CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209607Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 209607
OPQ Integrated Quality Assessment final
Review Date: 7/09/2018

Drug Product	Azedra (iobenguane I 131) Injection
Strength	555 MBq/mL (15 mCi/mL); see page 9 for composition statement (therapeutic, diagnostic)
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	Progenics Pharmaceuticals, New York New York 10007
US agent, if applicable	N/A

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505b2**

2. **RELATED/SUPPORTING DOCUMENTS:**
   A. DMFs:

Table 1 Drug Master Files (DMFs)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETE	REVIEWER
(b) (4)	II	(b) (4)		Adequate	11/06/2017	David Place, Ph.D., CDER/OLDP/DP MA1

   B. Other Documents: IND 70,663 (Molecular Insight Pharmaceuticals, Inc.)

3. **CONSULTS: N/A**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (b) (4)	Sithamalli Chandramouli, Ph.D.	ONDP/DNDAPI
Drug Product	Dhanalakshmi Kasi, Ph.D.	ONDP/Branch VI/Division II
Microbiology	Julie Nemecek, Ph.D.	OPQ/OPF/Microbiology
Facility	Rebecca Dombrowski, PhD	OPQ/OPF/DIA/B1
Project/Manager (R.Ph)	Steven Kinsley, Ph.D.	OMPT/CDER/OND/ODEIV/DMIP
Application Technical Lead	Eldon E.Leutzinger, Ph.D.	ONDP/Branch VII/Division II
Environmental Assessment (EA)	Dhanalakshmi Kasi, Ph.D.	ONDP/Branch VII/Division II

Table 2 Documents

DOCUMENT	RECEIPT DATE	DESCRIPTION	Section/reviewer
Original & IR's as detailed in primary reviews	02/28/2017	3.2.S and 3.2.P	3.2.S (Sithamalli Chandramouli, Ph.D.); 3.2.P (Dhanalakshmi Kasi, Ph.D.)

Executive Summary

I. Recommendations

APPROVAL on the basis of recommendation from CMC, Microbiology and Facilities.

A. Recommendation and Conclusion on Approvability

N/A

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

AZEDRA (iobenguane I 131) Injection is a high specific activity form of Iobenguane I 131, manufactured (b) (4) (b) (4) The drug product consists of **m-[^{131}I]iodobenzylguanidine** drug substance, along with ascorbate and (b) (4) (b) (4) in sterile WFI. The pH is acidic (4.5 – 5.5). The therapeutic dose of Azedra contains 337 mCi, and the dosimetric contains 30 mCi. Dosimetric batches were initially manufactured at Molecular Insights Pharmaceuticals (subsidiary of Progenics Pharmaceuticals, Inc.) and used in the early clinical trials, then later transferred to (b) (4) Subsequently, the (b) (4) became the contract manufacturer of batches for the registrational clinical trial. (b) (4) (b) (4) a new facility, is proposed as the sole commercial manufacturer of Azedra

(b) (4)

♦ DRUG SUBSTANCE / DRUG PRODUCT:

Category	Issue
Reference Standard for Drug Substance, m-[^{131}I]iodobenzylguanidine	**Source** – absence of sufficient characterization for establishment of authenticity of the standard (b) (4) (b) (4) details needed to support results of physicochemical studies. Also, there were (b) (4)
ASSESSMENT: issue resolved with description of method of (1) preparation and (2) characterization (2 (b) (4) (b) (4)	
Quality Controls	(b) (4)
ASSESSMENT: their quality (in verification was p (b) (4) (3.2.P.4.1). They proposed limits for chemical impurities (2) at release and stability for (b) (4) RRT (b) (4) and RRT (b) (4) and additionally limits for any other unknown impurity. The total impurity is set it at (b) (4) at stability. (3) Progenics established a "tolerance range" of (b) (4) ^{131}I]MIBG. Also, the color specification is changed to "colorless to slightly yellow (b) (4)," based on their batch results.	
Stability	**Optimization of Shipping Conditions** – absence of procedures (e.g., visual and free $^{131}I^-$ tests prior to administration) to address deviations in shipping conditions potentially impacting product stability
ASSESSMENT: a request is made for a shipping study with product at the receiving site. It was learned in the tcon (5/22/2018), **not only was a (b) (4) TempTale device used in the shipping studies, but would also be included routinely in each shipment of product to a user.** (b) (4) (b) (4) **However, there needs to be a Life Cycle follow-up. The Life Cycle ("post-marketing") reviewer should monitor the annual reports for any discarded drug product samples, due to deviations in the temperature profile of the shipped samples.**	

