note that if you seek to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. If you plan to support the safety of your product with articles from the published literature, you must identify any differences between your to-be-marketed product and the product(s) used in the published studies. If such products are not identical to your drug product, you must justify in your submission why you do not expect the identified differences to result in a different efficacy and safety profile for your own product.
- If there are differences between your drug product and the listed drug(s), you may be required to qualify the impact these differences have on safety and effectiveness with additional nonclinical and/or clinical studies.
- We agree that if your application is not for a new active ingredient, new indication(s), new dosage form, new dosing regimen, or new route of administration, then PREA requirements will not be triggered by this application and an agreed initial pediatric study request would not be required.
- We agree in principle that no nonclinical studies are required to support the proposed NDA submission pending that the levels of impurities, excipients, leachables, and extractables meet the appropriate ICH qualification thresholds or are adequately justified.
- A bioequivalence study to 'bridge' your product to the reference product is needed. If bioequivalence to the referenced drug (Novartis' Sandostatin injection) is demonstrated in adults, additional bioequivalency, efficacy, or safety studies in the intended population (e.g., patients with acromegaly) would not be required.
- FDA would waive the CFR requirement for submission of bioavailability/bioequivalence data on the three lower strengths of the proposed drug product if the following criteria are met:
    a. A biowaiver request is included in the NDA submission for the proposed lower strengths not tested clinically.
    b. Acceptable BA/BE data for the highest 200 μg strength.
    c. The lower strengths are proportionally similar in their active and inactive ingredients to the corresponding highest strength product for which the BA/BE study was conducted. FDA defines proportionally similar in the following ways:
        i. All active and inactive ingredients are in exactly the same proportion between different strengths.
        ii. For high potency drug substances (<5 mg), where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within + 10 % of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.
    d. All the strengths are the same dosage form, have the same release mechanism, and manufacturing process.
    e. Dissolution profile comparisons between the highest and lower strengths meet the f2 similarity requirements in three different pH media (i.e., pH 1.2, 4.5, and 6.8). For dissolution profile comparisons using the Similarity Factor f2, please refer to the FDA guidance document, "Dissolution Testing of Immediate Release Solid Oral Dosage Forms, Aug 1997".
    f. Evidence of linear PK over the proposed dose range is included in the NDA.

3. Product Quality

Drug Substance:
Chemistry, manufacturing, and controls (CMC) information related to the drug substance in the application was reviewed (Panorama, 09/17/2019) by the CMC reviewer, Dr. Patel, who concluded that CMC information provided in the NDA and DMF is adequate to support the approval of the NDA from drug substance quality perspective.

Drug Product:
The drug product composition, excipients, container closure system, product compatibility with excipients and container closure system, drug product specification, batch analysis, impurity information, reference standard, and stability information including in-use stability data were reviewed by Dr. Amartey (Panorama, 12/10/2019). Based on stability information for product quality attributes, Dr. Amartey granted an expiration period of 24 months for the drug product when stored at 2-8°C in carton. The applicant had also provided break loose force and glide force data for 3 stability batches. The Application Technical Lead, Dr. Ramaswamy noted that one of the three stability batches did not meet the glide force acceptance criteria for the 18-month time point. The stability results for all attributes were acceptable for the 12-month time point for all three batches. Based on this information, Dr. Ramaswamy granted a 12-month expiry period for the finished product when stored at 2-8°C.

The manufacturing process and process control for the octreotide acetate test product was reviewed by Dr. Thakur, the CMC reviewer (Panorama, 12/10/2019). Her review concluded that the proposed drug product manufacturing process controls are adequate to support the NDA. The facility compliance information for the drug product and the drug substance manufacturing facilities were also reviewed by Dr. Thakur. Her review concluded that facilities are acceptable to support the approval of NDA.

