Clinical Policy: Tazemetostat (EPZ-6438, E7438)
Reference Number: CP.PHAR.452
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
Tazemetostat is a first-in-class small molecule selective inhibitor of the histone-lysine methyltransferase EZH2 gene.

FDA Approved Indication(s) [Pending]
Tazemetostat is indicated for the treatment of metastatic or locally advanced epithelioid sarcoma (ES) not eligible for curative surgery after receipt of at least two prior lines of 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 tazemetostat is medically necessary when the following criteria are met:

I. Initial Approval Criteria*
   *Criteria will mirror the clinical information from the prescribing information once FDA-approved.
   A. Epithelioid Sarcoma (must meet all):
      1. Diagnosis of ES;*
      2. Prescribed by or in consultation with an oncologist;*
      3. Age ≥ 18 years;*
      4. Disease is metastatic or locally advanced and not eligible for curative surgery; *
      5. Tumor is INI1-negative (i.e., inactivation, deletion, or mutation of INI1 [SMARCB-1] gene);*
      6. Member has received ≥ 2 lines of systemic therapy* (see examples at Appendix B);*
         *Prior authorization may be required.
      7. Tazemetostat is prescribed as monotherapy;
      8. Request meets one of the following (a or b):*
         a. Dose does not exceed 800 mg twice daily;*
         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
Commercial – Length of Benefit

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. Epithelioid Sarcoma (must meet all):
   1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving tazemetostat for a covered indication* and has received this medication for at least 30 days;
   2. Member is responding positively to therapy;
   3. If request is for a dose increase, request meets one of the following (a or b):*
      a. New dose does not exceed 800 mg twice daily;*
      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
   Commercial – Length of Benefit

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
ES: Epithelioid sarcoma
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
STS: soft tissue sarcoma
Appendix B: Therapeutic Alternatives [Pending]

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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</thead>
<tbody>
<tr>
<td><strong>Examples of NCCN recommended therapies for non-specific histologic soft tissue sarcoma (STS) subtypes</strong></td>
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<tr>
<td>Single agent therapies - off-label:</td>
<td></td>
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<tr>
<td>Doxorubicin (Adriamycin®)</td>
<td>Varies</td>
<td>Varies</td>
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<tr>
<td>Ifosfamide (Ifex®)</td>
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<tr>
<td>Epirubicin (Ellence®)</td>
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<td></td>
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<tr>
<td>Gemcitabine (Infugem®)</td>
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<tr>
<td>Dacarbazine</td>
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<tr>
<td>Liposomal doxorubicin (Doxil®)</td>
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<td>Temozolomide (Temodar®)</td>
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<tr>
<td>Vinorelbine (Nevelbine®)</td>
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<tr>
<td>Combination therapies - off-label:</td>
<td></td>
<td></td>
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<tr>
<td>AD (doxorubicin, dacarbazine)</td>
<td>Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>AIM (doxorubicin, ifosfamide, mesna [Mesnex®])</td>
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<td></td>
</tr>
<tr>
<td>MAID (mesna, doxorubicin, ifosfamide, dacarbazine)</td>
<td>Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>Ifosfamide, epirubicin, mesna</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine and docetaxel</td>
<td></td>
<td></td>
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<tr>
<td>Gemcitabine and vinorelbine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine and dacarbazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single agent therapies - labeled:</td>
<td>STS, advanced</td>
<td>800 mg PO QD</td>
</tr>
<tr>
<td>Votrient® (pazopanib)</td>
<td>STS, advanced</td>
<td>800 mg/day</td>
</tr>
</tbody>
</table>

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 [Pending]

- Contraindication(s):
- Boxed warning(s):

Appendix F: Epithelioid Sarcoma: Phase 2 Data

ES tazemetostat phase 2 data presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; clinical trial information: NCT02601950

- ES is a rare STS that metastasizes in approximately 30% to 50% of cases. More than 90% of ES tumors lack expression of the tumor suppressor gene, INI1, an important component of epigenetic regulation. Loss of INI1 function allows another epigenetic modifier, EZH2, to become an oncogenic driver in tumor cells.
- Data from a phase 2 open-label, multicenter trial of patients with locally advanced or metastatic ES are reported. Efficacy was assessed with primary and secondary endpoints including objective response rate (ORR) by RECIST 1.1, disease control rate (DCR;
objective confirmed response of any duration or stable disease (SD) lasting ≥ 32 weeks), duration of response (DOR), progression-free survival (PFS), overall survival (OS); safety and tolerability were also evaluated.

- As of September 17, 2018, 62 INI1-negative ES pts were enrolled and treated with tazemetostat 800 mg BID. The median number of prior lines of therapy was 1 (range: 0-9). There were 9/62 (15%) confirmed partial responses (PRs) with an ORR of 15% and DCR of 26%. The DOR ranged from 7.1+ weeks to 103.0+ weeks (median: not reached) with a median OS of 82.4 weeks (95% CI: 47.4, not estimable) for all 62 pts. Tazemetostat was generally well tolerated. There were no drug-related deaths and a low discontinuation rate (1.7%).


V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>TBD pending FDA approval</td>
<td>TBD pending FDA approval</td>
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</table>

VI. Product Availability

Oral formulation: TBD pending FDA approval

VII. References


Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Policy created</td>
<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.
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distribution of this clinical policy or any information contained herein are strictly prohibited.
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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.

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