AZEDRA®

iobenguane I 131 injection for intravenous use

DOSIMETRY GUIDE

Please see Important Safety Information on pages 14 and 15 and click here for full Prescribing Information.

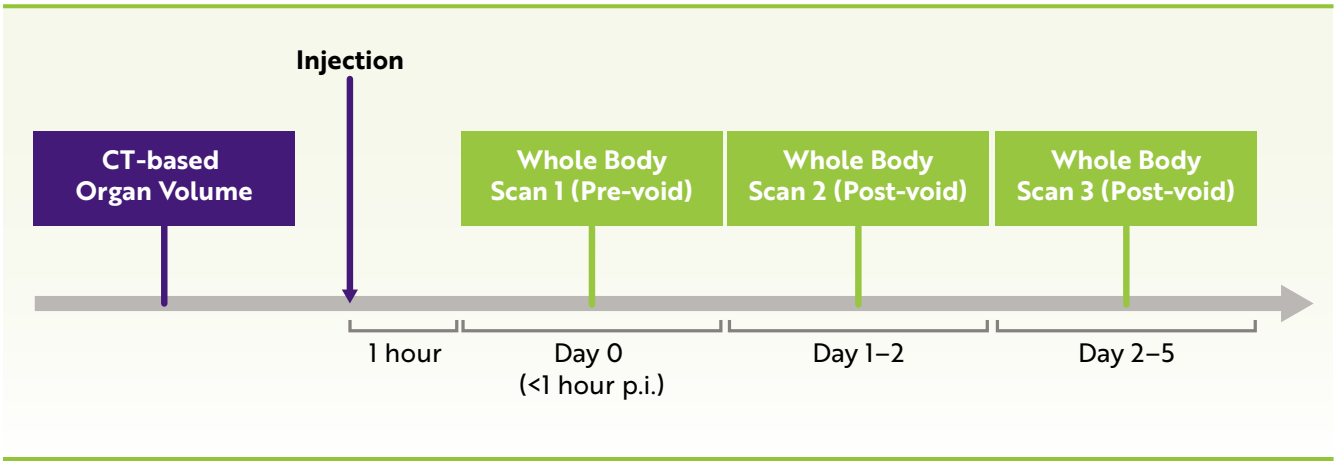
AZEDRA®
iobenguane I 131 injection for intravenous use

Patients will be administered a low dose (5 mCi to 6 mCi)* of AZEDRA® (iobenguane I 131) and will undergo a series of three (3) iobenguane I 131 scintigraphic scans to evaluate tumor avidity and assess biodistribution and clearance.

For each patient, calculate the radiation dose estimates to normal organs and tissues per unit activity [D (organ)] of administered dose using data extracted from these 3 images. Calculate in accordance with the Medical Internal Radiation Dose (MIRD) schema or related methodology. Whenever possible, use patient-specific organ masses (e.g. estimated from imaging).

Figure 1 gives a high-level overview of the dosimetric process.

Figure 1. AZEDRA Dosimetry Timeline



*The dosimetric dose activity for patients weighing 50 kg or less is 0.1 mCi/kg.

CT Scan

STEP 1: Measure Organ Volume*

- A patient-specific mass for the total* kidney volume must be used for the subsequent dosimetry calculations
  - Assume kidney density = 1.03 g/cc
- It may be helpful to also measure patient-specific organ volumes for the total (left plus right) lungs and liver in cases where the tumor burden is high in those organs
  - Assume liver density = 1.03 g/cc and lung density of 0.25 g/cc

*Left plus right, or single, kidney volume for each patient using a CT scan

Dosimetry Imaging

STEP 1: Imaging Equipment

- Quality control should be performed for each gamma camera per institutional protocol

STEP 2: Dosimetry Reference Standard

- Prepare the dosimetry reference standard per the Dose Preparation Guide
- **The same standard must be saved and used at each scan for a single patient**
  - DO NOT DISCARD

