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AZEDRA®

iobenguane I 131 injection for intravenous use

The following is a Brief Summary; refer to the full Prescribing Information for complete information at www.AZEDRA.com

INDICATIONS AND USAGE

AZEDRA 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.

DOSAGE AND ADMINISTRATION

Important Safety Information

AZEDRA is a radiopharmaceutical. Handle with appropriate safety measures to minimize radiation exposure. Use waterproof gloves and effective radiation shielding when handling AZEDRA. Radiopharmaceuticals, including AZEDRA, should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA.

Recommended Dosage

Administer thyroid blockade and other pre- and concomitant medications as recommended.

Dosimetric Dose

The recommended AZEDRA dosimetric dose administered as an intravenous injection is:

- Patients weighing greater than 50 kg: 185 to 222 MBq (5 or 6 mCi)
- Patients weighing 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)

Dosimetry and Biodistribution Assessment

Following the AZEDRA dosimetric dose:

- Acquire anterior/posterior whole body gamma camera images within 1 hour of the AZEDRA dosimetric dose and prior to patient voiding (Day 0; Scan 1).
- Acquire additional images on Day 1 or 2 following patient voiding (Scan 2).
- Acquire additional images between Days 2-5 following patient voiding (Scan 3).

For each individual 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).

Therapeutic Dosage

The recommended AZEDRA therapeutic dose is based on body weight and reduced, if necessary, based on the dosimetry data. Administer a total of 2 therapeutic doses intravenously a minimum of 90 days apart.

Weight Based Dose per Therapeutic Cycle

- Patients weighing greater than 62.5 kg: 18,500 MBq (500 mCi)
- Patients weighing 62.5 kg or less: 296 MBq/kg (8 mCi/kg)

Determine if Dose Reduction Needed Based on Critical Organ Limits

- Calculate the estimated critical organ absorbed-dose by multiplying the dosimetry-derived radiation absorbed-dose per unit activity [D (organ)] by weight based therapeutic total activity (Aw).
- If resulting estimated critical organ absorbed-dose is less than threshold absorbed-dose (T) shown in Table 1, no dose adjustment is necessary.
- If resulting estimated critical organ absorbed-dose exceeds threshold absorbed-dose (T) shown in Table 1, calculate the reduced therapeutic total activity (i.e., the cumulative activity that would be administered in 2 therapeutic cycles) using the following equation:

Reduced Therapeutic Total Activity= Aw × [T ÷ {Aw × D (organ)}]

- Example: A 75 kg patient qualifies for a therapeutic total activity of 1000 mCi (Aw). For the kidneys, the dosimetry yields an estimated critical organ absorbed dose per unit activity of 0.027 Gy/mCi [D (kidney)]. Thus, the estimated critical organ absorbed-dose to the kidney is 27 Gy [Aw x D (organ)], which exceeds the threshold absorbed-dose for the kidneys (T) of 18 Gy (Table 1). Using the equation above the reduced therapeutic total activity to be administered to this patient is 666.7 mCi.

1000 mCi × [18 Gy ÷ {1000 mCi × 0.027 Gy/mCi }]

Table 1: Absorbed-dose Threshold Values for Radiation Toxicity in Critical Organs

Organ	~ 1%-rate: mortality or organ failure associated with disease	Time to death or organ failure	Threshold* absorbed-dose for ~1%-rate mortality or organ failure (Gy)
Red marrow	H-ARS mortality	1-2 months	12
Lungs	Pneumonitis mortality	1-7 months	16.5
Kidneys	Renal failure	>1 year	18
Liver	Hepatomegaly, ascites: possible organ failure	0.5-3 months	31
Small intestine	GI-ARS mortality	6-9 days	40

* Threshold of ~0.5 Gy for both heart and carotid artery, derived from experience with external-beam radiotherapy and associated with fractionated exposure, has also been proposed to support an ~1% mortality rate of cardiovascular and cerebrovascular deaths in >10-15 years. Great uncertainty is associated with the value ~ 0.5 Gy cited for vascular disease (ICRP publication 118, p.300, Table 4.5), consider benefits/risks to patients.

Thyroid Blockade and Other Pre- and Concomitant Medications

Thyroid Blockade

Administer inorganic iodine starting at least 24 hours before and continuing for 10 days after each AZEDRA dose.

Hydration

Instruct patients to increase fluid intake to at least two liters a day starting at least 1 day before and continuing for 1 week after each AZEDRA dose to minimize irradiation to the bladder.

Drugs that Reduce Catecholamine Uptake or Deplete Stores

Discontinue drugs that reduce catecholamine uptake or deplete catecholamine stores 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.

