CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209607Orig1s000

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 Review:	July 11, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 209607
Product Name and Strength:	Azedra (iobenguane I 131) Injection 12 to 16.5 mCi/mL (444 to 610.5 MBq/mL)
Total Product Strength:	(b) (4)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Progenics Pharmaceuticals, Inc.
Submission Date:	May 18, 2018
OSE RCM #:	2017-1251-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

DOP2 requested that we review the revised Dosimetric and Therapeutic container labels and carton (lead pot) labeling for Azedra (Appendix A) to determine if they acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note the May 18, 2018 submission of revised container label and carton (lead pot) labeling included the introduction of a container label and carton labeling for a proposed Dosimetric Sample vial for use as part of a sample program for dosimetry dosing.

[a] Stewart J. Label and Labeling Review for Azedra (NDA 209607). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 07. RCM No.: 2017-1251.

2 CONCLUSION

The proposed Dosimetric sample container labels and carton labeling for Azedra may be improved for clarity.

3 RECOMMENDATIONS FOR PROGENICS PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Dosimetric Sample Container Label and Carton Labeling:

1. Revise the sample labels and labeling to include an independent statement "Professional Sample – Not for Sale" on the principal display panel (PDP) (e.g., the very top of the PDP), and remove the word (b) (4) from the statement (b) (4)

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/s/

JANINE A STEWART
07/11/2018

CHI-MING TU
07/11/2018

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

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

Memorandum

Date: June 1, 2018

To: Sharon Sickafuse, Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP 2)

Stacy Shord, Associate Director for Labeling, DOP 2

From: Carole Broadnax, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for Azedra (iobenguane I 131) injection, for intravenous use

NDA: 209607

In response to DOP 2 consult request dated November 15, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Azedra (iobenguane I 131).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP 2 (Sharon Sickafuse) on May 18, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 18, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or carole.broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
06/01/2018

Division of Medical Imaging Products (DMIP)
Radiation Dosimetry, Dose and Safety Consultative Report

NDA 209607

FDA/CDER/OND/ODE-IV/DMIP
April 20, 2018

From:	Stanley H. Stern, PhD, DMIP Health Physicist
Through:	Michele B. Fedowitz, MD, DMIP ADL Alex Gorovets, MD, DMIP Deputy Director Kimberly D. Ritenour-Miller, DMIP RPM
To:	Sharon Sickafuse, MS, CDER/OHOP/DOP-II RPM Shubhangi Mehta, PharmD, CDER/OHOP/DOP-II RPM Diana Bradford, MD, CDER/OHOP/DOP-II MO Suzanne Demko, PA-C, CDER/OHOP/DOP-II TL Steven Lemery, MD, MHS, CDER/OHOP/DOP-II ADD
Sponsor:	Progenics Pharmaceuticals, Inc.
Product:	AZEDRA® (iobenguane I 131) injection for intravenous use
Indications, usage:	AZEDRA is indicated for the treatment of adult and pediatric patients 12 years or older with iobenguane scan positive, recurrent or unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma.
Consult requested:	November 15, 2017
Desired completion:	March 5, 2018

OHOP/DOP2 Comments / Special Instructions

"Please review radiation dosimetry and expected organ and bone marrow exposure from treatment with this radionuclide therapy."

Preliminary/draft DMIP advice to DOP2

Via e-mail March 12, 13, 14, and April 12, 2018; DMIP-DOP2 internal meetings April 12 and 19, 2018

Conclusion and recommendation

- The prescribing information [1] is insufficiently up-to-date, omits dosing recommendations for critical organs, and does not adequately characterize potential risk for secondary cancers. These gaps might narrow the latitude and depth of provider assessment of radiation risk and safety as factors in the clinical management of patient disease.
- We recommend labeling revisions along lines suggested in the following section of this report.

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/s/

STANLEY H STERN
04/20/2018

MICHELE B FEDOWITZ
04/23/2018

ALEXANDER GOROVETS
04/23/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	209607
Brand Name	Azedra
Generic Name	Iobenguane I-131
Sponsor	Progenics Pharmaceuticals, Inc.
Indication	Treatment of iobenguane avid malignant and/or recurrent unresectable pheochromocytoma and paraganglioma
Dosage Form	IV injection
Drug Class	I-131 labeled iobenguane (MIBG); MIBG is a substrate of the norepinephrine transporter (NET)
Therapeutic Dosing Regimen	Regimen consists of a dosimetric step followed by therapeutic doses approximately 90 days apart. **Dosimetric Dose: IV injection** Patients weighing > 50 kg: 5 to 6 mCi (185 to 222 MBq) Patients weighing ≤ 50 kg: 0.1 mCi/kg (3.7 MBq/kg) **Therapeutic Doses: IV infusion over ~30 min** Patients weighing > 62.5 kg: 500 mCi (18.5 GBq) Patients weighing ≤ 62.5 kg: 8 mCi/kg (296 MBq/kg).
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	8 mCi/kg in patients with metastatic and/or recurrent PPGL
Submission Number and Date	002 / 6/30/2017
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Study IB12B supports no large mean increases in the ΔQTc interval (i.e., 20 ms) with proposed therapeutic dosing regimen of Azedra, based on central tendency analysis (largest 90% CI upper bound was 14.5 ms at 1 h post-dose after administration of second

therapeutic dose). None of the subjects had QTcF >500 ms and only one subject had ΔQTcF >60 ms. There was no placebo or positive control in the study.

In this open-label, multicenter, single-arm, Phase 2 study, 74 subjects received dosimetric doses (3-6 mCi by IV injection) and 68 subjects received at least one therapeutic dose of azedra (500 mCi for subjects > 62.5 kg and 8 mCi/kg for subjects ≤ 62.5 kg; 2 therapeutic doses 3 months apart). Overall summary of findings is presented in Table 1:

Table 1: The Point Estimates and the 90% CIs of ΔQTcF Corresponding to the Largest Upper Bounds for All-Treated Azedra Group (FDA Analysis for Study IB12B)

Dose Received	Time (hour)	N	Mean (ms)	90% CI (ms)
Dosimetric Dose	1 Week post-dose	38	3.7	(-1.6, 9.0)
Therapeutic Dose 1	1 h post-dose	51	0.9	(-4.6, 6.3)
Therapeutic Dose 2	1 h post-dose	41	8.3	(2.1, 14.5)

Dosimetric dose: 3-6 mCi; therapeutic dose: 500 mCi (8 mCi/kg for subjects ≤ 62.5 kg), 2 doses 3 months apart; mCi=millicurie

The dose used in Study IB12B is the proposed therapeutic dose for the oncology indication and is the MTD. The drug elimination is primarily by renal route and renal impairment could likely increase the exposures. Azedra is rapidly cleared via the kidney; by 24 and 120 hours post-administration, ~50% and 80% of the injected dose was present in the urine, respectively, as per the proposed label. Thus, no accumulation is anticipated with the second therapeutic dose, as the therapeutic treatment consists of 2 single doses given at least 3 months apart. Because, the Study IB12B did not assess the PK, a concentration-QTc relationship was not evaluated for the product.

The therapeutic dose of Azedra (500 mCi with (b) (4)) has comparable ((b) (4) chemical mass dose range of MIBG as the two approved conventional MIBG imaging products, GE AdreView® (Iobenguane I-123 Injection) and Pharmalucence (Iobenguane Sulfate I-131 Injection). The literature data for commercial experience of these products do not suggest a cardiovascular risk (Source: Sponsor's submission, \\cdsesub1\evsprod\IND070663\0213\m1\us\111-info-amend, page 24-26).

2 PROPOSED LABEL

The sponsor has proposed following language related (b) (4) in the label, but has not proposed any labeling language related to specifically QT effects.

