Clinical Policy: Ondansetron (Zofran, Zuplenz)

Reference Number: CP.CPA.173
Effective Date: 11.16.16
Last Review Date: 11.17 Revision Log
Line of Business: Medicaid – Medi-Cal

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

Description
Ondansetron (Zofran®, Zuplenz®) is an oral and parenteral serotonin (5-HT_3) receptor antagonist.

FDA approved indication
Zofran is indicated:
- For the treatment of prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.
- For the treatment of prevention of postoperative nausea and/or vomiting.

Zuplenz is indicated:
- For the treatment of prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- For the treatment of prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- For the treatment of prevention of nausea and vomiting associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen.
- For the treatment of prevention of postoperative nausea and/or vomiting.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with Centene Corporation® that Zofran and Zuplenz are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
A. All Indications (must meet all)**:**
1. One of the following criteria is satisfied:
   a. Patient has received or will receive highly or moderately emetogenic chemotherapy;
   b. Patient will receive radiation therapy;
   c. Patient suffers from hyperemesis due to pregnancy (hyperemesis gravidarum);
   d. Patient requires for prevention of postoperative nausea and vomiting;
   e. Prescribed for a pediatric patient with gastroenteritis;
2. Dose does not exceed the FDA recommended maximum dosing (see Section V).

Approval duration: Length of Benefit

B. Other diagnoses/indications
1. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the FDA recommended maximum dosing (see Section V).

Approval duration: 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 12 months (whichever is less); or
2. Refer to CP.PMN.53 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 – CP.PMN.53 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

HEC: highly emetogenic cancer chemotherapy
MEC: moderately emetogenic cancer chemotherapy
RINV: nausea and vomiting associated with radiotherapy
PONV: postoperative nausea and/or vomiting
ACOG: American College of Obstetrics and Gynecology
ASCO: American Society of Clinical Oncology
5-HT3: 5-hydroxytryptamine-3
NCCN: National Comprehensive Cancer Network

Appendix B: General Information

- The maximum injectable dose of Zofran is of 16 mg. A 32 mg single intravenous dose of Zofran (ondansetron) may affect the electrical activity of the heart (QT interval prolongation), which could pre-dispose patients to develop an abnormal and potentially fatal heart rhythm known as Torsades de Pointes.
- Micromedex has a Class IIA recommendation for oral ondansetron use for pediatric patients from 6 months to 12 years presenting with gastroenteritis.
- Use of ondansetron in pregnancy is supported in American College of Obstetrics and Gynecology (ACOG) guidelines when other agents have failed or when a patient is

unresponsive to other measures and is at risk for dehydration or other adverse outcomes. According to the 2011 American Society of Clinical Oncology (ASCO) Guideline for Antiemetics in Oncology, the Update Committee recommends the following:
  - For chemotherapy of high emetic risk - three-drug combination of 5-hydroxytryptamine-3 (5-HT3) serotonin receptor antagonist, dexamethasone, and aprepitant
  - For chemotherapy of moderate emetic risk - two-drug combination of a 5-HT3 serotonin receptor antagonist and dexamethasone
- Per practice guidelines from the National Comprehensive Cancer Network (NCCN), selection of emetogenic agents used should be based on the emetic risk, prior experience with antiemetics, as well as patient risk factors.
- The following table is NCCN's classification for emetogenic potential of significant chemotherapy and other agents.

Agents	Frequency of Emesis
AC combination defined as either doxorubicin or epirubicin with cyclophosphamide, carmustine > 250 mg/m^2, cisplatin, cyclophosphamide > 1,500 mg/m^2, dacarbazine, doxorubicin ≥ 60 mg/m², or epirubicin >90 mg/m², ifosfamide ≥ 2gm/m² per dose,,mechlorethamine, streptozocin	High Emetic Risk >90%
aldesleukin > 12-15 million IU/m^2, amifostine > 300 mg/m^2, arsenic trioxide, azacitidine, bendamustine, busulfan, carboplatin, carmustine ≤ 250 mg/m^2, , clofarabine, cyclophosphamide ≤ 1500 mg/m^2, cytarabine > 200 mg/m^2, dactinomycin, daunorubicin, doxorubicin <60 mg/ m², epirubicin ≤ 90 mg/m², idarubicin, ifosfamide <2 gm/m² per dose, interferon alpha ≥ 10 million IU/m^2, irinotecan, melphalan, MTX ≥ 250 mg/m^2, oxaliplatin, temozolomide	Moderate Emetic Risk 30-90%
ado-trastuzumab emtansine, amifostine ≤ 300 mg, aldesleukin ≤ 12 million IU/m^2, brentuximab vedotin, cabazitaxel, carfilzomib cytarabine (low dose) 100 - 200 mg/m^2, docetaxel, doxorubicin (liposomal), eribulin, etoposide, 5-fluorouracil, floxuridine, gemcitabine, interferon alpha > 5 <10 million IU/m^2, ixabepilone, MTX > 50 mg/m2 < 250 mg/m^2, mitomcyin, mitoxantrone, omacetaxine, paclitaxel, paclitaxel-albumin, pemetrexed, pentostatin, ,pralatrexate romidepsin thiotepa, topotecan, ziv-aflibercept	Low Emetic Risk 10-30%
alemtuzumab, asparaginase, bevacizumab, bleomycin, bortezomib, cetuximab, 2-chlorodeoxyadenosine (cladribine), cytarabine < 100mg/m^2, decitabine, denileukin diftitox, dexrazoxane, fludarabine ipilimumab,, interferon alpha ≤ 5 million IU/m^2, MTX ≤ 50 mg/m^2, nelarabine, ofatumumab, panitumumab, pegaspargase,peginterferon, pertuzumab, rituximab, temsirolimus, trastuzumab, valrubicin, vinblastine, vincristine,vincristine (liposomal) vinorelbine	Minimal Emetic Risk <10%
altretamine, busulfan (≥ 4 mg/d), crizotinib, cyclophosphamide (≥ 100 mg/m^2/d), estramustine, etoposide, lomustine (single day), mitotane, procarbazine, temozolomide (> 75 mg/m^2/d), vismodegib	Emetogenic potential of oral antineoplastic agents: Moderate to High