Antiemetic

Administer antiemetics 30 minutes prior to administering each AZEDRA dose.

Dose Modifications for Adverse Reactions

Recommended dose modifications of AZEDRA for adverse reactions are provided in Table 2 and the recommended dose or dose reduction for the second therapeutic dose of AZEDRA for myelosuppression are provided in Table 3.

Table 2: Recommended Dose Modifications of AZEDRA for Adverse Reactions

Adverse Reaction	Dose Modification
Myelosuppression	Do not administer the first therapeutic dose for platelet counts less than 80,000/mcL or absolute neutrophil counts (ANC) less than 1,200/mcL. Do not administer the second therapeutic dose until platelets and neutrophils return to baseline or to the normal range. Reduce the second therapeutic dose for the following: • platelet count less than 25,000/mcL, ANC less than 500/mcL, or life-threatening anemia for more than 7 days • febrile neutropenia • platelet count less than 50,000/mcL with active bleeding
Pneumonitis	• Do not administer the second therapeutic dose if pneumonitis is diagnosed after the first therapeutic dose.

Table 3: Recommended Dose or Dose Reduction for Second Therapeutic Dose of AZEDRA for Myelosuppression

Patient Population	If first therapeutic dose was weight based,	If first therapeutic dose was reduced based on critical organ limits,
Patients weighing greater than 62.5 kg	Reduce the second therapeutic dose to 425 mCi	Reduce second therapeutic dose to 85% of the first dose
Patients weighing 62.5 kg or less	Reduce the second therapeutic dose to 7 mCi/kg	Reduce second therapeutic dose to 85% of the first dose

DOSAGE FORMS AND STRENGTHS

Injection: 555 MBq/mL (15 mCi/mL) as a clear, colorless to pale yellow solution in a single-dose vial.

WARNINGS 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. In Study IB12B following the first therapeutic dose, patients who experienced Grade 4 neutropenia reached neutrophil nadir at a median of 36 days (27 – 55 days) and remained at nadir for a median of 12 days (8 – 22 days) until recovery to less than or equal to Grade 3. Following the second dose, patients who experienced Grade 4 neutropenia reached nadir at a median of 43 days (38 – 47 days) and remained at nadir for a median of 18.5 days (8 – 31 days) until recovery to less than or equal to Grade 3.

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 based on severity of the cytopenia.

Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies

Myelodysplastic syndrome (MDS) or 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. One patient developed colon cancer at 18 months and one patient developed lung adenocarcinoma at 27 months following the first therapeutic dose.

Hypothyroidism

Hypothyroidism was reported in 3.4% of the 88 patients who received a therapeutic dose of AZEDRA. The time to worsening of hypothyroidism was 4 months in one patient, and the time to development of hypothyroidism was less than one month in one patient and 18 months in one patient. 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 (creatinine clearance <30 mL/min).

Pneumonitis

Fatal pneumonitis occurred 9 weeks after a single dose in one patient in the expanded access program for Study IB12B (n=11). Pneumonitis was not diagnosed among the 88 patients enrolled in Study IB12 or IB12B. 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. There are no available data on the use of AZEDRA in pregnant women. No animal studies using iobenguane I 131 have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including AZEDRA, have the potential to 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. Advise females of reproductive potential 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. The recommended cumulative dose of 37 GBq of AZEDRA results in a radiation absorbed dose to the testes and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Myelosuppression
- Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies
- Hypothyroidism
- Elevations in Blood Pressure
- Renal Toxicity
- Pneumonitis

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in Warnings and Precautions reflect exposure to AZEDRA in 88 patients with iobenguane-scan positive recurrent or unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who received a therapeutic dose of AZEDRA in one of two clinical studies (IB12 or IB12B). The Warnings and Precautions also include data from 11 patients enrolled in an expanded access program for Study IB12B.

The safety data below was evaluated in two studies in patients with recurrent or unresectable, locally advanced or metastatic PPGL. Study

IB12 was an open-label, multi-center, single-arm dose-finding study in adult patients with malignant or recurrent PPGL. The study consisted of a 12-month efficacy phase with a 1 year follow-up. Twenty-one patients received a dosimetric dose (~5 mCi), followed by one therapeutic dose (~500 mCi) of AZEDRA. Study IB12B was an open-label, multi-center, single-arm study in 68 adult and pediatric patients age 12 years and older with recurrent or unresectable, locally advanced or metastatic PPGL.

