Clinical Policy: Iobenguane I-131 (Azedra)

Reference Number: CP.PHAR.459
Effective Date: 03.01.20
Last Review Date: 02.22
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Iobenguane I-131 (Azedra®) injection is a radioactive agent.

FDA Approved Indication(s)

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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Azedra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Pheochromocytoma and Paraganglioma (must meet all)**:**

1. Diagnosis of pheochromocytoma or paraganglioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Tumor is unresectable, locally advanced, or metastatic;
5. Member currently receives medication to control tumor secretion of catecholamines (e.g., epinephrine, norepinephrine, dopamine) and related symptoms (e.g., hypertension, arrhythmia, hyperglycemia);
6. Documentation of positive metaiodobenzylguanidine (MIBG) scan;
7. Concurrent radiopharmaceuticals have not been prescribed (e.g., Lutathera® [lutetium lu-177 dotatate]);
8. Request meets one of the following (a or b):*
   a. Dose does not exceed (i or ii):
      i. Dosimetric dose (one dose only - dosimetry is used to calculate therapeutic dosing and must be administered first):
         a) For member weight > 50 kg: 185 to 222 MBq (5 to 6 mCi);
         b) For member weight ≤ 50 kg: 3.7 MBq/kg (0.1 mCi/kg);
      ii. Therapeutic dose (up to two doses at least 90 days apart):
         a) For member weight > 62.5 kg: 18,500 MBq/kg (500 mCi);
         b) For member weight ≤ 62.5 kg: 296 MBq/kg (8 mCi/kg);

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 6 months (one dosimetric dose and up to two therapeutic doses)
Commercial – 6 months or to the member's renewal date, whichever is longer (one dosimetric dose and up to two therapeutic doses)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Pheochromocytoma and Paraganglioma (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Azedra for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy as evidenced by but not limited to reduction or discontinuation of medication needed to control catecholamine-related symptoms (e.g., reduction in hypertension medication);
3. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed (i or ii):
      i. Dosimetric dose (one dose only - dosimetry is used to calculate therapeutic dosing and must be administered first):
         a) For member weight > 50 kg: 185 to 222 MBq (5 to 6 mCi);
         b) For member weight ≤ 50 kg: 3.7 MBq/kg (0.1 mCi/kg);
      ii. Therapeutic dose (up to two doses at least 90 days apart):
         a) For member weight > 62.5 kg: 18,500 MBq/kg (500 mCi);
         b) For member weight ≤ 62.5 kg: 296 MBq/kg (8 mCi/kg);
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:

Medicaid/HIM – 6 months (one dosimetric dose and up to two therapeutic doses)
Commercial – 6 months or to the member's renewal date, whichever is longer (one dosimetric dose and up to two therapeutic doses)

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MBq: megabecquerel
mCi: millicurie
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives

Not applicable.

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: Dosing Guidelines (Azedra Website and Prescribing Information)

- The manufacturer's website offers the following PDF dosing and administration resources (https://azedra.com/site-setup-resources/):
  - Dose preparation guide
  - Dosing and administration guide
  - Dosimetry guide

- Patient schedule and release instructions
- Patient treatment card

- Prescribing 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 [i.e., Nuclear Regulatory Commission and state Health Departments].
  - Verify pregnancy status in females of reproductive potential prior to administering Azedra.
  - Do not administer if platelet count is less than 80,000/mcL or absolute neutrophil count is less than 1,200/mcL.
  - Block thyroid prior to administering Azedra.
  - 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 or a therapeutic dose of Azedra. Do not administer these drugs until at least 7 days after each Azedra dose *(see Package Insert - Dosage and Administration (2.3) and Drugs that Reduce Catecholamine Uptake or Deplete Stores (7.1)).*
    - CNS stimulants or amphetamines (e.g. cocaine, methylphenidate, dextroamphetamine)
    - Norepinephrine and dopamine reuptake inhibitors (e.g. phentermine)
    - 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, bupropion, duloxetine, mirtazapine, venlafaxine)
    - Botanicals that may inhibit reuptake of norepinephrine, serotonin or dopamine (e.g. ephedra, ma huang, St John's Wort, yohimbine)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Pheochromocytoma or paraganglioma	Dosing regimen (see dosing guidelines at Appendix D):	See regimen

Indication	Dosing Regimen	Maximum Dose

	Administer Azedra intravenously as a dosimetric dose followed by up to two therapeutic doses administered at least 90 days apart.
	• Recommended dosimetric dose:
	  ○ Patients greater than 50 kg: 185 to 222 MBq (5 to 6 mCi)
	  ○ Patients 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)
	• Recommended therapeutic dose (adjust Azedra therapeutic dose(s) based on radiation dose estimates results from dosimetry):
	  ○ Patients greater than 62.5 kg: 18,500 MBq (500 mCi)
	  ○ Patients 62.5 kg or less: 296 MBq/kg (8 mCi/kg)	

VI. Product Availability

Injection: 555 MBq/mL (15 mCi/ml) at TOC as a clear solution in a single-dose vial

Detailed description:

- Azedra injection, containing 555 MBq/mL (15 mCi/mL) of I-131 (as iobenguane I 131) and 0.006 mg/mL of iobenguane, is a sterile, clear, colorless to pale yellow solution for intravenous use supplied in a colorless Type 1 borosilicate glass 30 mL single-dose vial
- Azedra is supplied in dosimetric (2 mL) and therapeutic (22.5 mL) presentations:
  - Dosimetric: 1,110 MBq (30 mCi) of iobenguane I 131 at calibration time (NDC 71258-015-02)
  - Therapeutic: 12,488 MBq (337.5 mCi) of iobenguane I 131 at calibration time (NDC 71258-015-22)
- The product vial is in a lead shielded container placed in a re-sealable plastic bag. The product is shipped on dry ice in a USA DOT Type A Radioactive package. Store at -70°C (-94°F). The shelf life is 6 days post calibration time. Discard appropriately at 144 hours

VII. References

1. Azedra Prescribing Information. New York, NY: Progenics Pharmaceuticals, Inc.; March 2021. Available https://azedra.com/full-prescribing-information.pdf. Accessed September 14, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed September 14, 2021.
3. National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors Version 3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed September 14, 2021.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
A9590	Iodine I-131, iobenguane 1 millicurie

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	01.21.20	02.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.10.20	02.21
1Q 2022 annual review: no significant changes; updated Appendix D and HCPCS code; references reviewed and updated.	09.14.21	02.22
Template changes applied to other diagnoses/indications.	09.28.22	

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan

retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.