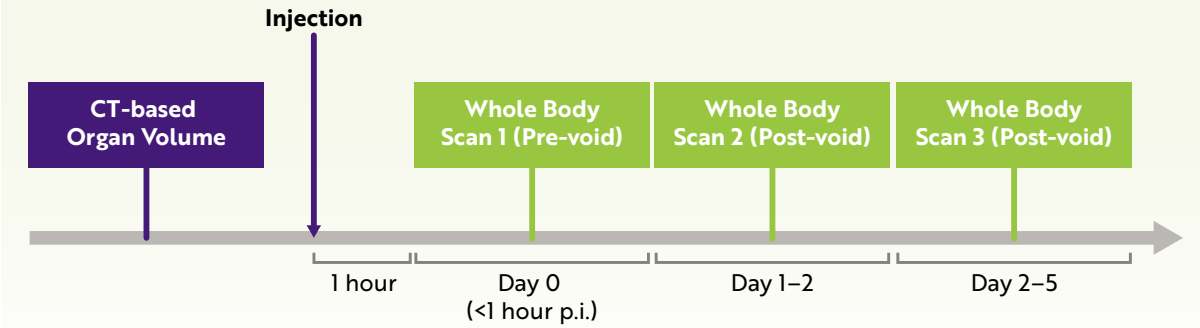
STEP 3: Dosimetric Dose Administration

- Prepare the dosimetric dose (10 mL syringe) per the Dose Preparation Guide
- **Have the patient void (urinate) immediately prior to dose administration**
- Obtain IV access and ensure patency with normal saline. Preferred IV access sites: Antecubital or equivalent vein. A central catheter may also be used
- Measure the activity in the syringe prior to injection using the dose calibrator
- Inject the AZEDRA® (iobenguane I 131) dosimetric dose over 60 seconds

STEP 4: Imaging Sequence

- The same gamma camera and imaging parameters (other than scanning rate) should be utilized when acquiring anterior and posterior images of the patient across all time points
- Place the dosimetry reference standard in the field of view during each image taking care not to allow the standard to touch the patient

Scan 1	▶ Day 0 within 1 hour of injecting the dosimetric dose ▶ **Prior to the patient voiding***
Scan 2	▶ Day 1 or 2 post injection ▶ **Have the patient void immediately prior to scanning** ▶ Use the same dosimetry reference standard from Scan 1
Scan 3	▶ Day 2–5 post injection ▶ **Have the patient void immediately prior to scanning** ▶ Use the same dosimetry reference standard from Scan 1 and 2



*If the patient has to void between dose administration and the first scan, the urine must be collected and imaged in the field of view with the patient (first whole body image sequence only)

STEP 5: Imaging Parameters

- Position the subject centered and parallel to the scanning axis with the arms down along each side so that they do not overlap organs in the abdomen. Placement of a pillow or support under the subject's knees, lower back, and neck is acceptable to reduce the tendency for some patients to move or shift their position due to back discomfort
- Obtain anterior and posterior images. For tall or large patients, please see ***Appendix A***
- Scan the subject from the top of head at a fixed point on imaging table to the feet
- Follow guidelines below

Guidelines for 5-6 mCi* Dosimetric Dose AZEDRA® (iobenguane I 131) Whole Body Scans

	Scan 1	Scan 2	Scan 3
Photopeak	364 KeV	364 KeV	364 KeV
Energy Window	15 percent	15 percent	15 percent
Collimator	Medium or high energy	Medium or high energy	Medium or high energy
Imaging Schedule	Within 1 hour post injection	1 or 2 days post injection	2–5 days post injection
Subject Preparation	Subjects should be well hydrated **and void immediately before receiving dosimetric dose.** Subject should not void again until end of scan 1	Subjects should be well hydrated **and void immediately prior to scan.**	Subjects should be well hydrated **and void immediately prior to scan.**
Acquisition Matrix	256x1024	256x1024	256x1024
Scanning Rate	15 cm/min	10 cm/min	5 cm/min
View	Anterior and posterior whole body images should be acquired, including arms, from vertex of skull through toes.		

*The dosimetric dose activity for patients weighing 50 kg or less is 0.1 mCi/kg.

Note: Subjects with varying body builds may require alternative imaging techniques. Please refer to Appendix A for suggestions regarding common imaging situations.

Dosimetry Calculations

Regions of Interest and Counts

Total counts and pixels per region will be recorded in **Step 1**. The dosimetry reference standard will be used to perform corrections for decay and camera speed. Camera speed values should be recorded for each whole body acquisition. Do not apply attenuation, scatter, or background corrections.

