Clinical Policy: Ondansetron (Zuplenz)

Reference Number: CP.PMN.45
Effective Date: 09.01.06
Last Review Date: 02.23
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Ondansetron (Zuplenz®) is a serotonin (5-HT_3) receptor antagonist.

FDA Approved Indication(s)

Zuplenz is indicated for the prevention of:

- Nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m^2, in adults
- Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in adults and pediatric patients 4 years of age and older
- Nausea and vomiting associated with radiotherapy in adult patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen
- Postoperative nausea and/or vomiting (PONV) in adults

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

I. Initial Approval Criteria

A. Prevention of Nausea and Vomiting (must meet all)**:**

1. Prescribed for the prevention of nausea/vomiting due to one of the following (a, b, or c):
   a. Cancer chemotherapy (*see Appendix D*);
   b. Radiation therapy;
   c. Surgery;
2. Member meets one of the following:
   a. For moderately emetogenic cancer chemotherapy: Age ≥ 4 years;
   b. For highly emetogenic cancer chemotherapy: Age ≥ 18 years;
   c. For total body irradiation: Age ≥ 18 years;
   d. For PONV: Age ≥ 18 years;
3. Member meets one of the following (a or b):
   a. Both of the following (i and ii):
      i. Member is contraindicated or has experienced clinically significant adverse effects to the excipients in all formulary generic ondansetron products (regular tablet, orally disintegrating tablet, oral solution);

ii. Documentation supports member's inability to use all formulary generic ondansetron products (regular tablet, orally disintegrating tablet, oral solution);

b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;

4. Dose does not exceed one of the following (a or b):
   a. Chemotherapy, radiation therapy: both of the following (i and ii):
      i. 24 mg per day;
      ii. 3 films per day;
   b. Postoperative: both of the following (i and ii):
      i. 16 mg as a single dose;
      ii. 2 films.

Approval duration:
Chemotherapy-induced nausea/vomiting: Projected course of chemotherapy up to 72 hours after completion of chemotherapy
Radiation therapy-induced nausea/vomiting: Projected course of radiation therapy up to 48 hours after completion of radiation therapy
Postoperative nausea/vomiting: One time approval (3 days)

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. Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

2. Member is responding positively to therapy;
3. Member continues to receive cancer chemotherapy (*see Appendix D*) or radiation therapy;
4. If request is for a dose increase, new dose does not exceed both of the following (a and b):
   a. 24 mg per day;
   b. 3 films per day.

Approval duration:
Chemotherapy-induced nausea/vomiting: Projected course of chemotherapy up to 72 hours after completion of chemotherapy
Radiation therapy-induced nausea/vomiting: Projected course of radiation therapy up to 48 hours after completion of radiation therapy

B. Postoperative Nausea and Vomiting

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

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.

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

5-HT_3: serotonin 5-hydroxytryptamine, type 3
ASCO: American Society of Clinical Oncology
FDA: Food and Drug Administration

NCCN: National Comprehensive Cancer Network

PONV: postoperative nausea and vomiting

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
ondansetron (Zofran®, Zofran ODT)	**Prevention of nausea and vomiting associated with moderately emetogenic chemotherapy** 8 mg PO given 30 min prior to chemotherapy, then repeat dose 8 hrs after initial dose, then 8 mg PO BID for 1 to 2 days after chemotherapy completion **Prevention of nausea and vomiting associated with highly emetogenic chemotherapy** 24 mg PO given 30 min prior to start of single-day chemotherapy **Prevention of nausea and vomiting associated with emetogenic chemotherapy** 0.15 mg/kg/dose IV given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose **Treatment of nausea and vomiting associated with chemotherapy*** 16 to 24 mg PO daily or 8 to 16 mg IV **Prevention of nausea and vomiting associated with radiation therapy** Total body irradiation: 8 mg PO given 1 to 2 hrs prior to radiotherapy Single high-dose radiotherapy: 8 mg PO given 1 to 2 hrs prior to irradiation, then 8 mg PO Q8H for 1 to 2 days after completion of radiotherapy Daily fractionated radiotherapy: 8 mg PO given 1 to 2 hrs prior to irradiation, then 8 mg PO Q8H for each day of radiotherapy **Prevention of PONV** 16 mg PO given 1 hr prior to anesthesia or 4 mg IM/IV as a single dose given 30 min before end of anesthesia	PO: 24 mg/day IV: 16 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Treatment of PONV* 4 mg IV as a single dose	

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.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity (e.g., anaphylaxis) to ondansetron or any components of the formulation
  - Concomitant use of apomorphine
- Boxed warning(s): none reported

Appendix D: American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Recommendations in Oncology

