Clinical Policy: Ondansetron (Zuplenz)

Reference Number: ERX.NPA.119
Effective Date: 09.01.19
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

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

Description
Ondasetron oral soluble film (Zuplenz®) is 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 total body irradiation, single high-dose fraction to 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 and vomiting due to one of the following (a, b, or c):
   a. Cancer chemotherapy (*see Appendix D*);
   b. Radiation therapy;
   c. Surgery;
2. Age is one of the following (a, b, c, or d):
   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 Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings *(see Appendix E*);
4. Dose does not exceed one of the following (a or b):
   a. Chemotherapy, radiation therapy: 24 mg (3 films) per day;
   b. Postoperative: 16 mg (2 films) as a single dose.

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
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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 24 mg (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. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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 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**	PO: 24 mg/day IV: 16 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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 **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):concomitant use of apomorphine, hypersensitivity to ondansetron
- 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, alemtuzumab, bendamustine, carboplatin, clofarabine, cyclophosphamide < 1,500 mg/m^2, cytarabine < 1,000 mg/m^2, daunorubicin, doxorubicin, epirubicin, 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, dactinomycin, 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 antipsychotic (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 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
Nausea and vomiting associated with highly emetogenic cancer chemotherapy	≥ 18 years: 24 mg (successively as three 8 mg films) PO 30 minutes before the start of single-day highly emetogenic chemotherapy Multiday, single-dose administration of a 24 mg dosage has not been studied	24 mg once
Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy	≥ 12 years: one 8 mg film PO BID 4 to 11 years: one 4 mg film PO BID Administer for 1-2 days after completion of chemotherapy	16 mg/day
Nausea and vomiting associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen	≥ 18 years: one 8 mg film PO TID Administer for 1-2 days after completion of radiotherapy	24 mg/day
Postoperative nausea and/or vomiting	≥ 18 years: 16 mg (successively as two 8 mg films) PO 1 hour before induction of anesthesia	16 mg once

VI. Product Availability

Oral soluble film: 4 mg, 8 mg

VII. References

1. Zuplenz Prescribing Information. Portland, OR: Galena Biopharma, Inc.; August 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022524s007lbl.pdf. Accessed October 1, 2021.
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 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed October 1, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	05.02.19	08.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.01.19	02.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	11.12.20	02.21
1Q 2022 annual review: no significant changes; 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; references reviewed and updated.	10.01.21	02.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.