STEP 1

- Draw ROI and obtain pixel count data (**Table 1**):
  - Whole body, lungs, liver, kidneys, and dosimetry reference standard on one anterior and posterior planar whole body scan

Table 1. Example ROI Count and Pixel Data

Organ Counts Report

Protocol: AZEDRA EAP-1	**Pt. Dose (mCi):** 6.0		**Std Activity (µCi):** 91.2		**Report Date:** 28-Jan-16		
Pt ID: Pt-1001	**Injection Date:** 20-Jan-16		**Injection Time:** 14:34				
Scan	1		2		3		
Date/Time	20-Jan-16	15:18	21-Jan-16	14:33	22-Jan-16	11:15	
ROI Name	**Counts**	**Pixels**	**Counts**	**Pixels**	**Counts**	**Pixels**	**Pixel COV**
Lt Kidney_ant	10651	795	7219	796	9386	795	0.044%
Lt Kidney_post	6942	795	5329	795	7200	796	0.015%
Rt Kidney_ant	-	-	-	-	-	-	NA
Rt Kidney_post	-	-	-	-	-	-	NA
Liver_ant	153902	5249	82546	5248	99352	5248	0.013%
Liver_post	94864	5247	56818	5246	68531	5247	0010%
Lt Lung_ant	30843	1904	15591	1904	19492	1904	0.009%
Lt Lung_post	27542	1903	14604	1904	18822	1903	0.026%
Rt Lung_ant	32650	2631	20732	2631	25638	2629	0.031%
Rt Lung_post	29488	2630	19355	2630	24588	2630	0.017%
Standard_ant	12737	2568	17205	2568	32738	2570	0.039%
Standard_post	12696	2570	20014	2569	36575	2568	0.029%
WB_ant	774507	144768	560404	145938	755668	146732	0.678%
WB_post	525631	144802	452915	145632	619062	146697	0.652%

STEP 2

- Apply the same ROI template to each time point (Scans 2 and 3) by positioning over the organs or tissues in the same manner
  - In cases where organs overlap one another in the planar image, use either a reduced or contralateral ROI to avoid the overlapping area (see ***Appendix B***)
  - If copying the ROI template is not possible, care must be taken to replicate ROIs manually at each time point to ensure the sampling is done in a consistent manner

STEP 3

- Extract count data from each ROI and image
  - The geometric mean (GM) count of the first whole body ROI (Scan 1 obtained prior to excretion) will represent 100% of administered activity
  - ROI data (counts) from each time point (Scans 2 and 3) will be compared to the initial figure (Scan 1) and calculated as a percentage of initially administered activity (%IA)
    - In the case of other overlapping organs, see ***Appendix B*** for further details

Table 2. Example Image Quantification Data

	Image #1 Elapsed Time (hr)		Image #2 Elapsed Time (hr)		Image #3 Elapsed Time (hr)	
	0.73 hr		23.98 hr		44.68 hr	
Source Organ	**Geo Mean**	**%IA**	**Geo Mean**	**%IA**	**Geo Mean**	**%IA**
Lt Kidney	8598	1.35%	6202	0.67%	8221	0.47%
Rt Kidney	-	-	-	-	-	-
Liver	120830	18.94%	68484	7.36%	82515	4.75%
Lt Lung	29145	4.57%	15089	1.62%	19154	1.10%
Rt Lung	31028	4.86%	20032	2.15%	25107	1.45%
Standard	12716	1.99%	18556	1.99%	34603	1.99%
Whole Body	638048	100.0%	503801	54.1%	683963	39.4%

NOTE: All "Standard" %IA values must be within 2%.

STEP 4

- Calculate the elapsed time from infusion to acquisition of each of the three (3) images (Δt) **(Table 3)**

Table 3. Example Image Timing Data

Date and Time	Event	Δt (hr)	Camera Velocity (cm/min)
1/20/2016 14:34	Injection	NA	NA
1/20/2016 15:18	Scan 1	0.73	15
1/21/2016 14.33	Scan 2	23.98	10
1/22/2016 11:15	Scan 3	44.68	5

STEP 5

- Percentage of injected activity is calculated from the ROI data from each time point