Patients with evidence of liver dysfunction (aspartate aminotransferase or alanine aminotransferase ≥ 2.5 times the upper limit of normal or total bilirubin > 1.5 times the upper limit of normal), a history of liver disease (including hepatitis and chronic alcohol abuse), or severe renal impairment (creatinine clearance < 30 mL/min) were excluded. Patients who had received external beam radiation to > 25% of bone marrow, received whole body radiotherapy, or who had received any systemic radiotherapy resulting in myelosuppression within 3 months of study entry, were also excluded. The safety data described below are based on pooled safety data from studies IB12 and IB12B. A total of 88 patients received at least one therapeutic dose of AZEDRA and 50 patients received two therapeutic doses (one patient received treatment in both studies).

Adverse reactions from studies IB12 and IB12B are presented in Table 4. The most common severe (Grade 3-4) adverse reactions 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).

Table 4: Adverse Reactions Occurring in ≥10% of Patients with PPGL Receiving Therapeutic Dose of AZEDRA in Studies IB12B and IB12

Adverse Reaction	All Grades[a], (%)	Grades[a] 3 - 4, (%)
Hematologic[b]		
Lymphopenia	96	78
Anemia	93	24
Thrombocytopenia	91	50
Neutropenia	84	59
Gastrointestinal		
Nausea	78	16
Vomiting[c]	58	10
Dry mouth	48	2
Sialadenitis[d]	39	1
Diarrhea	25	3
Abdominal pain[e]	23	6
Constipation	19	7
Oropharyngeal pain	14	0
Dyspepsia	10	0
General		
Fatigue[f]	71	26
Pyrexia	14	2
Injection site pain	10	0
Hyperhidrosis	10	0
Alopecia	10	0
Infections		
Upper respiratory tract infection[g]	16	2
Urinary tract infection	11	1
Investigations[b]		
International normalized ratio increased[h]	85	18
Increased blood alkaline phosphatase	53	5
Increased aspartate aminotransferase	50	2
Increased alanine aminotransferase	43	2
Metabolism and nutrition		
Decreased appetite	30	5
Dehydration	16	4
Decreased weight	16	1
Musculoskeletal and connective tissue disorders		
Back pain	17	2
Pain in extremity	15	0
Nervous system		
Dizziness[i]	34	13
Headache	32	6
Dysgeusia[j]	24	1
Respiratory, thoracic, and mediastinal disorders		
Cough	18	0
Dyspnea	18	7
Vascular		
Hypotension	24	4
Hypertension[k]	20	11
Tachycardia	10	3

[a] NCI CTCAE version 3.0.
[b] Based on laboratory data.
[c] Includes vomiting and retching.
[d] Includes sialoadenitis, salivary gland pain, and salivary gland enlargement.
[e] Includes abdominal pain, abdominal pain upper, and abdominal pain lower.
[f] Incudes fatigue, asthenia.
[g] Includes upper respiratory tract infection, sinusitis, rhinorrhea, upper-airway cough syndrome, nasopharyngitis.
[h] Only assessed in Study IB12B (N=68).
[i] Includes dizziness and dizziness postural.
[j] Includes dysgeusia, hypogeusia and ageusia.
[k] Includes blood pressure increased and hypertension.

The following clinically significant adverse reactions were observed in < 10% of patients treated with AZEDRA:

Cardiac: palpitations (9%), syncope and presyncope (8%)

Endocrine: decreased TSH (5%), hypothyroidism (3%)

Gastrointestinal: dysphagia (7%), abdominal distension (6%), gastroesophageal reflux disease (6%), stomatitis (3%)

General: insomnia (9%), chills (8%), chest pain (6%)

Infections: candida infection (6%)

Investigations: prolonged prothrombin time (9%)

Musculoskeletal and connective tissue: arthralgia (8%), neck pain (8%), pain in jaw (7%), muscle spasms (6%)

Renal and urinary disorders: proteinuria (9%), renal failure (7%),

Respiratory: epistaxis (9%), nasal congestion (7%), pulmonary embolism (3%)

Skin and subcutaneous tissue: dry skin (8%), rash (8%), petechiae (7%)

Vascular: orthostatic hypotension (9%).

DRUG INTERACTIONS

Drugs that Reduce Catecholamine Uptake or Deplete Stores
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 drugs that reduce catecholamine uptake or deplete catecholamine stores, such as those listed below, 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.

