Clinical Policy: Ibrutinib (Imbruvica)
Reference Number: CP.PHAR.126
Effective Date: 10.01.15
Last Review Date: 02.20
Line of Business: Commercial, HIM, Medicaid

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

Description
Ibrutinib (Imbruvica®) is a Bruton tyrosine kinase (BTK) inhibitor.

FDA Approved Indication(s)
Imbruvica is indicated for the treatment of:
- Adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
  - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion
- Adult patients with Waldenström’s macroglobulinemia (WM)
- Adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
  - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic 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 Imbruvica is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Mantle Cell Lymphoma (must meet all):
      1. Diagnosis of MCL;
      2. Prescribed by or in consultation with an oncologist or hematologist;
      3. Age ≥ 18 years;
      4. Member meets one of the following (a or b):
         a. Prescribed in combination with rituximab as pretreatment for HyperCVAD;
b. Received at least one prior therapy (see Appendix B), unless contraindicated or clinically significant adverse effects are experienced to all;
5. If request is for tablets, medical justification supports inability to use capsules;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 560 mg (4 capsules or 1 tablet) per day;
   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. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (must meet all):
   1. Diagnosis of CLL or SLL;
   2. Prescribed by or in consultation with an oncologist or hematologist;
   3. Age ≥ 18 years;
   4. Prescribed as a single agent;
   5. If request is for tablets, medical justification supports inability to use capsules;
   6. Request meets one of the following (a or b):*
      a. Dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
      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

C. Waldenström’s Macroglobulinemia (must meet all):
   1. Diagnosis of WM;
   2. Prescribed by or in consultation with an oncologist or hematologist;
   3. Age ≥ 18 years;
   4. If request is for tablets, medical justification supports inability to use capsules;
   5. Request meets one of the following (a or b):*
      a. Dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
      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

D. Marginal Zone Lymphoma (must meet all):
   1. Diagnosis of MZL;
   2. Prescribed by or in consultation with an oncologist or hematologist;
   3. Age ≥ 18 years;
   4. Received at least one prior anti-CD20-based therapy (e.g., Rituxan®), unless contraindicated or clinically significant adverse effects are experienced to all;
5. If request is for tablets, medical justification supports inability to use capsules;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 560 mg (4 capsules or 1 tablet) per day;
   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

E. Chronic Graft-Versus-Host Disease (must meet all):
1. Diagnosis of cGVHD;
2. Prescribed by or in consultation with an oncologist, hematologist, or bone marrow
   transplant specialist;
3. Age ≥ 18 years;
4. Member has a history of bone marrow/stem cell transplant;
5. Member meets one of the following (a or b):
   a. Failure of a systemic corticosteroid (e.g., prednisone) at up to maximally
      indicated doses, unless contraindicated or clinically significant adverse effects are
      experienced;
   b. If intolerance or contraindication to systemic corticosteroids, failure of an
      immunosuppressant [e.g., mycophenolate mofetil, calcineurin inhibitors (e.g.,
      cyclosporine, tacrolimus), sirolimus] at up to maximally indicated doses, unless
      contraindicated or clinically significant adverse effects are experienced;
6. If request is for tablets, medical justification supports inability to use capsules;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the
      relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration:
Medicaid/HIM – 6 months
Commercial – Length of Benefit

F. NCCN Compendium Indications (off-label) (must meet all):
1. Diagnosis of one of the following (a, b, or c):
   a. Non-Hodgkin’s (B-cell) lymphoma or any of its subtypes *(see Appendix D for
      NCCN-recommended subtypes)*;
   b. Hairy cell leukemia (HCL);
   c. Primary CNS lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Disease is relapsed, recurrent, or progressive;
5. Member meets one of the following (a or b):
   a. For HCL: Received at least two prior therapies *(see Appendix B)*, unless
      contraindicated or clinically significant adverse effects are experienced to all;
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b. For CNS lymphoma or non-Hodgkin’s (B-cell) lymphoma: Received at least one prior therapy (see Appendix B), unless contraindicated or clinically significant adverse effects are experienced to all;

6. If request is for tablets, medical justification supports inability to use capsules;

7. Request meets one of the following (a or b):*
   a. Dose does not exceed FDA maximum per day;
   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

G. 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. All Indications in Section I (must meet all):
   1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Imbruvica for a covered oncology-related 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, b, or c):*
       a. MCL and MZL: New dose does not exceed 560 mg (4 capsules or 1 tablet) per day;
       b. CLL/SLL, WM, and cGVHD: New dose does not exceed 420 mg (3 capsules or 1 tablet) per day;
       c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*For oncology indications, prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration:
Medicaid/HIM – 12 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
   