	Equation	Example
Scan 1	$\frac{\text{GM for each organ (including the image standard)}}{\text{Whole body's GM}} \times 100 = \%IA$	$\frac{12{,}716}{638{,}048} = 0.0199 \times 100 = 1.99\%$
	• Whole body %IA value for the Image 1 should be 100% • Image standard %IA should be between 1% and 5%	
Scan 2	**Equation** Calculate the image standard correction factor: $\frac{\text{Image 1 Standard GM}}{\text{Image 2 Standard GM}} = \text{Correction Factor}$	**Example** The ratio of the initial image standard's GM counts to the later image's GM counts. $\frac{12{,}716}{18{,}556} = 0.685$
	$\frac{\text{GM for each Image 2 ROI (including the image standard)}}{\text{Whole body's GM } \textit{for Image 1}} \times 100 = \text{Uncorrected}$	$\frac{503{,}801}{638{,}048} = 0.7896 \times 100 = 78.96\%$
	Multiply the uncorrected %IA by the correction factor	$78.96\% \times 0.685 = 54.1\%$
	Once corrected, %IA values of the standard for each imaging time point should be equal to that of Image 1's standard	$\frac{18{,}556}{638{,}048} \times 100 \times 0.685 = 1.99\%$
Scan 3	Same as Scan 2	

STEP 6

- Biodistribution data for curve fitting
  - Convert %IA to fraction of injected activity (%IA/100)
  - Organize the data for curve fitting (**Table 4**)
    - Time points 1–3
    - Consolidate the left and right kidney and left and right lung data (**Table 5**)

Table 4. Example Biodistribution Data* (Biologic decay corrected)

X exp (λ_P x t) λ_P is 0.0036 h-1 for I-131

Time (hr)	Lt Kidney	Rt Kidney	Liver	Lt Lung	Rt Lung	Whole Body
0.73	0.01348	0.02321	0.1894	0.0457	0.0486	1.000
23.98	0.00666	0.01147	0.0736	0.0162	0.0215	0.541
44.68	0.00473	0.00815	0.0475	0.0110	0.0145	0.394

* Note data in fraction of IA not %IA.

Table 5. Example Biodistribution Data for Curve Fitting*

Time (hr)	Kidneys	Liver	Lungs	Whole Body
0.73	0.0367	0.1894	0.0943	1.000
23.98	0.0181	0.0736	0.0377	0.541
44.68	0.0129	0.0475	0.0255	0.394

* Fractional biodistribution data (decay corrected)

- Mathematically simulate using the mono-exponential formula: **$A(t) = A \times \exp(-\lambda_B \times t)$** where A is the fractional uptake and **λ_B** is its associated biological removal rate (h-1)
- Integrate the curve-fit equation A(t) from t=0 to infinity, after multiplying each term by the physical decay term (**Table 6**)
  - AUC = $A/(\lambda_B + \lambda_P)$

Table 6. Example Curve Fit Parameters*

	Kidneys	Liver	Lungs	Whole Body	Remainder
A-value	0.03535	0.1790	0.0884	1.000	-
λ_B-value (/hr)	0.02397	0.0317	0.0300	0.0221	-
AUC for I-131 (MBq x hr/MBq)	1.282	5.065	2.628	38.90	29.92

Remainder = Whole Body - Σ(kidneys, liver, and lungs)
* Values may vary a few percent based on the curve fitting program used.

- Calculate the area under curve (AUC) for each ROI and remainder
  - Remainder = whole body – Σ(kidneys, liver, and lungs)

STEP 7

- Radiation Absorbed Dose Calculations
  - Estimate the radiation absorbed doses using the MIRD schema or related methodology
    - Choose the model that most closely aligns with the patient's age and body weight
    - Scaling kidney radiation doses using patient-specific kidney volumes (from CT data) is required
  - Choose the appropriate model and I-131 as the nuclide
  - Enter the AUC values for kidney, liver, lungs, and remainder of the body
  - Modify the target organ mass and change the kidney value to that for the total kidney mass for your patient
  - Compute the complete set of target organ radiation doses in (rad/mCi) (**Table 7**)
  - Compare the patient-specific target organ radiation doses to the parameters of AZEDRA® (iobenguane I 131) (**Table 8**)
    - kidney ≤18 Gy
    - liver ≤31 Gy
    - lungs ≤16.5 Gy
    - red marrow ≤12 Gy
    - small intestines ≤40 Gy

Table 7. Example Target Organ Radiation Doses (rad/mCi)