12.1 Pharmacodynamics

(b) (4)

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of AZEDRA on the QTc interval was evaluated in an open-label, single arm Phase 2 study in 74 patients with malignant or relapsed/refractory pheochromocytoma/paraganglioma. At the recommended therapeutic dosing regimen of AZEDRA, no large mean increases from baseline in the QTc interval (i.e., >20 ms) were detected in the study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Azedra is a proprietary form of small molecule meta-iodobenzylguanidine (MIBG), which is a known substrate for norepinephrine reuptake transporters (NET) available on cell surface of tumors of neural crest origin, such as pheochromocytoma/paraganglioma (PPGL). It is labeled with I-131 and binds to NET in an identical manner as conventional MIBG. It is being developed by Progenics for the treatment of iobenguane-avid metastatic and/or recurrent PPGL. The proposed therapeutic dose for Azedra is 500 mCi (or 8 mCi/kg for patients weighing 62.5 kg or less) containing (b) (4) chemical mass of MIBG at Time of Calibration (TOC). There is no accumulation anticipated as the therapeutic treatment consists of 2 single doses given at least 3 months apart.

3.2 MARKET APPROVAL STATUS

Azedra is not approved for marketing in any country. As per the sponsor, the low likelihood of cardiovascular risks posed by administration of AZEDRA is supported by commercial experience from two approved conventional MIBG imaging products, with a chemical mass dose range of MIBG ((b) (4)) comparable to that in therapeutic doses of Azedra (500 mCi with (b) (4) MIBG at TOC).

3.3 PRECLINICAL INFORMATION

AZEDRA: Cardiovascular pharmacological safety of I-127-MIBG was evaluated in the hERG channel assay and the IC_{50} was found to be 93.6 µM, a concentration 200-fold higher than maximum theoretical instantaneous blood concentration following a therapeutic dose in humans. Supratherapeutic doses of MIBG have also been tested in a dog cardiovascular safety pharmacology study. Intravenous injection of MIBG resulted in a dose-dependent increase in arterial pressure and a compensatory decrease in heart rate. Cardiovascular related effects reported include episodes of hypertension and reflex bradycardia in conscious dogs treated with MIBG at >184 multiples of the human equivalent dose (HED), observations consistent with the mechanism of action of MIBG (inhibition of norepinephrine reuptake). The ECG analysis showed various intervals to be within normal physiological limits (with the exception of the RR interval, which is prolonged secondary to the bradycardia) and there was no impact on QTc values.

Conventional MIBG: Conventional MIBG has been commercially available as imaging agent for the detection of pheochromocytoma and neuroblastoma (GE AdreView®

(Iobenguane I-123 Injection) and Pharmalucence (Iobenguane Sulfate I-131 Injection)), as well as for assessment of sympathetic innervation of the myocardium (GE AdreView® (Iobenguane I-123 Injection)). The cardiovascular effects of MIBG were evaluated in a two-week repeat-dose IV toxicity study in dogs to support the approval of the Pharmalucence I-131 MIBG imaging agent. Although ECG changes were observed in dogs at 18 times of the HED, MIBG was not found to affect the duration of the QRS wave and QT interval.

3.4 PREVIOUS CLINICAL EXPERIENCE

Conventional MIBG: Conventional ^{131}I-MIBG and ^{123}I-MIBG have been approved and marketed as diagnostic imaging agents for decades and have been studied in the context of numerous clinical trials and widely used in clinical practice. To date, there have been no reports suggesting evidence for QT prolongation or an increased risk of cardiac arrhythmia associated with these products. Furthermore, high doses of conventional ^{131}I-MIBG have become a first line drug for the treatment of metastatic or recurrent PPGL and neuroblastoma in Europe, as well as being used on a compassionate basis in the US. The therapeutic use of conventional ^{131}I-MIBG, with a chemical mass dose of MIBG far in excess that found in an AZEDRA therapeutic dose, also has not shown any evidence for increasing the risk of QT prolongation or arrhythmia. In addition, conventional ^{123}I-MIBG was approved by FDA in 2013 as a diagnostic tool in patients with congestive heart failure, and other forms of heart disease, including prolonged QT syndrome, who have an increased risk of developing arrhythmias. Despite this increased risk, the use of ^{123}I-MIBG has been shown to be safe and has not been associated with reports of QT prolongation or increased risk of developing arrhythmias.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Azedra's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

In our review for the sponsor's QT waiver request (submitted to IND 70663, dated 10/11/2016 in DARRTS) we stated that "Given the results from non-clinical and clinical studies with AZEDRA and the commercial experience with approved conventional MIBG products with similar or higher dose than AZEDRA, the sponsor's proposal to not conduct a TQT study with AZEDRA for their oncology development program is acceptable. The sponsor's proposed alternative approach of continuing to perform intense monitoring and assessments of patient ECGs throughout the clinical development program to evaluate potential QTc prolongation risk is reasonable. The sponsor should provide the mean values and confidence interval for all the relevant intervals (e.g. QT, QTc, QRS, RR etc.) by time (and by dose if applicable) for the pooled data from their clinical studies where Holter monitoring was conducted. The analysis could be useful to rule out large changes in QTc prolongation (e.g. >20 ms) for the product. Also the sponsor should provide a brief summary of commercial post-marketing clinical experience for relevant adverse events with the already approved MIBG products.". (file://fdawodcnas1/IRT-QT/QT-IRT_Reviews/IND70663/QTWaiver_Review).

With the current submission in NDA, the sponsor has provided their ECG findings from 4 studies (IB11, IB12, IB12B, IB13) as part of the Integrated Summary of Safety and also provided the datasets. The sponsor had provided literature information for commercial post-marketing experience with approved MIBG products in the QT waiver request (source: \\cdsesub1\evsprod\IND070663\0213\m1\us\111-info-amend, page 24-26), and has not provided any additional information with the current submission.

The sponsor has presented data pooled from 4 studies and not by each study separately. So, the sponsor's analysis in this review is shown as the pooled analysis. These studies had different dosing regimen (dosimetric doses only in IB11; single therapeutic doses in IB12 and IB13 with radiological dosing different than that proposed for current indication; and up to two therapeutic doses with IB12B with same radiological dosing as proposed for current indication) and different sample sizes. Study IB12B had large sample size and same radiological dosing as is proposed for the current indication. The reviewers' analysis focused on the data from this study as the definitive assessment.

4.1 QT Study

4.1.1 Title

Multiple studies are pooled together (See Table 2 below).

4.1.2 Protocol Number

See Table 2 below.

4.1.3 Study Dates

See Table 2 below.

4.1.4 ECG Objective

Characterization of QTc prolongation to support NDA submission for the treatment of malignant and/or recurrent and/or unresectable PPGL.

4.1.5 Study Description

4.1.5.1 Design

Table 2 below summarizes the design elements of the four studies including Study IB12B (study used for reviewers' assessments).

Table 2: Description of Clinical Safety Studies

Protocol	IB12B	IB12	IB11	IB13
Study Start - Stop Date	04Jun2009 – LTFU Ongoing	24Apr2007 – 06 Jun2011	20Jun2006 – 18Jan2007	13Jun2008 – 03Aug2010
Population Studied	PPGL	PPGL	PPGL (n=4); metastatic carcinoid (n=7)	Relapsed/refractory high-risk neuroblastoma
Study Objectives	Efficacy and safety	MTD, safety, dosimetry, and efficacy	Dosimetry, distribution and metabolism, safety	MTD, toxicity, estimation of radiation absorbed doses to measurable lesions and to normal organs, efficacy, dose response, QoL
Study Design (Country)	Open-label, single arm, multicenter (US)	Open-label, single arm, dose escalation, multicenter (US)	Open-label, dosimetry, single center (US)	Open-label, dose escalation, single arm, multicenter (US)
Number Enrolled/ Treated (complete/ ongoing)	81 unique subjects enrolled 74 received dosimetric dose(s) 68 received at least one therapeutic dose (45 complete through Month 12: 18 in follow-up, years 2 – 5, 5 completed 5-year follow-up)	24/21 (21/0)	11/11 (11/0)	19/15 (15/0)
Gender (M:F) Treated	41: 33	13: 8	7: 4	9: 6
Age Mean/ Range (years)	51.1 (16-76)	50.4 (30-72)	61.8 (47-71)	11.3 (3-30)
Planned Dose	Dosimetry: 3.0-6.0 mCi AZEDRA Therapeutic: 500 mCi (8 mCi/kg for subjects ≤ 62.5 kg) AZEDRA; 2 doses 3 months apart	Dosimetry: 5.0 mCi AZEDRA with 185 µg unlabeled MIBG Therapeutic: ≤ 500 mCi, > 500 mCi AZEDRA	Dosimetry: 5.0 mCi AZEDRA with 185 µg unlabeled MIBG	Dosimetry: 0.1 mCi/kg (1.0-5.0 mCi) AZEDRA with 185 µg unlabeled MIBG Therapeutic Dose Groups 11.2, 15.5, and 18.2 mCi/kg AZEDRA
Post-therapeutic	Up to 5 years post first therapeutic dose	Up to 2 years	2 weeks	60 days
Dose Follow-up				
Efficacy Analyses	Proportion of subjects with ≥ 50% reduction in use of antihypertensive medications for ≥ 6 months; OTR per RECIST; biochemical tumor marker response; bone lesion status; evaluation of QoL and symptom response; changes in the use of analgesics; Karnofsky Performance Status; OS	OTR by CT or MRI scans assessed by RECIST; analysis of plasma and urinary tumor markers; assessment of lesions on bone scans	None	OTR, dose response, QoL
Safety Analyses	TEAEs, AESIs, ECGs, physical examinations, vital signs, clinical chemistry, hematology, urinalysis	MTD of AZEDRA, TEAEs, AESIs, ECGs, physical examinations, vital signs, clinical chemistry, hematology, urinalysis	Physical examinations, ECGs, vital signs, clinical chemistry, hematology, urinalysis, and TEAEs	MTD of AZEDRA (primary objective), physical examinations, vital signs, clinical chemistry, hematology, urinalysis, ECGs, monitoring for delayed engraftment, radiation exposure (based on whole body dosimetry and I-131 scan after therapeutic dose), concomitant medications, TEAEs