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>Bruton’s tyrosine kinase</td>
</tr>
<tr>
<td>cGVHD</td>
<td>chronic graft-versus-host disease</td>
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<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FL</td>
<td>follicular lymphoma</td>
</tr>
<tr>
<td>HCL</td>
<td>hairy cell leukemia</td>
</tr>
<tr>
<td>HyperCVAD</td>
<td>cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine</td>
</tr>
<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
</tr>
<tr>
<td>MCL</td>
<td>mantle cell lymphoma</td>
</tr>
<tr>
<td>MZL</td>
<td>marginal zone lymphoma</td>
</tr>
<tr>
<td>PTLD</td>
<td>post-transplant lymphoproliferative disorders</td>
</tr>
<tr>
<td>SLL</td>
<td>small lymphocytic lymphoma</td>
</tr>
<tr>
<td>WM</td>
<td>Waldenström’s macroglobulinemia</td>
</tr>
</tbody>
</table>

   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>
</tr>
</thead>
<tbody>
<tr>
<td>EPOCH [etoposide, prednisone, vincristine (Vincasar PFS®), cyclophosphamide, doxorubicin (Adriamycin®)] + Rituxan® (rituximab)</td>
<td>DLBCL</td>
<td>Varies</td>
</tr>
<tr>
<td>RCHOP [cyclophosphamide, doxorubicin (Adriamycin®), vincristine (Vincasar PFS®), prednisone]/RDHAP</td>
<td>DLBCL, FL, MCL, MZL, PTLD</td>
<td>Varies</td>
</tr>
<tr>
<td>HyperCVAD [cyclophosphamide, vincristine (Vincasar PFS®), doxorubicin (Adriamycin®), dexamethasone] + Rituxan® (rituximab)</td>
<td>MCL</td>
<td>Varies</td>
</tr>
<tr>
<td>NORDIC [dose-intensified induction immunochemotherapy with Rituxan® (rituximab)]</td>
<td>MCL</td>
<td>Varies</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/ Maximum Dose</td>
</tr>
<tr>
<td>-----------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>cyclophosphamide, vincristine (Vincasar PFS&lt;sup&gt;®&lt;/sup&gt;), doxorubicin, prednisone] alternating with Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab) and high-dose cytarabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDHAP [Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab), dexamethasone, cytarabine, cisplatin]</td>
<td>MCL</td>
<td>Varies</td>
</tr>
<tr>
<td>RDHAX [Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab), dexamethasone, cytarabine, oxaliplatin]</td>
<td>MCL</td>
<td>Varies</td>
</tr>
<tr>
<td>VR-CAP [bortezomib (Velcade&lt;sup&gt;®&lt;/sup&gt;), Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab), cyclophosphamide, doxorubicin (Adriamycin&lt;sup&gt;®&lt;/sup&gt;), and prednisone]</td>
<td>MCL</td>
<td>Varies</td>
</tr>
<tr>
<td>Bendeka&lt;sup&gt;®&lt;/sup&gt;, Treanda&lt;sup&gt;®&lt;/sup&gt; (bendamustine) + Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab)</td>
<td>MCL, FL</td>
<td>Varies</td>
</tr>
<tr>
<td>Revlimid&lt;sup&gt;®&lt;/sup&gt; (lenalidomide) + Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab)</td>
<td>FL</td>
<td>Varies</td>
</tr>
<tr>
<td>Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab)</td>
<td>FL, HCL, MZL, PTLD</td>
<td>Varies</td>
</tr>
<tr>
<td>RCVP [Rituxan&lt;sup&gt;®&lt;/sup&gt; (rituximab), cyclophosphamide, doxorubicin (Adriamycin&lt;sup&gt;®&lt;/sup&gt;), vincristine (Vincasar PFS&lt;sup&gt;®&lt;/sup&gt;)]</td>
<td>FL, MZL, PTLD</td>
<td>Varies</td>
</tr>
<tr>
<td>Bendeka&lt;sup&gt;®&lt;/sup&gt;, Treanda&lt;sup&gt;®&lt;/sup&gt; (bendamustine) + Gazyva&lt;sup&gt;®&lt;/sup&gt; (obinutuzumab)</td>
<td>FL</td>
<td>Varies</td>
</tr>
<tr>
<td>CHOP + Gazyva&lt;sup&gt;®&lt;/sup&gt; (obinutuzumab)</td>
<td>FL</td>
<td>Varies</td>
</tr>
<tr>
<td>cladribine</td>
<td>HCL</td>
<td>0.09 mg/kg/day IV per cycle (7 days)</td>
</tr>
<tr>
<td>Intron&lt;sup&gt;®&lt;/sup&gt; A (interferon alfa-2b)</td>
<td>HCL</td>
<td>6 million units/m&lt;sup&gt;2&lt;/sup&gt;/week</td>
</tr>
<tr>
<td>Nipent™ (pentostatin)</td>
<td>HCL</td>
<td>4 mg/m&lt;sup&gt;2&lt;/sup&gt; IV every other week</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose methotrexate-based regimen [methotrexate (Rheumatrex®) + Rituxan® (rituximab) and other agents (e.g., temozolomide, vincristine (Vincasar PFS®), procarbazine, cytarabine)]</td>
<td><strong>Primary CNS Lymphoma</strong></td>
<td>Varies</td>
</tr>
<tr>
<td>RCEPP [Rituxan® (rituximab), cyclophosphamide, etoposide, prednisone, procarbazine]</td>
<td><strong>PTLD</strong></td>
<td>Varies</td>
</tr>
<tr>
<td>RCEOP (Rituxan® (rituximab), cyclophosphamide, etoposide, vincristine (Vincasar PFS®), prednisone)</td>
<td><strong>PTLD</strong></td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Immunosuppressive Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mycophenolate mofetil (Cellcept®)</td>
<td><strong>cGVHD</strong></td>
<td>2 g/day</td>
</tr>
<tr>
<td>cyclosporine (Gengraf®, Neoral®, Sandimmune®)</td>
<td><strong>cGVHD</strong></td>
<td>2 g/day</td>
</tr>
<tr>
<td>tacrolimus (Prograf®)</td>
<td><strong>cGVHD</strong></td>
<td>1 g/day</td>
</tr>
<tr>
<td>sirolimus (Rapamune®)</td>
<td><strong>cGVHD</strong></td>
<td>Maintenance: 2 mg/day</td>
</tr>
<tr>
<td>systemic corticosteroids (e.g., prednisone, prednisolone, methylprednisolone)</td>
<td><strong>cGVHD</strong></td>
<td>Varies</td>
</tr>
</tbody>
</table>