Subject ID	Pt-1001
	rad/mCi
Adrenals	4.5E-01
Brain	2.7E-01
Breasts	2.9E-01
Gallbladder Wall	4.9E-01
LLI Wall	3.4E-01
Small Intestine	3.7E-01
Stomach Wall	3.7E-01
ULI Wall	3.7E-01
Heart Wall	3.9E-01
Kidneys	2.64E+00
Liver	1.57E+00
Lungs	1.33E+00
Muscle	3.1E-01
Ovaries	3.5E-01
Pancreas	4.3E-01
Red Marrow	2.9E-01
Osteogenic Cells	6.2E-01
Skin	2.6E-01
Spleen	3.yE-01
Testes	2.9E-01
Thymus	3.4E-01
Thyroid	3.1E-01
Urinary Bladder Wall	3.3E-01
Uterus	3.5E-01
Total Body	3.8E-01

Note: 3 significant figures used for critical organ doses only

Table 8. Example Therapy Radiation Doses and Limits on Injected Activity

Subject ID	Pt-1001			
Injected Activity (mCi) →	500	1000	Limiting Values (Gy)	Limiting IA (mCi)
Kidneys	13.2	26.4	18.0	859
Liver	7.9	15.7	31.0	1911
Lungs	6.7	13.3	16.5	1316
Red Marrow	1.5	2.9	12	4128
Small Intestines	1.9	3.7	40	10,811
			Max allowable activity (mCi) =	**859**

  - Determine which (if any) of the target organ radiation doses is the limiting value and reduce the therapeutic dose proportionally

Appendix A – Tall or Large Subjects

Subjects with varying body habitus may require alternative imaging techniques. The following guidelines provide suggestions for common imaging situations.

Tall Subject Scanning Parameters

- Acquire two (2) whole body scans (upper and lower) including both arms in the field of view
- Acquire both scans using the same scan settings (rate and matrix)
- Place the standard next to the head for the upper scan, next to the foot on the same side as it was placed for the upper scan, accordingly. Do not allow the standard to touch the subject's body to avoid interference with body counting. The standard must be completely visualized on both scans
- Place a marker source next to the subject's body at the level of the umbilicus. Do not allow the marker source to touch the subject's body to avoid interference with body counting
- The entire bladder must be included in both scans
- Repeat this procedure with the same subject and standard placement at each subsequent time point

Large Subject Scanning Parameters

- Scan speed may have to be slowed by 2 to 5 cm per minute for very large subjects, as noted in the table
- Acquire two (2) sets of anterior and posterior whole body scans from head to toe shifting the patient or the camera laterally so that left and right images are acquired
- Acquire both scans using the same scan settings (rate and matrix)
- Place the standard next to the left foot for the left-side scan, next to the right foot for the right-side scan. Do not allow the standard to touch the subject's body to avoid interference with body counting. The standard must be completely visualized on both scans
- The entire bladder must be included in both scans
- Repeat this procedure with same subject and standard placement at each subsequent time point

Appendix B – Permutations to the Procedure (Overlapping Organs)

It is common for the right kidney to be overlapped by a portion of the liver on planar images. To alleviate this issue, use only the ROI count data of the left kidney ROI as it is rarely overlapped by other significant sources of radioactivity. When a single kidney's ROI is used, its ROI counts can be scaled based on the relative sizes of the left and right kidney (obtained from the CT scan) to estimate the uptake/retention of the other kidney. This process is not performed when only a single kidney is present.

For example, if the right kidney is obscured, and the kidney masses for right and left kidneys are 155 grams and 90 grams, respectively, right kidney retention values can be computed by multiplying the extrapolation factor (155g/90g=1.72) by the left kidney retention values.

Critical Organ Mass/Volume Data

Number of kidneys =	2	kidney(s)				
Kidney mass =	245	gram	**Rt Kidney**	**155**	**Lt Kidney**	**90**
Liver mass =	not done	gram				
Lung mass =	not done	gram				

NOTE: If single kidney ROI used, and TWO kidneys present, must scale %IA for total kidney %IA.

Body Mass	93.4	kg	**Use Adult Male Phantom for calculations**

NOTES: Right Kidney overlapped by liver so it's ROI counts not accurate. Scale left kidney %IA to estimate right kidney %IA (using mass ratios). Extrapolation factor = (155 g/90 g) = 1.72.

1.72 x %IA for the left kidney will give the %IA for the right kidney. Once the kidney scaling is complete, the summary table of fractional biodistribution is available.