AE = adverse event; AESI = adverse event of special interest; CT = computed tomography; DLT = dose limiting toxicity; ECG = electrocardiogram; ITT = Intent to Treat Population; LTFU = long-term follow-up; mCi = milliCurie; MIBG = metaiodobenzyl-guanidine; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; OTR = objective tumor response; OS = overall survival; PPGL = pheochromocytoma/paraganglioma; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TEAE = treatment-emergent adverse event; US = United States.

4.1.5.2 Controls

There were no placebo and no positive controls.

4.1.5.3 Blinding

The studies were open-label.

4.1.6 Treatment Regimen

4.1.6.1 Treatment Arms

See Table 2 above.

4.1.6.2 Sponsor's Justification for Doses

No justification provided.

Reviewer's Comment: The dose used in Study IB12B is the proposed therapeutic dose for the oncology indication. Primarily, the drug elimination is by renal route and renal impairment could affect the PK. Azedra is rapidly cleared via the kidney; by 24 and 120 hours post-administration, ~50% and 80% of the injected dose was present in the urine, respectively. Thus, there would be no accumulation anticipated as the therapeutic treatment consists of 2 single doses given at least 3 months apart.

4.1.6.3 Instructions with Regard to Meals

Reviewer's Comment: Not relevant. There won't be any impact of food on PK as the dose is administered by IV route.

4.1.6.4 ECG and PK Assessments

No PK measurement were done in the 4 clinical studies.

ECG:

Dosimetric dose: 12-lead ECGs were done prior to dose and immediately following dosing, and again at 10, 15 and 20 minutes post dose and at later time points. In study IB12B, additional ECGs were recorded prior to the second and third I-131 whole body scans as safety monitoring.

Therapeutic dose: Due to the risks of radiation, instead of standard 12-lead ECGs following administration of AZEDRA therapeutic doses a 24-hour 12-lead ECG ambulatory Holter monitor was applied to the study subjects in studies IB12B (and IB13, IB12). 12-lead ECG data from Holter device were recorded within the first few minutes and the first hour following IV administration of AZEDRA, when drug levels and activity were at their highest. Subjects were required to be at rest in a supine position at the designated time points from which QT data would be extracted from the recording. Efforts were undertaken to ensure that the quality of the QT and other interval-related data was comparable to the high standards of the state of the art 12-lead ECG systems that were used. The Holter monitors used in the AZEDRA studies were all 12-lead digital recording devices; the data were analyzed manually by experienced cardiologists at the central ECG lab ((b) (4)). In addition, a standard 12-lead ECG was also recorded within seven days following each therapeutic dose when radiation exposure risks decreased to acceptable levels.

Reviewer's Comment: The ECG sampling in Study IB12B (used in reviewers' assessments) is adequate to capture T_{max} (~30 min at end of infusion) and any potential delayed effects up to 24 h.

4.1.6.5 Baseline

Due to multiple enrollments of the same subject and different doses received among 4 studies, two types of baseline values were calculated:

1. Absolute baseline refers to the untreated baseline value, which is the last available assessment prior to the start of the first dosimetric dose received by each subject.
2. Relative baseline refers to the last available assessment prior to the start of each dosimetric and therapeutic dose.

4.1.7 ECG Collection

12-lead Holter recordings were done following each of the therapeutic doses up to 24 h post-dosing (when there was high amount of radiation exposure). 12-lead ECGs were assessed for dosimetric dosing and other time points with therapeutic dosing.

4.1.8 Sponsor's Results

4.1.8.1 Study Subjects

A total of 118 subjects received Azedra at any dose (dosimetric and/or therapeutic) in the clinical development program. One hundred and three subjects received at least one therapeutic dose: 53 subjects received one dose and 50 subjects received two doses. When evaluated on the basis of AZEDRA exposure, 41 subjects received < 600 mCi and 62 subjects received ≥ 600 mCi total exposure.

Subjects exposed to at least some amount of Azedra treatment group assigned as All Treated Group. Of 118 subjects in All Treated group, the majority of whom (74, 62.7%) were enrolled in IB12B. The remaining subjects in the Main Safety Population were enrolled in IB12 (21, 17.8%), IB13 (15, 12.7%), and IB11 (11, 9.3%).

Among 118 subjects, 56 subjects were in the <600 mCi and 62 subjects were in the ≥600 mCi exposure groups. The number and percentage of subjects for disposition in each study is given in Table 3 and discontinuation by reasons given in Table 4.

Table 3: Number of Subjects in Each Study, Main Safety Population

Study	All Treated (N = 118) n (%)	< 600 mCi (N = 56) n (%)	≥ 600 mCi (N = 62) n (%)
IB11	11 (9.3)	11 (19.6)	0
IB12	21 (17.8)	13 (23.2)	8 (12.9)
IB12B[1]	74 (62.7)	24 (42.9)	50 (80.6)
IB13	15 (12.7)	10 (17.9)	5 (8.1)
Total[2]	118 (100.0)	56 (100.0)	62 (100.0)

Source: ISS Table 1.1.

[1] Two subjects who participated in IB12B twice are counted only once under the total exposure group and All Treated Group.

[2] Two other subjects participated in more than one study: one in IB12 and IB12B, and another in IB11, IB12 and IB12B. They are counted only once in the total row.

Source: ISS Table 1.1

Table 4: Subject Disposition

	All Treated (N = 118)	< 600 mCi (N = 56)	≥ 600 mCi (N = 62)
Subjects enrolled	118	56	62
Subjects dosed	118	56	62
Subjects completed study[1]	83 (70.3)	28 (50.0)	55 (88.7)
Subjects did not complete study[2]	35 (29.7)	28 (50.0)	7 (11.3)
Reason for discontinuation			
Adverse event requiring discontinuation	11 (9.3)	11 (19.6)	0
Received another anti-cancer therapy	8 (6.8)	4 (7.1)	4 (6.5)
Progressive disease	7 (5.9)	5 (8.9)	2 (3.2)
Lost to follow-up	2 (1.7)	1 (1.8)	1 (1.6)
Death	2 (1.7)	2 (3.6)	0
Screen failure[3]	5 (4.2)	5 (8.9)	0

Source: ISS Table 1.2.1.
[1] For IB12, IB12B, and IB13, a completed subject is a subject who has completed the short-term Efficacy Phase of the respective study. Participation in the long-term phase of each study is not counted in this summary.
[2] Seventeen subjects discontinued from the Efficacy Phase in IB12B, but continued to be followed.
[3] Screen failed subjects are subjects who only received the Dosimetric Dose in IB12, IB12B, and IB13.

Reviewer's Comments: We provided our independent subjects disposition in Section 5.2.

