Clinical Policy: Crizanlizumab-tmca (Adakveo)
Reference Number: CP.PHAR.449
Effective Date: 03.01.20
Last Review Date: 02.20
Line of Business: Commercial, TBD HIM*, Medicaid

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

*For Health Insurance Marketplace members, if request is through the pharmacy benefit, this policy applies only when the referenced drug is on the health plan approved formulary. Request for non-formulary drugs must be reviewed using the policy: HIM.PA.103.

Description
Crizanlizumab-tmca (Adakveo®) is a selectin blocker

FDA Approved Indication(s)
To reduce the frequency of vasoocclusive crises (VOC) in adults and pediatric patients aged 16 years and older with sickle cell disease (SCD).

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 Adakveo are medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Sickle Cell Disease (must meet all):
      1. Diagnosis of SCD with one of the following genotypes (a, b, c, or d):
         a. Homozygous hemoglobin S;
         b. Hemoglobin Sβ⁰-thalassemia;
         c. Hemoglobin Sβ⁺-thalassemia;
         d. Hemoglobin SC;
      2. Age ≥ 16 years;
      3. Prescribed by or in consultation with a hematologist;
      4. Hb level ≥ 4 g/dL;
      5. Member meets one of the following (a or b):
         a. Member has experienced at least 2 VOC within the past 6 months while on hydroxyurea at up to maximally indicated doses (see Appendix D);
         b. Member has intolerance* or contraindication to hydroxyurea and has experienced at least 2 VOC within the past 12 months (see Appendix D);

*Myelosuppression and hydroxyurea treatment failure: Myelosuppression is dose-dependent and reversible and does not qualify for treatment failure. NIH guidelines recommend a 6 month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. A lack of increase in mean
corpuscular volume (MCV) and/or fetal hemoglobin (HbF) levels is not indication to discontinue therapy.

6. Documentation of baseline incidence of VOC over the last twelve months;
7. Adakveo is prescribed concurrently with hydroxyurea, unless contraindicated or clinically significant adverse effects are experienced;
8. Adakveo is not prescribed concurrently with Oxbryta®;
9. Dose does not exceed 5 mg/kg doses on Day 1 and Day 15, followed by 5 mg/kg every 4 weeks.

Approval duration: 6 months

B. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy
A. Sickle Cell Disease (must meet all):
   1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
   2. Member is responding positively to therapy as evidenced by a documented improvement in the incidence of VOC from baseline;
   3. Adakveo is prescribed concurrently with hydroxyurea, unless contraindicated or clinically significant adverse effects are experienced;
   4. Adakveo is not prescribed concurrently with Oxbryta;
   5. If request is for a dose increase, new dose does not exceed 5 mg/kg every 4 weeks.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

   Approval duration: Duration of request or 6 months (whichever is less); or

   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 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
- Hb: hemoglobin
- SCD: sickle cell disease
- VOC: vaso-occlusive crises
Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
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</table>
| hydroxyurea (Droxia®)      | *Age ≥ 18 years*

Initial: 15 mg/kg/day PO single dose; based on blood counts, may increase by 5 mg/kg/day every 12 weeks to a max 35 mg/kg/day | 35 mg/kg/day             |
| hydroxyurea (Siklos®)      | *Age ≥ 2 years*

Initial: 20 mg/kg/day PO QD; based on blood counts, may increase by 5 mg/kg/day every 8 weeks or if a painful crisis occurs | 35 mg/kg/day             |

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): none reported

Appendix D: General Information

- A VOC is defined as a previously documented episode of acute painful crisis or acute chest syndrome (ACS) for which there was no explanation other than VOC that required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain.
- Myelosuppression and hydroxyurea treatment failure: Myelosuppression is dose-dependent and reversible and does not qualify for treatment failure. NIH guidelines recommend a 6 month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. A lack of increase in mean corpuscular volume (MCV) and/or fetal hemoglobin (HbF) levels is not indication to discontinue therapy.
- Hydroxyurea dose titration: Members should obtain complete blood counts (CBC) with white blood cell (WBC) differential and reticulocyte counts at least every 4 weeks for titration. The following lab values indicate that it is safe to increase dose.
  - Absolute neutrophil count (ANC) in adults ≥ 2,000/uL, or ANC ≥ 1,250/uL in younger patients with lower baseline counts
  - Platelet counts ≥ 80,000/uL

If neutropenia or thrombocytopenia occurs: hydroxyurea dosing is held, CBC and WBC differential are monitored weekly, members can restart hydroxyurea when values have recovered.
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>SCD</td>
<td>Administer 5 mg/kg by intravenous infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter.</td>
<td>5 mg/kg</td>
</tr>
</tbody>
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VI. Product Availability
Single-dose vial for injection: 100 mg/10 mL (10 mg/mL)

VII. References

ICD-10-CM Diagnosis Codes that Support Coverage Criteria
The following is a list of diagnosis codes that support coverage for the applicable covered procedure code(s).

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>D57.0*</td>
<td>Hb-SS disease with crisis</td>
</tr>
<tr>
<td>D57.1</td>
<td>Sickle-cell disease without crisis</td>
</tr>
<tr>
<td>D57.2*</td>
<td>Sickle-cell/Hb-C disease</td>
</tr>
<tr>
<td>D57.4*</td>
<td>Sickle-cell thalassemia</td>
</tr>
</tbody>
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Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>12.10.19</td>
<td>02.20</td>
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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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.
For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.