Important Safety Information

Indication

AZEDRA® (iobenguane I 131) is indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Important Safety Information

Warning and Precautions:

- **Risk from radiation exposure:** AZEDRA contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. These risks of radiation associated with the use of AZEDRA are greater in pediatric patients than in adults. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with AZEDRA consistent with institutional good radiation safety practices and patient management procedures.
- **Myelosuppression:** Severe and prolonged myelosuppression occurred during treatment with AZEDRA. Among the 88 patients who received a therapeutic dose of AZEDRA, 33% experienced Grade 4 thrombocytopenia, 16% experienced Grade 4 neutropenia, and 7% experienced Grade 4 anemia. Five percent of patients experienced febrile neutropenia. Monitor blood cell counts weekly for up to 12 weeks or until levels return to baseline or the normal range. Withhold and dose reduce AZEDRA as recommended in the prescribing information based on severity of the cytopenia.
- **Secondary myelodysplastic syndrome, leukemia, and other malignancies:** Myelodysplastic syndrome (MDS) and acute leukemias were reported in 6.8% of the 88 patients who received a therapeutic dose of AZEDRA. The time to development of MDS or acute leukemia ranged from 12 months to 7 years. Two of the 88 patients developed a non-hematological malignancy.
- **Hypothyroidism:** Hypothyroidism was reported in 3.4% of the 88 patients who received a therapeutic dose of AZEDRA. Initiate thyroid-blocking medications starting at least 1 day before and continuing for 10 days after each AZEDRA dose to reduce the risk of hypothyroidism or thyroid neoplasia. Evaluate for clinical evidence of hypothyroidism and measure thyroid-stimulating hormone (TSH) levels prior to initiating AZEDRA and annually thereafter.
- **Elevations in blood pressure:** Eleven percent of the 88 patients who received a therapeutic dose of AZEDRA experienced a worsening of pre-existing hypertension defined as an increase in systolic blood pressure to ≥160 mmHg with an increase of 20 mmHg or an increase in diastolic blood pressure to ≥100 mmHg with an increase of 10 mmHg. All changes in blood pressure occurred within the first 24 hours post infusion. Monitor blood pressure frequently during the first 24 hours after each therapeutic dose of AZEDRA.
- **Renal toxicity:** Of the 88 patients who received a therapeutic dose of AZEDRA, 7% developed renal failure or acute kidney injury and 22% demonstrated a clinically significant decrease in glomerular filtration rate (GFR) measured at 6 or 12 months. Monitor renal function during and after treatment with AZEDRA. Patients with baseline renal impairment may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. AZEDRA has not been studied in patients with severe renal impairment.

Please see additional Important Safety Information on next page and click here for full Prescribing Information.

Important Safety Information (continued)

Warning and Precautions (continued):

- **Pneumonitis:** Fatal pneumonitis occurred 9 weeks after a single dose in one patient in the expanded access program. Monitor patients for signs and symptoms of pneumonitis and treat appropriately.
- **Embryo-fetal toxicity:** Based on its mechanism of action, AZEDRA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with AZEDRA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose.
- **Risk of infertility:** Radiation exposure associated with AZEDRA may cause infertility in males and females. Radiation absorbed by testes and ovaries from the recommended cumulative dose of AZEDRA is within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

Adverse Reactions:
The most common severe (Grade 3–4) adverse reactions observed in AZEDRA clinical trials (≥10%) were lymphopenia (78%), neutropenia (59%), thrombocytopenia (50%), fatigue (26%), anemia (24%), increased international normalized ratio (18%), nausea (16%), dizziness (13%), hypertension (11%), and vomiting (10%). Twelve percent of patients discontinued treatment due to adverse reactions (thrombocytopenia, anemia, lymphopenia, nausea and vomiting, multiple hematologic adverse reactions).

Drug Interactions:
Based on the mechanism of action of iobenguane, drugs that reduce catecholamine uptake or that deplete catecholamine stores may interfere with iobenguane uptake into cells and therefore interfere with dosimetry calculations or the efficacy of AZEDRA. These drugs were not permitted in clinical trials that assessed the safety and efficacy of AZEDRA. Discontinue the drugs listed in the prescribing information for at least 5 half-lives before administration of either the dosimetry dose or a therapeutic dose of AZEDRA. Do not administer these drugs until at least 7 days after each AZEDRA dose.

For important risk and use information about AZEDRA, please click here for full Prescribing Information.

To report suspected adverse reactions, contact Progenics Pharmaceuticals, Inc. at 844-668-3950 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: AZEDRA® prescribing information. New York, NY: Progenics Pharmaceuticals, Inc.; 08 2018.

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