4.1.8.2 Statistical Analyses

4.1.8.2.1 Primary Analysis

The primary endpoint is the change from baseline of QTcF. All analyses are based on data pooled from 4 studies. The descriptive statistics are listed in Table 5 for All-Treated group and Table 6 for analysis by total exposure groups. Tables present the summary statistics (n, mean, SD, median and standard deviation (SD)) and the 90% confidence interval for mean changes from baseline of Azedra, by dose received (Dosimetric Dose, Therapeutic Dose 1, and Therapeutic Dose 2), by total exposure group (<600 mCi, ≥600 mCi), and by time (baseline, 10-min post, 15-min post, 20-min post, 1-hour post, 3-hour post, 6-hour post, 24-hour post, 48-hour post, 1-week post, 12-week post, 6-month post, 18- month post and 24-month post).

Table 5: Sponsor's Results of ΔQTcF for All-Treated Azedra Group by Dose Received and by Time (data pooled from Studies IB11, IB12, IB12B, and IB13)

Dose Received*	Time**	N	Mean	Std Dev	95% CI for Mean
Dosimetric Dose	10 Min Post	100	1.0	11.79	(-1.3, 3.4)
	15 Min Post	96	-1.1	16.04	(-4.3, 2.2)
	20 Min Post	92	2.9	13.04	(0.2, 5.6)
	1 Hour Post	10	-4.9	15.8	(-16.2, 6.4)
	3 Hour Post	10	-0.1	14.2	(-10.3, 10.1)
	6 Hour Post	9	-5.1	17.1	(-18.2, 8.0)
	24 Hour Post	78	-4.3	18.3	(-8.4, -0.2)
	48 Hour Post	92	-6.7	16.4	(-10.1, -3.3)
	1 Week Post	54	-0.7	22.0	(-6.7, 5.3)
Therapeutic Dose 1	10 Min Post	71	1.6	23.0	(-3.8, 7.1)
	15 Min Post	16	0.5	23.9	(-12.2, 13.2)
	20 Min Post	16	3.7	26.8	(-10.6, 17.9)
	1 Hour Post	68	2.8	22.5	(-2.7, 8.2)
	3 Hour Post	17	14.4	22.4	(2.9, 25.8)
	6 Hour Post	17	7.4	22.5	(-4.2, 18.9)
	24 Hour Post	74	-2.2	23.4	(-7.6, 3.2)
	48 Hour Post	12	-6.2	18.6	(-18.0, 5.6)
	1 Week Post	74	-9.3	21.4	(-14.2, -4.3)
	6 Month Post	10	12.1	19.8	(2.1, 26.3)
	18 Month Post	9	9.1	10.2	(1.2, 17.0)
Therapeutic Dose 2	10 Min Post	40	6.2	22.5	(-1.0, 13.4)
	1 Hour Post	41	8.3	23.6	(0.9, 15.8)
	24 Hour Post	33	-2.7	20.2	(-9.9, 4.4)
	48 Hour Post	5	-7.8	25.3	(-39.2, 23.6)
	1 Week Post	40	-4.4	19.4	(-10.6, 1.8)

*Therapeutic dose levels are slightly different for each of the studies (refer to Table 2 for dosing information)

***Post-dose time*

Source: ISS Appendix, Table 5.1.2

Table 6: Sponsor's Results of ΔQTcF for Azedra by Dose Received, Total Exposure and Time (data pooled from Studies IB11, IB12, IB12B, and IB13)

		<600 mCi				≥600 mCi			
Dose Received*	**Time****	**N**	**Mean**	**Std Dev**	**90% CI for Mean**	**N**	**Mean**	**Std Dev**	**90% CI for Mean**
Dosimetric Dose	10 Min	45	-0.2	11.1	(-3.5, 3.2)	55	2.0	12.3	(-1.3, 5.3)
	15 Min	42	-1.9	14.3	(-6.4, 2.5)	54	-0.4	17.4	(-5.2, 4.3)
	20 Min	39	-0.2	11.5	(-3.9, 3.5)	53	5.2	13.7	(1.4, 9.0)
	1 Hour	10	-4.9	15.8	(-16.2, 6.4)	Not Done			
	3 Hour	10	-0.1	14.3	(-10.3,10.1)				
	6 Hour	9	-5.1	17.1	(-18.2, 8.0)				
	24 Hour	31	-1.1	16.3	(-7.0, 4.9)	47	-6.4	19.3	(-12.1, -0.7)
	48 Hour	41	-8.6	16.7	(-13.9, -3.3)	51	-5.2	16.1	(-9.7, -0.6)
	1 Week	26	-4.6	19.7	(-12.5, 3.4)	28	3.0	23.7	(-6.2, 12.2)
Therapeutic Dose 1	10 Min	26	-1.1	19.5	(-8.9, 6.8)	45	3.2	24.9	(-4.3, 10.7)
	15 Min	10	-9.1	20.1	(-23.5, 5.3)	6	16.5	22.3	(-6.9, 39.9)
	20 Min	10	-5.4	23.3	(-22.1, 11.3)	6	18.8	27.1	(-9.6, 47.2)
	1 Hour	26	2.7	19.4	(-5.1, 10.6)	42	2.8	24.4	(-4.8, 10.4)
	3 Hour	11	9.5	22.7	(-5.8, 24.7)	6	23.3	20.5	(1.8, 44.6)
	6 Hour	11	1.3	18.6	(-11.2, 13.8)	6	18.5	26.2	(-9.0, 46.0)
	24 Hour	36	-5.4	24.6	(-13.8, 2.9)	38	0.9	22.1	(-6.4, 8.2)
	48 Hour	Not Done				11	-0.4	17.8	(-16.0, 8.0)
	1 Week	26	-4.7	21.0	(-13.2, 3.8)	48	-11.7	21.4	(-17.9, -5.5)
	6 Month	Not Done				10	12.1	8.8	(-0.2, 27.7)
	18 Month	5	5.4	10.6	(-7.8, 18.6)	4	13.8	20.1	(-8.6, 4.9)
Therapeutic Dose 2	10 Min	Not Done				40	6.2	22.5	(-1.0, 13.4)
	1 Hour					41	8.3	23.7	(0.9, 15.8)
	24 Hour					33	-2.7	20.2	(-9.9, 4.4)
	48 Hour					5	-7.8	25.3	(-39.2, 23.6)
	1 Week					40	-4.4	19.4	(-10.6, 1.8)

*Therapeutic dose levels are slightly different for each of the studies (refer to Table 2 for dosing information)

***Post-dose time*

Source: ISS Appendix, Table 5.1.2

Reviewer's Comments: We provided our independent analyses in Section 5.2. Our analyses are based on Study IB12B whereas sponsor analyses are based on data pooled from 4 studies.

4.1.8.2.2 Assay Sensitivity

Not applicable.

4.1.8.2.3 Categorical Analysis

Table 7 below presented the sponsor's outliner analysis.

Table 7: Sponsor's Categorical Analysis

Potentially Clinically Significant ECG Findings by Total Exposure
Main Safety Population - Studies: IB11, IB12, IB12B, IB13

Parameter	PCS Criterion (a)	All Treated (N=118) n (%)	<600 mCi (N=56) n (%)	>=600 mCi (N=62) n (%)
Heart rate (bpm)	Increase or decrease > 20	48/115 (41.7)	24/54 (44.4)	24/61 (39.3)
PR interval(msec)	Increase or decrease > 30	28/112 (25.0)	11/52 (21.2)	17/60 (28.3)
QRS duration (msec)	Increase or decrease > 16	22/115 (19.1)	11/54 (20.4)	11/61 (18.0)
QT interval (msec)	450 - 480 msec	15/115 (13.0)	5/54 (9.3)	10/61 (16.4)
	> 480 - 500 msec	5/115 (4.3)	0	5/61 (8.2)
	> 500 msec	2/115 (1.7)	0	2/61 (3.3)
	Increase 30 - 60 msec	41/115 (35.7)	15/54 (27.8)	26/61 (42.6)
	Increase > 60 msec	11/115 (9.6)	3/54 (5.6)	8/61 (13.1)
QTcB interval (msec)	450 - 480 msec	68/115 (59.1)	33/54 (61.1)	35/61 (57.4)
	> 480 - 500 msec	18/115 (15.7)	8/54 (14.8)	10/61 (16.4)
	> 500 msec	6/115 (5.2)	3/54 (5.6)	3/61 (4.9)
	Increase 30 - 60 msec	47/115 (40.9)	14/54 (25.9)	33/61 (54.1)
	Increase > 60 msec	10/115 (8.7)	3/54 (5.6)	7/61 (11.5)
QTcF interval (msec)	450 - 480 msec	25/115 (21.7)	10/54 (18.5)	15/61 (24.6)
	> 480 - 500 msec	4/115 (3.5)	1/54 (1.9)	3/61 (4.9)
	> 500 msec	1/115 (0.9)	0	1/61 (1.6)
	Increase 30 - 60 msec	31/115 (27.0)	10/54 (18.5)	21/61 (34.4)
	Increase > 60 msec	5/115 (4.3)	2/54 (3.7)	3/61 (4.9)

Note: Subjects are summarized based on cumulative dose received across all studies.
(a) The percentage is calculated based on the number of subjects meeting the corresponding criterion among the subjects with non-missing baseline and post-baseline values.