	[redacted] (b) (4)
	[redacted] (b) (4) vial, requiring information (along with the results of media fill studies) for its resolution.
CONCLUSION: decision by microbiology – **could approve the NDA, providing that there is a commitment from Progenics to use only the vials** [redacted] (b) (4) in which case no additional information (including media fill studies) would be required. The commitment was made by Progenics, thus resolving the final issue for microbiology (Julie Nemecek, Microbiology Reviewer). See Microbiology Reviews for details.	
Facilities	Catalant Pharma, Almac Sciences, [redacted] (b) (4) [redacted] (b) (4) Wickham Laboratories and Butterworth Laboratoties were approved based on file review (low risk). [redacted] (b) (4) Sofie received a PAI (with initial high risk), and was approved on the basis of the PAI results. No issues remain for the manufacturing/testing facilities. See Facilities Review for details.

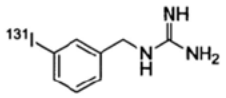
♦ DRUG PRODUCT / LABELING:

Category	Issue
Structure of Drug Substance	**Counterion** – absence of a complete structure (in relation to other MIBG's)
ASSESSMENT: in discussions with the USAN names expert in OPQ (David Lewis, Ph.D.), active ingredients that are salts can be represented in both the free base and as a salt. A plan forward to resolve the counterion issue is to leave the active ingredient as in the protonated form, m-[^{131}I]iodobenzylguanidineH^+.	
Vial and Carton Labels User QC	Generally (**1**), there is need to revise for improvement of the prominence of various elements in the labeling, as well as some additions, and revisions of information pertinent to the dose range. Aside from issues regards improvement of prominence and additions to the container label (**2**), there is the direction to (**3**) revise the statement "(b) (4)" to "Must Dilute Before Intravenous Injection" in order to minimize the risk of administering the drug undiluted. Critical information (**4**) relative to use of the drug product is directed to be included on the carton label.
ASSESSMENT: all directives and recommendations for labeling were made satisfactorily by the applicant.	

A. Drug Substance [USAN Name] Quality Summary

Iobenguane I 131 (USP; USAN)

By 21 CFR 314.108(a), **the active moiety is defined as "m-[^{131}I]iodobenzylguanidine."** Iobenguane (^{131}I), and has chemical structure,



, based on "Iobenguane" [CAS 80663-95-2], with the only difference being the specific isotope of iodine. It appears (with ^{131}I) as a monograph in the USP (as sulfate salt) and USA (sulfate salt as well). m-[^{131}I]iodobenzylguanidine of Azedra has a specific activity of ~ 2.5 mCi/μg; 0.135 mg MIBG. It exists as the m-[^{131}I]iodobenxylguanidiniumH^+, salt in the Azedra formulation at pH 5.0. Since there was an approved drug (diagnostic "m-[^{131}I]iodobenzylguanidine sulfate by CIS-

(b) (4)

(b) (4)

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(b) (4)

131

(b) (4)

(b) (4)

m-[I]iodobenzylguanidine	12,488 MBq (337.5 mCi) (0.135 mg)	1,110 MBq (30 mCi) (0.012 mg)
(b) (4)		
SWI		(b) (4)

The drug product is filled into 30 mL borosilicate glass vials (USP Type 1), and capped with 20 mm rubber stoppers with a (b) (4) coating and sealed with aluminum crimp seals. The secondary container is a 50 mL lead pot, with lead shielding on the sides and 0.949 inch lead shielding on the top and bottom. The product is frozen (- 70^{0}C) immediately following manufacture, and is shipped frozen to users. It must be kept frozen until time of use. Administration must be within 8 hours of thawing, and cannot be re-frozen.