*Off-label

**Appendix C: Contraindications/Boxed Warnings**
None reported

**Appendix D: General Information**
- **cGVHD:**
  - The National Institutes of Health Working Group recommends that the diagnosis of cGVHD require at least 1 diagnostic manifestation of cGVHD (e.g., poikiloderma or esophageal web) or at least 1 distinctive manifestation (e.g., keratoconjunctivitis
sicca) confirmed by pertinent biopsy or other relevant tests in the same or another organ.

- Corticosteroids are the mainstay of initial systemic treatment for patients with cGVHD. Alternatives to, or add-on therapy to corticosteroids includes but is not limited to: mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), sirolimus.
- Steroid-refractory chronic GVHD is defined as either failure to improve after at least 2 months, or progression after 1 month of standard immunosuppressive therapy, including corticosteroids and cyclosporine.

- Non-Hodgkin’s (B-cell) lymphoma subtypes supported as NCCN category 2A recommended uses for Imbruvica:
  - Follicular lymphoma (grade 1-2)
  - Gastric MALT lymphoma
  - Nongastric MALT lymphoma
  - Nodal marginal zone lymphoma
  - Splenic marginal zone lymphoma
  - Histologic Transformation of Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma
  - Diffuse large B-cell lymphoma
  - AIDS-related non-germinal center diffuse large B-cell lymphoma
  - Post-transplant lymphoproliferative disorders

- MCL:
  - Imbruvica in combination with Rituxan as a pre-treatment to limit the number of cycles of HyperCVAD with Rituxan is recommended category 2A per NCCN guidelines.

- MZL:
  - Imbruvica as a second-line or later agent is recommended category 2A per NCCN guidelines for MZL subtypes including gastric mucosa-associated lymphoid tissue (MALT) lymphoma, nongastric MALT lymphoma, splenic marginal zone lymphoma, and nodal marginal zone lymphoma.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCL and MZL</td>
<td>560 mg PO QD</td>
<td>560 mg/day</td>
</tr>
<tr>
<td>CLL/SLL, WM, and cGVHD</td>
<td>420 mg PO QD</td>
<td>420 mg/day</td>
</tr>
</tbody>
</table>

VI. Product Availability

- Capsules: 70 mg, 140 mg
- Tablets: 140 mg, 280 mg, 420 mg, 560 mg

VII. References


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed ‘and’ to ‘or’ in I.E.1 per package insert</td>
<td>01.16</td>
<td></td>
</tr>
<tr>
<td>Updated disclaimer language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy converted to new template. Removed age and prescriber specialty requirements. Removed question related to moderate or severe hepatic impairment as it is not listed as a contraindication per PI. Added maximum dosage requirement for MCL, CLL/SLL, and WM. Modified CLL/SLL criteria to allow use of Imbruvica as first line therapy for members without 17p deletion per PI and NCCN compendium. Added disease progression or unacceptable toxicity to reasons to discontinue per PI.</td>
<td>07.16</td>
<td>10.16</td>
</tr>
<tr>
<td>Added new FDA approved indication: MZL. MCL: added off-label use per NCCN compendium. CLL/SLL: removed “with or without 17p deletion” as that has no impact on coverage. Other diagnoses/indications: added hairy cell leukemia per NCCN compendium. Continued approval: Removed reasons to discontinue. Added requirement for documentation of positive response to therapy.</td>
<td>03.17</td>
<td>03.17</td>
</tr>
</tbody>
</table>
**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.

**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.

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