Source: ISS Appendix Table 5.2

Reviewer's Comments: We provided our independent categorical analyses in Section 5.2. Our categorical analyses of QTcF, ΔQTcF, HR, PR and QRS are based on Study IB12B whereas sponsor's analyses are based on data pooled from 4 studies.

4.1.8.3 Clinical Pharmacology

Azedra is rapidly cleared via renal clearance, with ~50% and 80% of the injected dose present in the urine by 24 and 120 hours post-administration, respectively. There is no accumulation anticipated with multiple dose as the therapeutic treatment consists of 2 single doses given at least 3 months apart. Furthermore, there are no major metabolites for azedra. PK data were not collected in any of the 4 studies used in the sponsor's analysis.

4.1.8.3.1 Pharmacokinetic Analysis

Not applicable because no PK data were collected.

4.1.8.3.2 Exposure-Response Analysis

Not applicable.

5 REVIEWERS' ASSESSMENT

The statistical reviewer performed independent analyses using data from Study IB12B. The rationale to focus on Study IB12B rather than pooled 4 studies are the following: 1) 12-lead Holter ECGs were collected over 24 h period after the therapeutic dose and normal 12-lead ECGs at other timepoints, also the same dosing regimen was studied as the proposed labeling dose, and sample size was relatively large in Study IB12B. 2) Sample size was relatively small in Studies IB11, IB12, and IB13. 3) Different ECG collection times across studies can lead to small sample sizes at some ECG timepoints, which can result in wide confidence intervals.

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate were observed (see section 5.2).

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

The primary endpoint is the change from baseline in QTcF in Study IB12B. The descriptive statistics are listed in Table 8, showing the summary statistics (mean and standard deviation) and the 90% confidence interval for mean changes from baseline for Azedra by dose received and time.

The actual relevant period for evaluation of changes in QTc would be up to ~1 week post-dose. Based on the central tendency analysis up to 1 week period, the highest mean change from baseline in QTcF (upper 90% CI) was 8.3 ms (14.5 ms) at 1 h post therapeutic dose 2. There was a higher mean **Δ**QTcF (upper 90% CI) of 13.9 ms (21.7 ms) which occurs at 6 month post-dose, but the sample size for the timepoint was small and the causality due to drug effect is unlikely because of negligible amount of drug being present at that time in the system based on the PK characteristics of the drug (Table 8).

Table 8: Central Tendency Analysis Results of ΔQTcF for All-Treated Azedra Group by Dose Received and Time (Study IB12B)

Dose Received	Time	N	Mean	Std Dev	90% CI for Mean
Dosimetric Dose	10 min Post	65	0.4	11.5	(-2.0, 2.8)
	15 min Post	65	-2.6	16.4	(-6.1, 0.8)
	20 Min Post	63	3.1	13.3	(0.3, 5.9)
	24 hour Post	67	-4.2	18.1	(-7.9, -0.6)
	48 hour Post	62	-6.0	16.0	(-9.4, -2.6)
	1 Week Post	38	3.7	19.4	(-1.6, 9.0)
Therapeutic Dose 1	10 Min Post	54	0.2	22.8	(-5.0, 5.4)
	1 hour Post	51	0.9	23.2	(-4.6, 6.3)
	24 hour Post	47	-0.0	21.0	(-5.2, 5.1)
	48 hour Post	7	-8.3	23.5	(-25.5, 9.0)
	1 Week Post	56	-11.7	20.6	(-16.3, -7.1)
	12 Week Post	4	5.5	3.8	(1.0, 10.0)
	6 Month Post	20	13.9	20.2	(6.0, 21.7)
Therapeutic Dose 2	10 Min Post	40	6.2	22.5	(0.2, 12.2)
	1 Hour Post	41	8.3	23.6	(2.1, 14.5)
	24 Hour post	33	-2.7	20.2	(-8.7, 3.2)
	48 hour Post	8	-3.3	20.6	(-17.1, 10.6)
	1 Week Post	46	-6.7	20.0	(-11.6, -1.7)

For Study IB12B, therapeutic dose: 500 mCi (8 mCi/kg for subjects ≤ 62.5 kg); 2 therapeutic doses 3 months apart

5.2.1.1 Assay Sensitivity Analysis

No applicable.

5.2.1.2 Categorical Analysis

Table 9 and Table 10 presents the categorical analysis of QTcF and ΔQTcF. No subject's QTcF is above 500 ms from the pre-treatment and post-treatment groups. One subject's ΔQTcF is above 60 ms from the post-treatment group.

Table 9: Categorical Analysis for QTcF (Study IB12B)

Pre/Post Treatment	Total Exposure	Total N	Value<=450 ms	450 ms<Value <=480 ms	480 ms<Value<=500 ms	Value>500
Pre-Treatment	All Treated	68	62 (91.2%)	6 (8.8%)	0	0
Post-Treatment	All Treated	68	55 (80.9%)	2 (2.94%)	11 (16.2%)	0

Table 10: Categorical Analysis of ΔQTcF (Study IB12B)

Pre/Post Treatment Group	Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
Post-Treatment	All Treated	67	49 (73.1%)	17 (25.4%)	1 (1.5%)	0

5.2.2 HR Analysis

Table 11 presents the central tendency analysis of HR.
Table **12** presents the categorical analysis of HR. Nine subjects in the pre-treatment group and twenty-two subjects in the post-treatment group experienced HR interval greater than 100 bpm.

Table 11: Central Tendency Analysis Results of ΔHR for All-Treated Azedra Group by Dose Received and Time (Study IB12B)

Dose Received	Time	N	Mean	Std Dev	90% CI for Mean
Dosimetric Dose	10 min Post	65	-1.7	8.0	(-3.3, 0.0)
	15 min Post	65	-0.1	8.5	(-1.8, 1.7)
	20 Min Post	63	-0.0	8.0	(-1.7, 1.6)
	24 hour Post	67	0.6	9.4	(-1.3, 2.5)
	48 hour Post	62	2.2	8.4	(0.4, 4.0)
	1 Week Post	38	-0.3	9.9	(-3.1, 2.4)
Therapeutic Dose 1	10 Min Post	54	0.8	11.1	(-1.7, 3.3)
	1 hour Post	51	-1.6	14.0	(-4.9, 1.7)
	24 hour Post	47	2.3	16.3	(-1.7, 6.3)
	48 hour Post	7	3.9	6.5	(-0.9, 8.6)
	1 Week Post	57	5.7	14.4	(2.5, 8.9)
	12 Week Post	4	-7.5	4.8	(-13.1, -1.9)
	6 Month Post	20	3.3	8.8	(-0.2, 6.7)
Therapeutic Dose 2	10 Min Post	40	-0.1	10.3	(-2.9, 2.6)
	1 Hour Post	41	-0.4	10.9	(-3.3, 2.5)
	24 Hour post	33	0.2	12.3	(-3.4, 3.9)
	48 hour Post	8	6.0	11.5	(-1.7, 13.7)
	1 Week Post	46	4.6	11.7	(1.7, 7.5)

Table 12: Categorical Analysis for HR (Study IB12B)

Pre/Post Treatment	Treatment Group	Total N	HR ≤ 100 bpm	HR >100 bpm
Pre-Treatment	All Treated	68	59 (86.8%)	9 (13.2%)
Post-Treatment	All Treated	68	46 (67.7%)	22 (32.3%)

5.2.3 PR Analysis

Table 13 presents the central tendency analysis of PR. Table 14 presents the categorical analysis of PR. Three subjects in the pre-treatment and four subjects in the post-treatment groups experienced PR interval greater than 220 ms.