Because of the numer ion, I have collected the totality of these issue tion, quality controls, Reference Standard

Manufacturing	(b) (4)	IR (2/22/2018, 4/3/2018, 5/17/2018)
Formulation		IR (2/22/2018, 4/3/2018)
Quality controls		IR (2/7/2018, 2/21/2018, 2/22/2018, 1/22/2018, 4/3/1018)
Reference standard		IR, 1/23/2018
Stability, Storage and Shipping	maintenance of stability during shipping from manufacturer to site of its use	IR, 2/22/2018, 5/8/2018

Within these groups are discussed only the critical ones as a subset (Critical Quality Attributes,

(b) (4)

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of prominence and additions to the container label (including product composition, revision of dose range), there is the direction to revise the statement "[redacted]" to "Must Dilute Before Intravenous Injection" in order to minimize the risk of administering the drug undiluted. A number of other revisions to the PI (sections for preparation and administration), and these revisions were made by the sponsor.

MICROBIOLOGY PRODUCT QUALITY

There were numerous review issues for microbiology. Many of the issues were adequately addressed, but one important one remained. Hence, in the microbiology review of 3/16/2018, there was a recommendation of non-approval (Julie Nemecek, Ph.D). Briefly, the issue that remained inadequate was the sterilization [redacted] of the container closure, and a list of information required to adequately assess this process was conveyed to the applicant. Upon review of the responses, Microbiology (Julie Nemecek, Ph.D.) conveyed to Progenics (6/20/2018) the directive that if they commit to use of only the vials [redacted] then the additional information regarding [redacted] of the 30 mL vials (including additional media fill studies) is not required for approval of the NDA from a product quality microbiology perspective. Progenics responded on 6/27/2018 that they commit to use only the vials [redacted] All other microbiology issues have been satisfactorily addressed. Dr. Nemecek's conclusion to this is acceptable, for a final decision of approval from a microbiology standpoint.

FACILITY INSPECTION STATUS

Facility	Responsibility
Catalent Pharma Solutions LLC, Philadelphia, PA	Labeling [redacted]
Almac Sciences Ltd, UK	Manufacture, [redacted]
Wickham Laboratories Ltd, UK	[redacted] testing
Butterworth Laboratories Ltd, UK	[redacted] testing [redacted]
[redacted] Sofie	[redacted] manufacture [redacted]

Catalent Pharma, Almac Sciences, (b) (4) Wickham Laboratories, and Butterworth Laboratories were approved based on file review. The Overall Initial Facility Risk Assessment for Catalina Pharma and Butterworth Laboratories was low. That for Almac Sciences and Wickham Laboratories was medium low, and for (b) (4) it was medium high. (b) (4) **Sofie had a PAI (with initial risk assessment of high), and the approval of this facility was based on the PAI**. Overall, the evaluation of the manufacturing and testing facilities were found to be adequate (Rebecca Dombrowski, Ph.D. (3/13/2018; OPF/OPQ). Regards the (b) (4) the target manufacturer was (b) (4) (b) (4) and there were 4 irradiation sites (b) (4) None of the latter sites were part of the facilities review of 3/13/2018. Details of the production of (b) (4) are found in the DMF (b) (4) Dhana Kasi, Ph.D. (drug product/process reviewer) was part of the inspection team (for (b) (4) Sofie) that turned in a recommendation for approval. See the Facilities Review 3/13/2018) for a detailed discussion of the review findings and conclusions.

C. Summary of Drug Product Intended Use

Azedra is proposed for (b) (4) The recommended clinical therapeutic dose is 500 mCi (mass dose of (b) (4). The drug is administered intravenously in approximately 50 mL saline formulation over a period of 30 minutes at a infusion rate of 100 mL/hr.

D. Biopharmaceutics Considerations: N/A

E. Novel Approaches: N/A

F. Any Special Product Quality Labeling Recommendations: N/A

G. Life Cycle Knowledge Information (see Attachment A): N/A

Risk Assessment - Drug Product (Azedra)

From Initial Risk Identification[1]			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking[2]**	**Risk Mitigation Approach**	**Final Risk Evaluation[3]**	**Lifecycle Considerations/ Comments**
Radionuclidic Purity	• Method of production & Purification (general – details in DMF (b) (4)	RPN<25	N/A (DMF (b) (4) & COA determined adequate)	RPN < 25	N/A
Radiochemical Identity	•Analytical method & validation characteristics •Congruence (RAD/VIS) methodology •Reference standard •Acceptance criteria	25<RPN<60	Proof of structure of MIBG reference standard completed; (b) (4)	RPN<25	N/A
Radiochemical Purity	•Analytical method & validation characteristics •Degree of resolution of radiochemical impurity peaks from drug substance peak •DL/QL	25<RPN<60	Radiochemical impurities better defined; total radiochemical impurities set at reasonable limits	RPN <25	N/A
Chemical Purity	•Source, (b) (4) (b) (4) •Method of production of drug substance & drug product •Method of purification	25<RPN<60	Reduced limits for individual chemical impurities, and the limit for totals (both for at release and stability)	RPN<25	N/A
Strength (mCi/mL)	•Radiochemical yield •Method of production of drug product; formulation	RPN<25	N/A	RPN<25	N/A
Stability	•Strength (mCi/mL) •Sensitivity of molecular structure to (b) (4) (b) (4)	RPN>60 (because of **propensity** for radiolytic degradation)	Maintenance of stability during shipping resolved by inclusion of TempTale device with each shipment	RPN<25	(4)

