AZEDRA®

iobenguane I 131 injection for intravenous use

DOSING AND ADMINISTRATION GUIDE

Please see Important Safety Information on pages 3 and 4 and click here for full Prescribing Information.

- **Before administration** of AZEDRA injection for intravenous (IV) use, administer inorganic iodine starting at least 24 hours before and continuing for 10 days after each AZEDRA dose
- **Before initiating AZEDRA:**
  - 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
  - Discontinue drugs that reduce catecholamine uptake or deplete catecholamine stores for at least 5 half-lives before administration of either the dosimetric dose or a therapeutic dose of AZEDRA. Do not administer these drugs until at least 7 days after each AZEDRA dose

- **During AZEDRA therapy:**
  - Increase frequency of laboratory monitoring for thrombocytopenia in patients receiving medications that interfere with platelet function or coagulation
  - 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 [see prescribing information, Dosage and Administration section 2.4]
  - Administer antiemetics 30 minutes prior to administering each AZEDRA dose

Dosimetric Dose

Patients weighing >50 kg:

185 to 222 MBq (5 or 6 mCi)

Patients weighing ≤50 kg (weight-adjusted dose):

3.7 MBq/kg (0.1 mCi/kg)

Dosimetric dose is administered as an intravenous injection in approximately 6 mL over 60 seconds.

Therapeutic Dose

Patients weighing >62.5 kg:

18500 MBq (500 mCi)

Patients weighing ≤62.5 kg:

296 MBq/kg (8 mCi/kg)

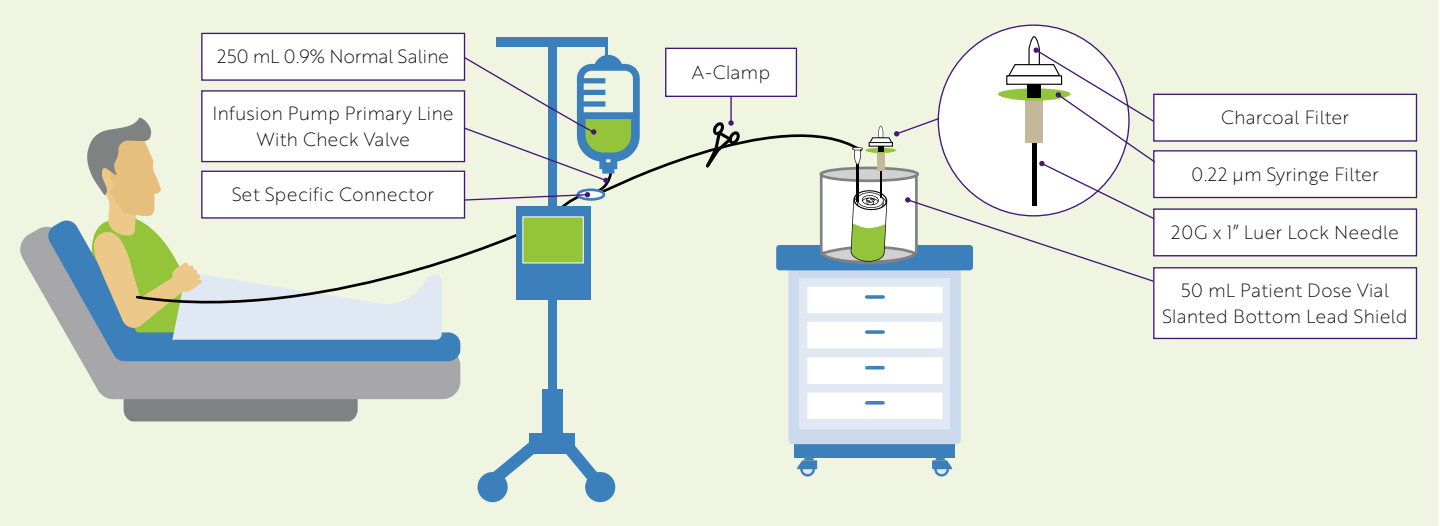
Therapeutic doses are administered intravenously in approximately 50 mL over 30 minutes (at a recommended rate of 100 mL/hour) 90 days apart. Administer pre- and concomitant medications and administer AZEDRA as recommended.

On the following page is a potential method for administration of the therapeutic doses of AZEDRA® (iobenguane I 131), which is provided for your reference only. Treatment sites should follow their own institutional guidelines for administration and radiation safety.

Infusion Pump Method

1. Obtain IV access and ensure patency
   a. Antecubital or equivalent vein is preferred. A central catheter may also be used
2. Assemble a second intravenous line using a 19 Gauge x 5-inch aspirating needle, 24-inch M-M arterial pressure tubing and a primary set specific connector
3. Clamp the second intravenous line and connect it to the primary intravenous line using the primary set specific connector. Flush the second intravenous line by releasing the clamp and then re-clamp the second intravenous line
4. Insert the needle of the second intravenous line into the 50-mL glass vial containing the AZEDRA therapeutic dose. Ensure the needle reaches the bottom of the glass vial without touching the sides of the vial
5. Clamp the primary intravenous line just above the second intravenous line and remove the clamp from the secondary intravenous line
6. Administer the AZEDRA therapeutic dose over 30 minutes at **a recommended rate of 100 mL/hour** for adults; for pediatrics 12 years and older administer over 60 minutes at a recommended rate of 50 mL/hr. Clamp the secondary intravenous line when the first air bubbles form
7. Remove the clamp from the primary intravenous line to flush any residual AZEDRA therapeutic dose within this intravenous line **with at least 50 mL of 0.9% Sodium Chloride Solution** for Injection, USP
8. Remove the clamp from the secondary intravenous line to flush any residual drug in the secondary intravenous line into the 50-mL glass vial

AZEDRA® (iobenguane I 131) Therapeutic Dose Infusion System Schematic



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.

Please see additional Important Safety Information on page 4 and click here for full Prescribing Information.

Important Safety Information (continued)

Warning and Precautions (continued):

- **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.
- **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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