Table 13: **Central Tendency Analysis Results of ΔPR for All -Treated Azedra by Dose Received and Time (Study IB12B)**

Dose Received	Time	N	Mean	Std Dev	90% CI for Mean
Dosimetric Dose	10 min Post	63	0.4	12.6	(-2.3, 3.0)
	15 min Post	63	-0.2	11.7	(-2.7, 2.3)
	20 Min Post	61	-0.6	11.5	(-3.0, 1.9)
	24 hour Post	65	-3.6	14.8	(-6.7, -0.5)
	48 hour Post	60	-3.0	11.0	(-5.4, -0.6)
	1 Week Post	38	1.5	20.6	(-4.1, 7.1)
Therapeutic Dose 1	10 Min Post	52	2.7	12.4	(-0.2, 5.5)
	1 hour Post	50	3.0	13.7	(-0.2, 6.2)
	24 hour Post	45	-2.9	13.9	(-6.4, 0.6)
	48 hour Post	7	0.3	10.5	(-7.4, 8.0)
	1 Week Post	54	-2.8	18.3	(-6.9, 1.4)
	12 Week Post	4	8.8	2.1	(6.3, 11.2)
	6 Month Post	20	3.2	19.6	(-4.4, 10.8)
Therapeutic Dose 2	10 Min Post	39	2.1	14.5	(-1.8, 6.0)
	1 Hour Post	40	4.1	16.2	(-0.3, 8.4)
	24 Hour post	32	0.6	16.7	(-4.4, 5.6)
	48 hour Post	8	8.8	7.7	(3.6, 13.9)
	1 Week Post	46	0.9	17.2	(-3.3, 5.2)

Table 14: Categorical Analysis for PR (Study IB12B)

Pre/Post Treatment	Treatment Group	Total N	PR <200 ms	200≤ PR >220 ms	PR >220
Pre-Treatment	All Treated	66	59 (89.4%)	4 (6.1%)	3 (4.5%)
Post-Treatment	All Treated	66	51 (77.3%)	11 (16.6%)	4 (6.1%)

5.2.4 QRS Analysis

Table 15 presents central tendency analysis of QRS. Table 16 presents the categorical analysis of QRS. Three subjects in each pre-treatment and post-treatment groups experienced QRS interval greater than 110 ms.

Table 15: Central Tendency Analysis Results of ΔQRS for All-Treated Azedra Group by Dose Received and Time (Study IB12B)

Dose Received	Time	N	Mean	Std Dev	90% CI for Mean

Dose Received	Time	N	Mean	Std Dev	90% CI for Mean
Dosimetric Dose	10 min Post	65	1.2	5.5	(0.0, 2.3)
	15 min Post	65	-0.4	5.0	(-1.4, 0.6)
	20 Min Post	63	1.0	5.5	(-0.1, 2.2)
	24 hour Post	67	0.9	7.7	(-0.7, 2.5)
	48 hour Post	62	0.7	9.7	(-1.3, 2.8)
	1 Week Post	38	1.1	7.5	(-0.9, 3.1)
Therapeutic Dose 1	10 Min Post	54	-0.6	7.3	(-2.2, 1.1)
	1 hour Post	51	-0.3	7.9	(-2.2, 1.5)
	24 hour Post	47	-0.1	7.4	(-1.9, 1.7)
	48 hour Post	7	-4.4	8.8	(-10.9, 2.0)
	1 Week Post	57	-0.2	6.3	(-1.6, 1.2)
	12 Week Post	4	-0.8	2.2	(-3.4, 1.9)
	6 Month Post	20	-0.8	7.6	(-3.7, 2.1)
Therapeutic Dose 2	10 Min Post	40	-1.5	6.6	(-3.3, 0.2)
	1 Hour Post	41	-0.9	7.2	(-2.8, 1.0)
	24 Hour post	33	-2.5	5.7	(-4.1, -0.8)
	48 hour Post	8	0.1	2.6	(-1.6, 1.9)
	1 Week Post	46	0.0	8.0	(-1.9, 2.0)

Table 16: Categorical Analysis for QRS (Study IB12B)

Pre/Post Treatment	Treatment Group	Total N	QRS ≤ 110 ms	QRS > 110 ms
Pre-Treatment	All-Treated	68	65 (95.6%)	3 (4.4%)
Post-Treatment	All Treated	68	65 (95.6%)	3 (4.4%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Not applicable as no PK was collected in the clinical studies related to this report.

5.4 CLINICAL ASSESSMENTS

5.4.1 ECG assessments

ECG waveforms were not submitted.

5.4.2 PR and QRS Interval

There are no clinically meaning effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	500 mCi (or 8 mCi/kg for patients weighing 62.5 kg or less), containing (b) (4) chemical mass of MIBG at TOC	
Maximum tolerated dose (Tested in Study MIP-IB12 submitted in SN0158)	8 mCi/kg in patients with metastatic and/or recurrent PPGL	
Principal adverse events	AZEDRA is generally well tolerated; adverse effects observed were consistent with exposure to radioactive iodine. These include: Gastrointestinal events, primarily reports of nausea, vomiting, and dry mouth; hematologic toxicities, primarily reports of thrombocytopenia, leukopenia, neutropenia and anemia; and fatigue, have been the most common events reported to date in subjects with metastatic and/or recurrent PPGL who have been treated with AZEDRA.	
Maximum dose tested (Tested in PK study: MIP-IB11 as submitted in SN0049; and dosimetry portion of Studies: MIP-IB12 submitted in SN0158 and MIP-IB13 submitted in SN0156))	Single Dose	5 mCi ((b) (4) chemical mass of MIBG at TOC) (b) (4) (b) (4)
	Multiple Dose	Not done.
Exposures Achieved at Maximum Tested Dose (See the PK Report in Section 16.5.2 of MIP-IB11 submitted in SN0049)	Single Dose	Cmax, Mean (SE): 0.060 (0.007) µCi/mL AUC, Mean (SE): 1.062 (0.102) hr*µCi/mL
	Multiple Dose	Not done.
Range of linear PK	N/A, single concentration level tested	
Accumulation at steady state	N/A, AZEDRA therapeutic treatment consists of 2 single doses given at least 3 months apart	
Metabolites	Two minor metabolites (free iodide and MIHA) were detected in urine samples of some subjects at 0-6 hr (4/11 for free iodide and 1/11 for MIHA) and 6-24 hr (2/11 for free iodide and 0/11 for MIHA) post dose. No metabolites were detected at all other time points through 120 post dose.	
Absorption	Absolute/Relative Bioavailability	IV infusion, 100 % absolute bioavailability
	Tmax	Approximately 30 minutes at end of infusion

Distribution	Vd/F or Vd	Vss, Mean (SE): 2959 (153) mL/kg
	% bound	Mean (SD): 63.0 (0.2)
Elimination	Route	Primarily renal; 131-I-MIBG blood levels declined rapidly in a biphasic manner; 50% and 80% of the injected dose were recovered in urine after 24 and 120 hours, respectively. Other routes: N/A
	Terminal t½	Mean for parent (131-I-MIBG): Mean (SE) 41.03 (3.14) hr Mean (% CV) for metabolites: N/A
	CL/F or CL	CL Mean (SE): 63.1 (6.9) mL/hr/kg
Intrinsic Factors	Age	N/A
	Sex	N/A
	Race	N/A
	Hepatic & Renal Impairment	Subjects with mild to moderate renal and hepatic impairment were not specifically excluded from participation in AZEDRA clinical trials. To ensure safety for patients who may have renal or hepatic insufficiency, adjustments of therapeutic dose were made based on dosimetry results to achieve delivery of a radiation exposure doses that would not harm the critical organs.
Extrinsic Factors	Drug interactions	In human hepatocytes and microsomes, at clinically-relevant concentrations MIBG did not affect cytochrome P450 (CYP) induction or inhibition indicating that in vivo drug interactions resulting from the induction or inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzyme activities are unlikely. In Caco2 cell assay, MIBG was shown to be neither a p-gp substrate nor inhibitor.
	Food Effects	None, IV administration
Expected High Clinical Exposure Scenario	Supratherapeutic doses of MIBG have been tested in nonclinical repeated dose toxicity studies (28-day in dogs and 12-day in rats). Based on the NOAELs from repeated dose toxicity studies in rat (>4.5 mg/kg, or 27000 µg/m2) and dog (>1.085 mg/kg, or 21700 µg/m2), the estimated safety margins in	

	humans are >83-fold and >67-fold HED, respectively. Cardiovascular pharmacological safety of I-127-MIBG was evaluated in the hERG channel assay and the IC50 was found to be 93.6 μM, a concentration 200-fold higher than maximum theoretical instantaneous blood concentration following a therapeutic dose in humans. Supratherapeutic doses of MIBG have also been tested in a dog cardiovascular safety pharmacology study. Cardiovascular related effects reported include episodes of hypertension and reflex bradycardia in conscious dogs treated with MIBG at >184 multiples of the HED, observations consistent with the mechanism of action of MIBG; however, no treatment effects were observed on corrected QT interval. Collectively these data indicate that AZEDRA is unlikely to pose cardiovascular risks in patients with PPGL at the proposed therapeutic dose.