- Minimal emetic risk chemotherapy: No routine prophylaxis is recommended.
- Low emetic risk chemotherapy: Recommended options include dexamethasone (recommended by both ASCO and NCCN) or metoclopramide, prochlorperazine, or a 5-HT_3 receptor antagonist (recommended by NCCN only). NK_1 receptor antagonists are not included in low risk antiemetic recommendations.
- Moderate emetic risk chemotherapy: 5-HT_3 receptor antagonists and dexamethasone may be used in combination and with or without NK_1 receptor antagonists. Olanzapine may also be used in combination with palonosetron and dexamethasone.
  - Examples of moderate emetic risk chemotherapy: azacitidine, bendamustine, carboplatin, clofarabine, cyclophosphamide ≤ 1,500 mg/m^2, cytarabine > 200 mg/m^2, daunorubicin, doxorubicin < 60 mg/m^2, epirubicin ≤ 90 mg/m^2, idarubicin, ifosfamide, irinotecan, oxaliplatin
- High emetic risk chemotherapy: NK_1 receptor antagonists are recommended for use in combination with 5-HT_3 receptor antagonists and dexamethasone. Olanzapine may also be used in combination with 5-HT_3 receptor antagonists, dexamethasone, and/or NK_1 receptor antagonists.
  - Examples of high emetic risk chemotherapy: carmustine, cisplatin, cyclophosphamide > 1,500 mg/m^2, dacarbazine, mechlorethamine, streptozocin
- Breakthrough emesis: Per NCCN, an agent from a different drug class is recommended to be added to the current antiemetic regimen. Drug classes include atypical antipsychotics (olanzapine), benzodiazepines (lorazepam), cannabinoids (dronabinol, nabilone), phenothiazines (prochlorperazine, promethazine), 5-HT_3 receptor antagonists (dolasetron, ondansetron, granisetron), steroids (dexamethasone), or haloperidol, metoclopramide, scopolamine. An NK_1 receptor antagonist may be added to the prophylaxis regimen of the next chemotherapy cycle if not previously included.

Appendix E: States with Regulations against Redirections in Stage IV or Metastatic Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial and HIM requests only** For stage 4 metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Prevention of nausea and vomiting associated with cancer chemotherapy	**Moderately emetogenic cancer chemotherapy:** Age 12 years or older: 8 mg PO given 30 min prior to chemotherapy, then repeat dose 8 hrs after initial dose, then 8 mg PO BID for 1 to 2 days after chemotherapy completion Age 4 to 11 years: 4 mg PO given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose, then 4 mg PO TID for 1 to 2 days after chemotherapy completion **Highly emetogenic cancer chemotherapy:** Age 18 or older: 24 mg PO given 30 min prior to start of single-day chemotherapy	24 mg/day
Prevention of nausea and vomiting associated with radiotherapy	Total body irradiation: 8 mg PO given 1 to 2 hrs prior to each daily fraction of radiotherapy Single high-dose radiotherapy: 8 mg PO given 1 to 2 hrs prior to irradiation, then 8 mg PO Q8H for 1 to 2 days after completion of radiotherapy Daily fractionated radiotherapy: 8 mg PO given 1 to 2 hrs prior to irradiation, then 8 mg PO Q8H for each day of radiotherapy	24 mg/day
Prevention of postoperative nausea	16 mg PO given 1 hr prior to anesthesia	16 mg/dose

Indication	Dosing Regimen	Maximum Dose
and vomiting		

VI. Product Availability

Oral soluble film: 4 mg, 8 mg

VII. References

1. Zuplenz Prescribing Information. Portland, OR: Galena Biopharma, Inc.; August 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022524s007lbl.pdf. Accessed October 4, 2022.
2. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. International Anesthesia Research Society 2020. Available at: https://www.ashp.org/-/media/assets/policy-guidelines/docs/endorsed-documents/endorsed-documents-fourth-consensus-guidelines-postop-nausea-vomiting.ashx?la=en&hash=D6B263AED7C1C1CBE64563F8BB6048C9D8DC6CEA. Accessed October 1, 2021.
3. Hesketh, PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Guideline Update. *J Clin Oncol*. 2020. 38:2,782-2,797. doi.org/10.1200/JCO.20.01296.
4. National Comprehensive Cancer Network. Antiemesis Version 2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed October 4, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.30.18	02.19
1Q 2020 annual review: no significant changes; added HIM line of business; references reviewed and updated.	01.22.20	02.20
1Q 2021 annual review: no significant changes; references HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.12.20	02.21
Added allowance for bypassing redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings with additional details in appendix E.	04.27.21	
Added Nevada to Appendix E.	08.03.21	
1Q 2022 annual review: no significant changes; added Commercial line of business; added age limits per PI; references reviewed and updated.	10.01.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.07.22	
1Q 2023 annual review: no significant changes; modified to generalize beyond Stage IV or metastatic cancer to the following redirection bypass: “Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings”; references reviewed and updated.	10.04.22	02.23

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.