Biowaiver:

The applicant conducted a pivotal bioequivalence study comparing the highest strength, 200 µg dose of the proposed product to the 200 µg dose the RLD and concluded bioequivalence. The applicant requested biowaiver for the lower strengths (50, 100, and 150 µg doses). Dr. Li reviewed (Panorama, 11/18/2019) the request and granted the biowaiver based on acceptable bioequivalence study results for the highest strength and self-evident bioequivalence of an injection solution per CFR 320.22(b).

4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were required or submitted in support of this NDA, as the proposed drug product formulation is similar to that of the RLD. The literature submitted by the Sponsor was additional information not relied upon for the approval. The Pharmacology/Toxicology reviewer, Dr. Basso did not identify any new impurities, degradants or leachables of concern in the SPIL drug/device combination (DARRTS 12/12/2019).

The Pharmacology/Toxicology reviewer concluded that the nonclinical data submitted in this application support the reliance on FDA's finding of safety and effectiveness for Sandostatin to support approval of the SPIL's octreotide acetate and recommended an approval of the application.

5. Clinical Pharmacology

The Clinical Pharmacology review (DARRTS 10/16/2019) recommends approval of this NDA application. The review concludes that study PKD_17_257 demonstrated that following a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) or the reference drug Sandostatin (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL), the 90% confidence intervals of the geometric mean ratios of octreotide C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ are all within 80-125% limit, indicating proposed octreotide acetate injection (2.5 mg/mL) is bioequivalent to the reference drug Sandostatin (octreotide acetate) Injection (1 mg/mL). This study and its results will be summarized next.

Study # PKD_17_257 was a randomized, open label, two treatment, two period, two sequence, single dose, crossover, relative bioavailability study in 20 healthy subjects under fasted condition. In each period, subjects were randomized to receive a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test, A) or the reference drug Sandostatin (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference, B). Drug administration was separated by a washout of 7 days between the 2 treatment periods.

The stated primary objectives of the study were: 1) the comparison of PK parameters between Zomacton and Humatrope following the administration of 4 mg of each somatropin product; 2) assessment of the pharmacodynamic profiles for insulin-like growth factor-1 (IGF-1) and IGF-1 binding protein 3 (IGFBP-3).

The study results demonstrated that the 90% confidence intervals of the geometric mean ratios (GMR) of octreotide C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ are all within the 80-125% limits, indicating the proposed octreotide acetate injection (2.5 mg/mL) is bioequivalent to the reference drug Sandostatin (octreotide acetate) Injection (1 mg/mL) (Tables 1, 2). Figure 1 of the Clinical Pharmacology review, reproduced below, illustrates the similarities in PK profiles between SPIL octreotide acetate and Sandostatin.

