Clinical Policy: Umbralisib (Ukoniq)

Reference Number: CP.PHAR.531
Effective Date: 05.01.21
Last Review Date: 05.22
Line of Business: Commercial, HIM, Medicaid Revision Log

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

Description

Umrbalisib (Ukoniq™) is a kinase inhibitor.

FDA Approved Indication(s)*

Ukoniq is indicated for the treatment of adult patients with:

- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen
- Relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy

***TG Therapeutics, Inc., the manufacturer of Ukoniq, voluntarily withdrew Ukoniq after a post-market safety trial found an increased risk of death in people who used Ukoniq and the FDA withdrew its approval for the product** *(see Appendix D).*

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 Ukoniq is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Marginal Zone Lymphoma (must meet all)**:**

1. Provider attestation of acknowledgement of FDA's request for withdrawal of product due to increased risk of death in members that have used Ukoniq;
2. Diagnosis of MZL (e.g., gastric/nongastric MALT, splenic/nodal MZL);
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age ≥ 18 years;
5. Relapsed or refractory disease after ≥ 1 anti-CD20-based regimen* (*see Appendix B for examples*);
   **Prior authorization may be required*
6. For Ukoniq requests, member must use umbralisib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 800 mg(4 tablets) 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 – 12 months or duration of request, whichever is less

B. Follicular Lymphoma (must meet all)**:**
1. Provider attestation of acknowledgement of FDA's request for withdrawal of product due to increased risk of death in members that have used Ukoniq;
2. Diagnosis of FL;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age ≥ 18 years;
5. Relapsed or refractory disease after ≥ 3 lines of systemic therapy* (*see Appendix B for examples*);
   **Prior authorization may be required*
6. For Ukoniq requests, member must use umbralisib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 800 mg(4 tablets) 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 – 12 months or duration of request, whichever is less

C. 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. All Indications in Section I (must meet all)**:**
1. Provider attestation of acknowledgment of FDA's request for withdrawal of product due to increase risk of death in members who have used Ukoniq;

2. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Ukoniq for a covered indication and has received this medication for at least 30 days;
3. Member is responding positively to therapy;
4. For Ukoniq requests, member must use umbralisib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 800 mg (4 tablets) per day;
   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 – 12 months
Commercial – 12 months or duration of request, whichever is less

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
FL: follicular lymphoma
MZL: marginal zone lymphoma

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.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Prior Line Regimens for Oncology Indications		
RCHOP [rituximab (Rituxan®), cyclophosphamide, doxorubicin (Adriamycin®), vincristine (Vincasar PFS®), prednisone]/RDHAP	**FL, MZL** Varies	Varies
RCVP [rituximab (Rituxan®), cyclophosphamide, vincristine (Vincasar PFS®), prednisone]	**FL, MZL** Varies	Varies
Rituxan® (rituximab)	**FL, MZL** Varies	Varies
bendamustine (Bendeka®, Treanda®) + rituximab (Rituxan®)	**FL, MZL** Varies	Varies
Revlimid® (lenalidomide) + rituximab (Rituxan®)	**FL** Varies	Varies
Gazyva® (obinutuzumab)	**FL** Varies	Varies
Revlimid® (lenalidomide)	**FL** Varies	Varies
bendamustine (Bendeka®, Treanda®) + Gazyva® (obinutuzumab)	**FL** Varies	Varies
CHOP + Gazyva® (obinutuzumab)	**FL** Varies	Varies
Zydelig® (idelalisib)	**FL** (third-line and subsequent therapy): 150 mg PO BID	300 mg/day
Copiktra® (duvelisib)	**FL** (third-line and subsequent therapy): 25 mg PO BID	50 mg/day
Aliqopa™ (copanlisib)	**FL** (third-line and subsequent therapy): 60 mg IV on days 1, 8, and 15 of a 28-day treatment cycle	60 mg/dose/ week

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
None reported

Appendix D: Withdrawal from Market

- TG Therapeutics, Inc., the manufacturer of Ukoniq, voluntarily withdrew Ukoniq after a post-market safety trial found an increased risk of death in people who used Ukoniq and the FDA withdrew its approval for the product.
- FDA believes that the risk of Ukoniq outweighs its benefits.
  - This is based on a review of results from the UNITY clinical trial. In February 2022, FDA announced they were reviewing clinical trial data and alterted the public about a possible increased risk of death associated with Ukoniq based on analysis of the data. The manufacturer's decision to withdraw Ukoniq was based on the withdrawal of the BLA and sNDA for U2 in chronic lymphocytic leukemia (CLL).
  - In the first analysis of overall survival (OS) that used a cut-off date of September 2021, there was an imbalance in favor of the control arm (HR: 1.23). In February 2022, considering the ad-hoc nature of the analysis where approximately 15% of patients had missing or outdated survival data and excluding deaths related to COVID-19, the two arms were approximately balanced (HR: 1.04). Pursuant to recent information request made by FDA, updated OS data was collected and showed an increasing imbalance in favor of the control arm, differing from the improved results provided to FDA in February 2022.
  - Neither the original preliminary OS results nor the updated preliminary OS results were statistically significant.
- Currently FDA recommends patients should stop taking Ukoniq.
  - FDA recommends patients should stop taking Ukoniq and talk to health care professionals about alternative treatments.
- Currently FDA recommends health care professionals stop prescribing and dispensing Ukoniq to patients.
  - Inform patients currently taking Ukoniq of the increased risk of death seen in the clinical trial and advise them to stop taking the medicine.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MZL, FL	800 mg PO QD	800 mg/day

VI. Product Availability

Tablet: 200 mg

VII. References

1. Ukoniq Prescribing Information. Edison, JN: TG Therapeutics; February 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213176s000lbl.pdf. Accessed February 2, 2022.
2. National Comprehensive Cancer Network. B-Cell Lymphomas Version 5.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed February 2, 2022.

3. FDA approval of lymphoma medicine Ukoniq (umbralisib) is withdrawn due to safety concerns. U.S. Food and Drug Administration. June 2022. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approval-lymphoma-medicine-ukoniq-umbralisib-withdrawn-due-safety-concerns#:~:text=6%2D1%2D2022%20FDA%20Drug,and%20follicular%20lymphoma%20(FL. Accessed June 22, 2022.
4. TG Therapeutics announces voluntary withdrawal of the BLA/sNDA for U2 to treat patients with CLL and SLL. TG Therapeutics. April 2022. Available at: https://ir.tgtherapeutics.com/node/17231/pdf. Accessed June 22, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	02.23.21	05.21
2Q 2022 annual review: modified commercial approval duration from length of benefit to "12 months or duration of request, whichever is less"; added generic redirection if available per template for oral oncology products; references reviewed and updated.	02.02.22	05.22
RT4: added disclaimer about FDA and manufacturer withdrawal; added requirement for prescriber attestation to all criteria sets; added Appendix D.	06.22.22	
Template changes applied to other diagnoses/indications.	10.05.22	

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.

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.