- CNS stimulants or amphetamines (e.g. cocaine, methylphenidate, dextroamphetamine)
- Norepinephrine and dopamine reuptake inhibitors (e.g. phenteramine)
- Norepinephrine and serotonin reuptake inhibitors (e.g. tramadol)
- Monoamine oxidase inhibitors (e.g. phenelzine and linezolid)
- Central monoamine depleting drugs (e.g. reserpine)
- Non-select beta adrenergic blocking drugs (e.g. labetalol)
- Alpha agonists or alpha/beta agonists (e.g. pseudoephedrine, phenylephrine, ephedrine, phenylpropanolamine, naphazoline)
- Tricyclic antidepressants or norepinephrine reuptake inhibitors (e.g. amitriptyline, buproprion, duloxetine, mirtazapine, venlafaxine)
- Botanicals that may inhibit reuptake of norephinephrine, serotonin or dopamine (e.g. ephedra, ma huang, St John's Wort, or yohimbine)

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary

Based on its mechanism of action, AZEDRA can cause fetal harm. There are no available data on AZEDRA use in pregnant women. No animal studies using iobenguane I 131 have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including AZEDRA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation
Risk Summary

There are no data on the presence of iobenguane I 131 in human milk or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with AZEDRA and for 80 days after the final dose.

Females and Males of Reproductive Potential
Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA.

Contraception

AZEDRA can cause fetal harm when administered to a pregnant woman.

Females
Advise women of reproductive potential to use effective contraception during treatment with AZEDRA and for 7 months following the final dose of AZEDRA.

Males
Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with AZEDRA and for 4 months following the final dose of AZEDRA.

Infertility

The recommended cumulative dose of 37 GBq of AZEDRA results in a radiation absorbed dose to the testes and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

Pediatric Use
The safety and effectiveness of AZEDRA have been established in patients 12 years and older with unresectable and iobenguane scan positive, locally advanced or metastatic, pheochromocytoma and paraganglioma (PPGL) which require systemic anticancer therapy. Use of AZEDRA for this indication is supported by evidence from an adequate and well-controlled study in adults and pediatric patients 12 years and older.

The risks of radiation associated with AZEDRA is greater in pediatric patients than that in adult patients due to greater absorbed radiation doses and longer life expectancy. Ensure the therapeutic benefit of AZEDRA outweighs these greater risks prior to administration in pediatric patients.

The safety and effectiveness of AZEDRA have not been established in pediatric patients younger than 12 years old with unresectable and iobenguane scan positive, locally advanced or metastatic PPGL which require systemic anticancer therapy.

Geriatric Use
Of the patients enrolled in all clinical studies of AZEDRA, 17% were 65 years or older and 1% were 75 years or older. Clinical studies of AZEDRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment
The radiation dose to patients with renal impairment may be increased due to the delayed elimination of the drug. Adjust the therapeutic dose based on radiation exposure estimates from the dosimetry assessment. The safety of AZEDRA in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease has not been studied.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies with iobenguane I 131 have not been conducted; however, radiation is a carcinogen and a mutagen. No animal studies were conducted to determine the effects of iobenguane I 131 on fertility.

PATIENT COUNSELING INFORMATION

Hydration

Advise patients to drink at least 2 liters of liquid a day before and for one week following each dose of AZEDRA to minimize irradiation of the bladder.

Radiation Risks

Advise patients to minimize radiation exposure to household contacts consistent with institutional good radiation safety practices and patient management procedures.

Myelosuppression

Advise patients to contact their health care provider for any signs or symptoms of neutropenia, thrombocytopenia, or anemia.

Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies

Advise patients of the potential for secondary cancers, including myelodysplastic syndrome, acute leukemia, and other malignancies.

Hypothyroidism

Advise patients to take thyroid-blocking agents as prescribed. Advise patients of the need for life-long monitoring for hypothyroidism.

Elevations in Blood Pressure

Advise patients to contact their health care provider for signs or symptoms that may occur following tumor-hormone catecholamines release and possible risk of increased blood pressure during or 24 hours following each therapeutic AZEDRA dose.

Pneumonitis

Advise patients to contact their health care provider for signs or symptoms of pneumonitis.

Drug Interactions

Advise patients that some medicines interact with AZEDRA and to contact their health care provider before starting any over the counter medicines or herbal or dietary supplements.

Embryo-Fetal Toxicity

Advise pregnant women and males and females of reproductive potential of the potential risk to a fetus. Advise females to inform their health care provider of a known or suspected pregnancy.

Advise females of reproductive potential to use effective contraception during treatment with AZEDRA and for 7 months after the final dose.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AZEDRA and for 4 months after the final dose.

Lactation

Advise females not to breastfeed during treatment with AZEDRA and for 80 days after the final dose.

Infertility

Advise females and males patients that AZEDRA may impair fertility.

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