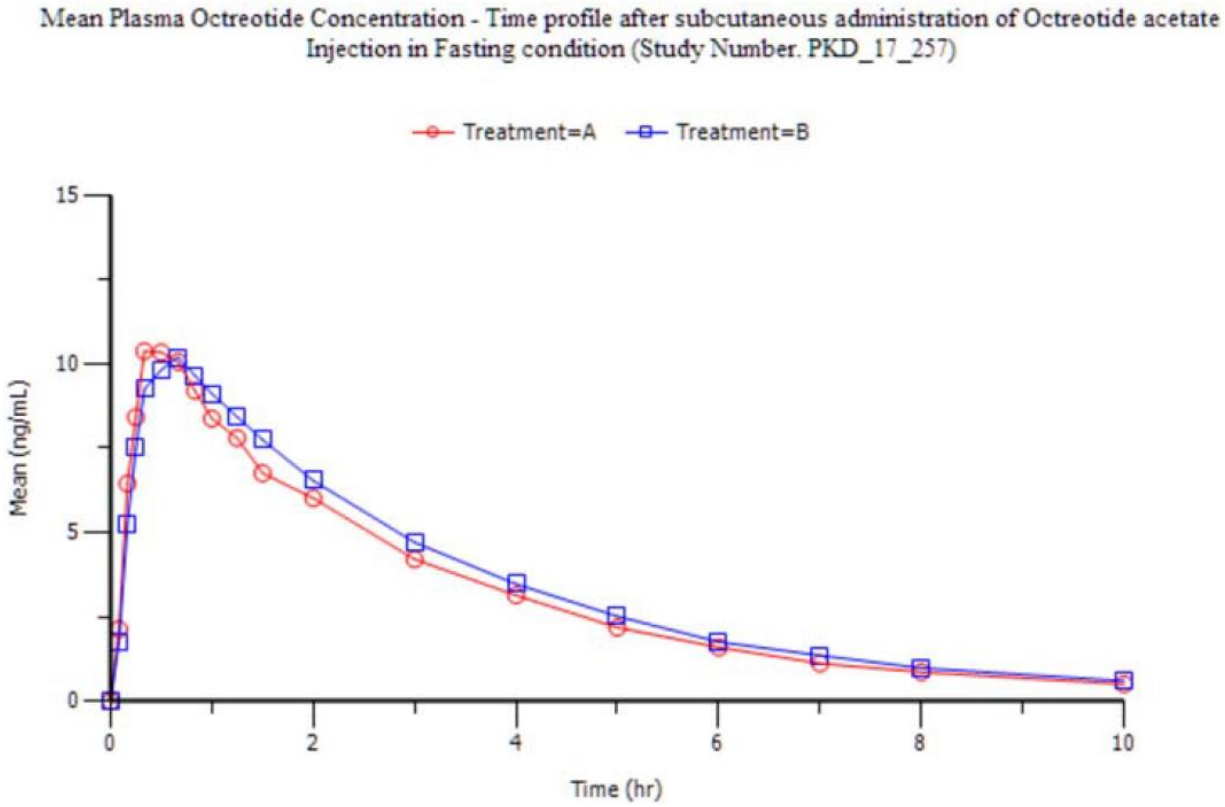

Figure 1 Mean (+SD) octreotide concentration-time profiles after a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test, A) or Sandostatin (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference, B)

Table 1 PK parameters of octreotide after a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test) or SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference)

Parameters	Octreotide acetate injection, 2.5 mg/mL, Pen Injector, 2.8 mL [0.08 mL dose] Test (A)				Sandostatin (Octreotide acetate) Injection 1000 mcg/mL (1 mg/mL), 5 mL Multi-dose vial [0.2 mL dose] Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (ng.h/mL)	32.4469	±	4.3094	13.28	35.0336	±	4.3440	12.40
AUC_{0-inf} (ng.h/mL)	34.2684	±	4.7656	13.91	37.0966	±	4.8843	13.17
C_{max} (ng/mL)	10.9920	±	1.8272	16.62	10.7246	±	2.0325	18.95
T_{max} (h)	0.5394	±	0.2397	44.44	0.5922	±	0.1688	28.50
T_{max}* (h)	0.500 (0.333 - 1.250)	-	-	-	0.667 (0.250 - 0.833)	-	-	-
K_{el} (h^{-1})	0.29741	±	0.05409	18.19	0.29792	±	0.02974	9.98
$t_{1/2}$ (h)	2.4078	±	0.4576	19.00	2.3506	±	0.2556	10.88
% AUC Extrapolation	5.225	±	1.888	36.14	5.466	±	1.256	22.98

*Median values (range) are presented. **Source:** Appendix 16.2.6.1

Table 2 Statistical analysis of the systemic exposure parameters of octreotide after a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test) or Sandostatin (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference)

	GeoMean (Test)	GeoMean (Reference)	90% CI of GMR (%) (Test/Reference)
C_{max} (ng/mL)	10.56	10.85	97.32 (91.60, 103.40)
$AUC_{(0-t)}$ (h·ng/mL)	34.79	32.20	108.04 (104.90, 111.25)
$AUC_{(0-inf)}$ (h·ng/mL)	36.80	33.98	108.30 (104.96, 111.75)

N=19 for each treatment.