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/s/

DHANANJAY D MARATHE
03/20/2018

MOH JEE NG
03/27/2018

DALONG HUANG
03/27/2018

MOHAMMAD A RAHMAN
03/28/2018

CHRISTINE E GARNETT
03/28/2018

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:	February 7, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 209607
Product Name and Strength:	Azedra (iobenguane I 131) Injection 12 to 16.5 mCi/mL (444 to 610.5 MBq/mL)
Total Product Strength:	(b) (4)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Progenics Pharmaceuticals, Inc.
Submission Date:	August 22, 2017
OSE RCM #:	2017-1251
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of this NDA review for Azedra, DOP2 requested that we review the proposed container labels and carton labeling for areas of vulnerability that may lead to medication errors.

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
Previous DMEPA Reviews	B- N/A
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials found the order and prominence of product information on the proposed container labels and carton labeling can be revised for improved readability and clarity.

Further, we note the usage of the non-standard dosage form "(b) (4)" in the established name. Therefore, we have contacted the Office of Product Quality (OPQ) for clarification and we defer to OPQ for the final determination of the established name for this proposed product.

In addition, we acknowledge that the dosimetric dose is administered by intravenous injection over 60 seconds while the therapeutic dose is administered by intravenous infusion over approximately 30 minutes. Therefore, the two vials require different cautionary statements to promote the safe use of the product between each treatment phase. Thus, we have provided recommendations in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Azedra labels and labeling can be improved to increase the clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR PROGENICS PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments
   1. Revise the dosage form statement, "(b) (4)", to read "Injection" (i.e. Azedra (iobenguane I 131) Injection)
   2. As proposed, the statements "Dosimetric" and "Therapeutic" have greater prominence than the proprietary and established names. Revise the order and prominence of information on the container label and carton (leadpot) labeling such that the proprietary name and the established name appear first and are the most prominent information on the label.
   3. Consider adding the product barcode to each individual package. The drug barcode is often used as an additional verification tool before drug administration in the patient care setting.

B. Container Label: ***Dosimetric Vial***
   1. Revise the statement (b) (4)" to read "Must Dilute Before Intravenous Injection" in mixed case letters. We recommend this to minimize the risk of administering the drug undiluted.
   2. Revise and relocate the statement "Single-Dose Vial" to appear underneath the "Must Dilute Before Intravenous Injection" statement and to read, "Single-Dose Vial. Discard Unused Portion".
   3. Revise the container label so activity, production time, lot and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed on the Principal Display Panel (PDP). This may be achieved by relocating other information to the side panel.

      The example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.

PDP	Side Panel
NDC# 71258-015-02 Azedra (iobenguane I 131) Injection Must Dilute Before Intravenous Injection. Single-dose vial. Discard unused portion. Vial No: ____ Volume: ____mL Activity at calibration time: _____MBq/mL (___ mCi/mL)- {DD MMM YYYY hh:mm UTC} Lot No: ____ EXP: {DD MMM YYY hh:mm UTC} Activity at infusion time: _____MBq/mL (___mCi/mL) Date: _____ Time: _____ DOSIMETRIC For use only as part of dosimetric step in Azedra therapeutic regimen.	Rx only statement Usual dosage: See Prescribing Information Storage and shelf life Warning statement Manufactured by information US contact information, such as distributor  

C. Container Label: ***Therapeutic Vial***

1. Revise the statement [redacted] (b) (4) to read "For Intravenous Infusion" in mixed case letters. We recommend this to minimize the risk of administering the drug as an intravenous bolus.
2. Revise and relocate the statement "Single-Dose Vial" to appear underneath the "For Intravenous Infusion" statement and to read, "Single-Dose Vial. Discard Unused Portion".
3. Revise the container label so activity, production time, lot and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed on the Principal Display Panel (PDP). This may be achieved by relocating other information to the side panel.

The example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.

PDP	Side Panel
NDC# 71258-015-22 Azedra (iobenguane I 131) Injection For Intravenous Infusion. Single-dose vial. Discard unused portion. Vial No: ____ Volume: ____mL Activity at calibration time: _____MBq/mL (___mCi/mL)- {DD MMM YYYY hh:mm UTC} Lot No: ____ EXP: {DD MMM YYY hh:mm UTC} Activity at infusion time: _____MBq/mL (___mCi/mL) Date: _____ Time: _____ THERAPEUTIC For use only as part of therapeutic step in Azedra therapeutic regimen.	Rx only statement Usual dosage: See Prescribing Information Storage and shelf life Warning statement Manufactured by information US contact information, such as distributor  

D. Carton Labeling

1. Consider providing perforated leadpot label with duplicate product information for use in the nuclear pharmacy. This would provide ease of use for verification and documentation by the nuclear pharmacy.
2. Revise the carton labeling such that the information which is critical for the use of the proposed drug product is prominently displayed on the Principal Display Panel (PDP).

The example layouts below demonstrate our recommendation only (not to size, spacing, color, etc.). Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Azedra that Progenics Pharmaceuticals, Inc. submitted on August 22, 2017.

Table 2. Relevant Product Information for Azedra	
Initial Approval Date	N/A
Active Ingredient	Iobenguane I-131
Indication	Treatment of iobenguane-avid malignant and/or recurrent and/or unresectable pheochromocytoma and paraganglioma.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	12 to 16.5 mCi/mL (444 to 610.5 MBq/mL)
Dose and Frequency	Dosimetric Dose Patients weighing >50 kg: 5 or 6 mCi (185 to 222 MBq) Patients weighing ≤ 50 kg: 0.1 mCi/kg (3.7 MBq/kg) Dosimetric dose is administered as an intravenous injection over a period of 60 seconds. Therapeutic Dose Patients weighing > 62.5 kg: 500 mCi (18.5 GBq) Patients weighing ≤ 62.5 kg: 8 mCi/kg (296 MBq/kg) Therapeutic doses are administered intravenously in approximately 50 mL over a period of ~30 minutes (100 mL/hour) and approximately 90 days apart.
How Supplied	Dosimetric: Sterile solution for intravenous administration supplied in a single-dose 30 mL vial with (b) (4) fill volume, capped with a gray septum and aluminum crimp housed in a lead pot and shipped frozen (≤ -70°C). The radioactivity concentration (RAC) is (b) (4) at the Time of Calibration (TOC). Therapeutic: Sterile solution for intravenous administration supplied in a single-dose 30 mL vial with (b) (4) fill volume, capped with a gray septum and aluminum crimp housed in a lead pot and shipped frozen (≤ -70°C). The radioactivity

	concentration (RAC) is (b) (4) at the Time of Calibration (TOC).
Storage	Store frozen at ≤ -70°C in the original lead pot until ready for use.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Azedra labels and labeling submitted by Progenics Pharmaceuticals, Inc. on August 22, 2017.