1. Based on FMECA (Failure Modes, Effects and Criticality Analysis) developed by Risk Ranking Team
2. RPN < 25 (Low Risk), 25 < RPN < 60 (Medium Risk), RPN > 60 (High Risk)
3. Final Risk & Overall Risk Assessment, RPN (<25) for CMC product quality
4. **Needs follow-up: the Life Cycle ("post-marketing") reviewer should monitor the annual reports for any discarded drug product samples, due to deviations in the temperature profile of the shipped samples**

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E. Leutzinger -S

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MICROBIOLOGY

Product Background:

NDA: 209607

Drug Product Name / Strength: Azedra (iobenguane I 131), 12-16.5 mCi/mL

Route of Administration: Sterile intravenous injection

Applicant Name: Progenics Pharmaceuticals, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: The submission is recommended for approval on the basis of sterility assurance.

Review Summary: The drug product is a sterile radiopharmaceutical solution for intravenous injection packaged in a single-dose vial.

List Submissions Being Reviewed: 8/22/2017, 10/31/2017, 1/16/2018, 2/21/2018, 3/12/2018, 5/30/2018, 6/18/2018

Highlight Key Outstanding Issues from Last Cycle: N/A.

Remarks: The drug product is an Orphan Drug and was granted rolling review (breakthrough therapy designation).

During development, manufacturing of the drug product was performed at three other facilities (Molecular Insights Pharmaceuticals, (b) (4) (b) (4) The applicant provides information, including validation studies and specifications, for each of these facilities. This review only covers information relevant to the (b) (4) facility which is proposed for manufacturing of the drug product.

An information request (IR) was conveyed to the applicant on 12/28/2017 following the microbiology review. The Applicant responded to the IR on 1/16/2018. A second IR was conveyed to the Applicant on 2/7/2018 and responses were provided on 2/21/2018 and 3/12/2018. A third IR was conveyed to the Applicant on 3/20/2018. A teleconference with the Applicant was held on 3/28/2018 and the Applicant provided follow-up written responses on 4/2/2018, 5/4/2018, 5/18/2018, 6/18/2018, and 6/27/2018. The responses are incorporated following the agency comments in relevant

sections of this review.

Concise Description Outstanding Issues Remaining: Not applicable.

Supporting Documents: DMF (b) (4) micro review (b) (4).doc, 7/6/2017, for information regarding sterilization of (b) (4)

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug substance is not the focus of this review as the drug product is sterilized during drug product manufacture.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Clear solution free of visible particles (Specifications, page 1 of 1).

- **Drug product composition**

Component	Quantity in the 2 mL dose	Quantity in the 22.5 mL dose
Iobenguane I 131 (mIBG)	30 mCi/0.012 mg	337.5 mCi/0.135 mg
Sodium ascorbate	116 mg	1305 mg
Sodium gentisate	45 mg	506.25 mg
(b) (4)		
Water for injection		(b) (4)

- **Description of container closure system**

Component	Description	Manufacturer
Vial	30 mL clear USP Type 1 borosilicate glass vial	(b) (4)
Stopper	20 mm (b) (4) coated stoppers	
Seal	20 mm open top aluminum seal	

Reviewer's Assessment: ***Adequate***

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

(b) (4)

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Post-Approval Commitments: Not applicable.

List of Deficiencies: *Not applicable.*

Primary Microbiology Reviewer Name and Date: Julie Nemecek, Ph.D., 6/28/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John Metcalfe, Ph.D., 6/28/2018

Julie Nemecek

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John Metcalfe

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Comments: I concur with the primary reviewer's assessment.