In conclusion, I agree with Dr. He that the Applicant has demonstrated that the proposed octreotide acetate injection (2.5 mg/mL) is bioequivalent to the reference drug Sandostatin (octreotide acetate) Injection (1 mg/mL) and the clinical pharmacology scientific justifications are acceptable.

6. Clinical Microbiology

The microbiological controls used in drug product manufacturing process were reviewed by the microbiology reviewer, Dr. Zheng (Panorama, 08/20/2019). She reviewed the CMC

information for (b) (4) processing, sterility, endotoxin controls, antimicrobial effectiveness testing, container closure integrity, filter validation, depyrogenation validation, component sterilization, media fill studies, hold times, stability, and post-approval stability commitment. Dr. Zheng also reviewed the Type V drug master file (DMF) (b) (4). Her review concluded that microbiological controls are adequate to support the NDA.

7. Clinical/Statistical- Efficacy

No new clinical data were submitted for this NDA submission. No formal statistical evaluation was needed. The statistical reviewer, Dr. Kim concluded that there are no statistical issues to refrain from approval of this submission (DARRTS 10/17/2019).

8. Safety

There are no new safety clinical data in this application other than those recorded in the single dose study PKD_17_257, which are unremarkable and consistent with the labeled safety information for Sandostatin.

9. Device

The device attributes were evaluated by the Center for Devices and Radiological Health (CDRH). The CDRH reviewer Dr. Petrochenko indicated approval for the device provided the Sponsor had a satisfactory resolution to the following query from CDRH:

> "We acknowledge you have established injection/activation force as a release specification. You have also provided data for injection force testing after shipping and aging which shows a potential out of specification batch; the batch was properly identified, and a root-cause analysis performed. It is unclear, however, if your sampling and rejection processes during your routine manufacturing and release testing (b) (4) will identify and reject such lots in the future. Please confirm whether you would reject such a batch during your release testing and provide a brief overview of your testing and release processes for injection force prior to distribution of the final finished product".

The resolution proposed by the Sponsor in a letter dated 09 Jan 2020, was found to be acceptable by CDRH, and they recommended approval (DARRTS 01/15/2020).

10. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

11. Pediatrics

This NDA application does not trigger PREA. SPIL is not proposing a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration for octreotide acetate injection, 2.5 mg/mL, 2.8 mL, pen injector.

12. Pregnancy and Lactation

The Division of Pediatric and Maternal Health (DPMH) reviewer, Dr. Ceresa, recommended (DARRTS 12/19/2019) that 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.

13. Other Relevant Regulatory Issues

Office of Scientific Investigations Consult

The Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection since OSIS recently inspected the requested sites and the inspectional outcome from the inspections was classified as No Action Indicated (NAI). For more detailed information, please refer to the consult review by Dr. Folaremi Adeyemo dated June 11, 2019 in DARRTS (Date 11 June 2019, Reference ID: 4446788)

14. Labeling

Proprietary Name:
The Division of Medication Error Prevention and Analysis (DMEPA) indicated that the proposed name "Bynfezia Pen" for the SPIL octreotide acetate injection product was conditionally acceptable.

Labeling:
The Division of Metabolism and Endocrinology Products (DMEP) had requested an oncology consult to the Division of Oncology 2 (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). DO2 recommended (DARRTS 01/07/2020) removal of (b) (4) from the Warnings & Precautions section and inclusion of these tests in the Indications and Usage section of the label.

Refer to the complete labeling in the approval letter.

15. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Not required

Post-marketing Requirements (PMRs) and Commitments (PMCs)

None.

Though DPMH is recommending that the Sponsor 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, DMEP believe that octreotide acetate injection is indicated in an orphan population, and as such there may not be enough patients who become pregnant to conduct a meaningful study. The Endocrine Society, in its guidelines[1] recommends that all treatment should be stopped during pregnancy as the tumors for which octreotide is used as a treatment usually do not grow during the pregnancy.

16. Recommended Comments to the Applicant

None.

[1] Katznelson L, Laws ER, Memmed S, et al. Acromegaly: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2014, **99**(11): 3933-3951.

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/s/

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