- Container labels
- Carton labeling

G.2 Label and Labeling Images

Container Label: Dosimetric Dose

(b) (4)

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

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/s/

JANINE A STEWART
02/07/2018

CHI-MING TU
02/07/2018

Clinical Inspection Summary

Date	
From	David Menschik, M.D., MPH, Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Sharon Sickafuse, Regulatory Project Manager Diana Bradford, Clinical Reviewer Division of Oncology Products 2
NDA	209607
Applicant	Progenics Pharmaceuticals, Inc. (PPI)
Drug	AZEDRA
NME	No
Therapeutic Classification	Antineoplastic
Proposed Indication(s)	Treatment of iobenguane-avid and/or recurrent pheochromocytoma and paraganglioma
Consultation Request Date	July 28, 2017
Summary Goal Date	Rolling submission
Action Goal Date	Rolling submission
PDUFA Date	Rolling submission

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from study MIPIB12B were submitted to CDER in support of NDA 209607. Three clinical sites, Dr. Bennett Chin (Site 2), Dr. Camilo Jimenez (Site 5), Dr. Daniel Pryma (sSte 11), and the study sponsor, Progenics Pharmaceuticals, Inc., were selected for audit.
In general, based on the inspections of the three clinical sites and the sponsor, the inspectional findings support validity of data as reported by the Applicant under this NDA.
. The inspection of clinical investigators Dr. Bennett Chin, Dr. Camilo Jimenez, and Dr. Daniel Pryma revealed no regulatory violations. The classification for Drs. Bennett Chin, Camilo Jimenez, Daniel Pryma is No Action Indicated (NAI). The EIRs for Dr. Camilo Jimenez was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. The inspections of the clinical investigators described aboce revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The classification for the sponosr Progenics Pharmaceuticals, Inc. is VAI. Although regulatory violations related to failure to enure proper monitoring were noted at the sponsor, the observations are unlikely to significantly impact primary safety and efficacy analyses.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Progenics Pharmaceuticals, Inc.is seeking approval of a New Drug Application (NDA) for Azedra® ([131I]-Iobenguane) injection indicated for treatment of iobenguane-avid and/or recurrent pheochromocytoma and paraganglioma.

Inspection was requested for the following study:

> Study MIP-IB12B, entitled "A Phase II Study Evaluating the Efficacy and Safety of AZEDRA in Patients with Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma", is a multi-center, open-label single arm study.
>
> The study was initiated (first subject enrolled) on June 4, 2009 and completed on February 14, 2017 (date of last completed subject). The last enrolled subject was on January 13, 2016. The final study report was released on June 23, 2017. There were a total of 81 subjects enrolled across ten sites in the U.S. (no non-U.S. sites). The three inspected sites were selected largely due to having the highest enrollment, covering ~65% (53 of 81) of enrolled patients.

The primary endpoint for the study was the proportion of study subjects with a reduction (including discontinuation) of all antihypertensive medication by at least 50% for at least 6 months.

OSI was consulted to verify safety and efficacy data from the primary study, MIP-IB12B, pertaining to AZEDRA (iobenguane I 131; also referred to as metaiodobenzylguanidine [MIBG] chemical mass (b) (4)) intended to treat Iobenguane-avid metastatic and/or recurrent pheochromocytoma/ paraganglioma (PPGL). The submission for this NDA is a rolling submission & the final part had not yet been submitted at time of the consult.

The primary efficacy endpoint, as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. The inspection also included verification of data for secondary efficacy endpoints, objective tumor response as determined by RECIST v1.1 and tumor response as determined by urine and plasma tumor markers (serum chromogranin A, plasmafree metanephrines, plasma catecholamines, 24-hour urinary vanillylmandelic acid and catecholamines, and urinary metanephrines).

Sites were chosen that had larger than average enrollment and larger proportion of patients drop out.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #1: Bennett Chin, M.D. 161D Bryan Research Bldg. 311 Research Drive Durham, NC 27710	Study: MIPIB12B Site ID: 2 Subjects: 15 screened/ 12 treated	9/11/2017-9/15/2017	NAI
CI #2: Daniel Pryma, M.D. Hospital of the University of Pennsylvania Department of Radiology 3400 Spruce Street Donner Room 110 Philadelphia, PA 19104	Study: MIPIB12B Site Id: 11 Subjects: 29 screened/ 29 treated	9/5/2017-9/8/2017	NAI
CI #3: Camilo Jimenez, M.D. MD Anderson Cancer Center Endocrine Neoplasm & Hormonal Disorder 1400 Pressler Street Unit 1461 Houston, TX 77030	Study: MIPIB12B Site ID: 5 Subjects: 12 screened/ 12 treated	9/28/2017-10/3/17	*NAI
Sponsor: Progenics Pharmaceuticals, Inc. 1 World Trade Center, 47th Floor, Suite J New York, NY 10007	Study: MIPIB12B	9/7/2017-9/11/2017	VAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Bennett Chin (Site 2)

The site screened 15 subjects and enrolled 12 subjects. At the time of this inspection 11 subjects had completed the study. Records of 12 subjects were reviewed during the inspection. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, IEC/IRB correspondence and approvals, financial disclosures, and investigator agreements. The source data was compared to the data listings submitted to the application. The inspection revealed no significant deficiencies. Efficacy data assessed during the inspection is consistent with the primary efficacy endpoint data reported in the application. There was no evidence of under-reporting of AEs.

2. Dr. Daniel Pryma (Site 11)

The site screened 14 subjects and enrolled 12 subjects. At the time of this inspection 11 subjects had completed the study. Records of 12 subjects were reviewed during the inspection. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, IEC/IRB correspondence and approvals, financial disclosures, and investigator agreements. The source data was compared to the data listings submitted to the application. The inspection revealed no significant deficiencies. Efficacy data assessed during the inspection is consistent with the primary efficacy endpoint data reported in the application. There was no evidence of under-reporting of AEs.

3. Dr. Camilo Jimenez (Site 5)

The site screened 15 subjects and enrolled 12 subjects. At the time of this inspection 11 subjects had completed the study. Records of 12 subjects were reviewed during the inspection. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, IEC/IRB correspondence and approvals, financial disclosures, and investigator agreements. The source data was compared to the data listings submitted to the application. The inspection revealed no significant deficiencies. Efficacy data assessed during the inspection is consistent with the primary efficacy endpoint data reported in the application. There was no evidence of under-reporting of AEs.

4. Sponsor: Progenics Pharmaceuticals, Inc.

The inspection focused on the control, oversight, and management of Study MIPIB12B. FDA form 483 was issued to the sponosr for failure to ensure proper monitoring of the study due to a gap of monitoring visits from 7/2013 through 4/2014. Otherwise, there were no other notable inspectional observations.

Monitoring records were reviewed from five clinical sites (#2, 4, 5, 10, and 11). Monitoring appeared adequate. There were no noncompliant sites, and no sites were closed during the conduct of the study. Documents reviewed for these sites included: FDA Form1572s, financial disclosure forms, IRB approvals, global informed consent template, alisting of subjects enrolled at each site, correspondences, and adverse events. Efficacy data assessed during the inspection is consistent with the primary efficacy endpoint data reported in the application. Standard Operating Procedures were also reviewed with no major deficiencies noted. Reporting practices for AEs and SAEs were reviewed. No deficiencies were noted. There was adequate oversight over the conduct of the study. There was no evidence of under-reporting of AEs or SAEs.

OSI Reviewer Comment: In response to the Form FDA-483, PPI sent a written response and indicated that the gap period corresponded to the time shortly after PPI acquired Molecular Insight Pharmaceuticals, Inc., the former sponsor of this trial. PPI stated that there was no gap in safety surveillance (e.g., including adverse event and periodic reporting to FDA) with all data corresponding to the gap period subsequently verified via source data. PPI further pointed out that during this gap period, all subjects had completed their core 12-month efficacy period, with none being dosed or in active treatment follow-up. No evidence was identified to suggest any data integrity concerns.

{See appended electronic signature page}

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Central Doc. Rm. NDA 209607
DOP2/Division Director/Patricia Keegan
DOP2/Clinical Reviewer/Diana Bradford
DOP2/Cross-Discipline Team Leader/Suzanne Demko
DOP2/Project Manager/Sharon Sickafuse
OSI/DCCE/ Division Director/Ni Khin
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OSI/GCCE/GCPAB/Team Leader/Susan Thompson
OSI/GCCE/GCPAB/Reviewer/David Menschik
OSI/GCPAB/Branch Support Staff/Yolanda Patague/Joseph Peacock

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