Agents	Frequency of Emesis
axitinib, bexarotene, bosutinib,busulfan (< 4 mg/d), cabozantinib, capecitabine, chlorambucil, cyclophosphamide (< 100 mg/m^2/d), dasatinib, dabrafenib, erlotinib, everolimus, fludarabine, gefitinib, hydroxyurea, imatinib, lapatinib, lenalidomide, melphalan, mercaptopurine, methotrexate, nilotinib, pazopanib, pomalidomide, ponatinib, regorafenib, ruxolitinib,sorafenib, sunitinib, temozolomide (≤ 75 mg/m^2/d), thalidomide, thioguanine, topotecan,trametinib, tretinoin, vandetanib, vemurafenib, vorinostat	Emetogenic potential of oral antineoplastic agents: Minimal to low

Appendix C: Therapeutic Alternatives

Drug	Dosing Regimen	Dosing Limit/Maximum Dose
5-HT$_3$ Serotonin Antagonists Aloxi® (palonosetron)*	MEC and HEC: Adults: 0.25 mg IV infused over 30 seconds beginning 30 minutes prior to chemotherapy. Pediatrics (1 month to less than 17 years): 20 mcg/kg (max 1.5 mg) infused over 15 minutes beginning 30 minutes prior to chemotherapy.	As specified by length of chemotherapy
5-HT$_3$ Serotonin Antagonists Aloxi® (palonosetron)*	Prevention of PONV: Adults: 0.075 mg IV infused over 10 seconds immediately before the induction of the anesthesia Efficacy beyond 24 hours has not been demonstrated.	Postoperative nausea and vomiting: One day
5-HT$_3$ Serotonin Antagonists Anzemet® (dolasetron)*	Prevention of cancer chemotherapy induced nausea and vomiting Adults: 100 mg PO within 1 hour prior to chemotherapy Children 2-16 years: 1.8 mg/kg up to a maximum of 100 mg PO given within 1 hour prior to chemotherapy Safety and effectiveness in pediatric patients under 2 years of age have not been established	As specified by length of chemotherapy
5-HT$_3$ Serotonin Antagonists	Prevention of PONV:	Postoperative nausea and vomiting: One day

Drug	Dosing Regimen	Dosing Limit/Maximum Dose
Anzemet® (dolasetron)*	Adults: 12.5 mg IV 15 minutes prior to cessation of anesthesia or as soon as nausea or vomiting presents Children 2-16 years: 0.35 mg/kg up to a maximum of 12.5 mg IV given as a single dose approximately 15 minutes before the cessation of anesthesia or as soon as nausea or vomiting presents. The injection may also be given as an oral administration mixed in apple juice as 1.2 mg/kg up to a maximum 100 mg dose given within two hours before surgery. Safety and effectiveness in pediatric patients under 2 years of age has not been established.	
5-HT$_3$ Serotonin Antagonists Granisetron*	MEC and HEC: Adults: 2 mg QD PO 1 hour prior to chemotherapy OR 1 mg BID PO 1 hour prior to chemotherapy and then 12 hours later Adults: 10 mcg/kg IV infused over 30 seconds beginning 30 minutes prior to chemotherapy Children 2-16 years: 10 mcg/kg IV prior to chemotherapy Safety and effectiveness in pediatric patients under 2 years of age has not been established.	As specified by length of chemotherapy
5-HT$_3$ Serotonin Antagonists Granisetron*	Prevention of PONV: Adults: 1 mg IV infused over 30 seconds prior to induction of anesthesia or immediately before reversal of anesthesia. Treatment of PONV: Adults: 1mg administered IV over 30 seconds	Postoperative nausea and vomiting: One day
5-HT3 Serotonin Antagonists	MEC and HEC: Adults: Apply a single patch to the upper outer arm from 24 to 48 hours before	As specified by length of chemotherapy

Drug	Dosing Regimen	Dosing Limit/Maximum Dose
Sancuso® (granisetron)*	chemotherapy. Remove the patch a minimum of 24 hours after completion of chemotherapy. The patch can be worn for up to 7 days depending on the duration of chemotherapy regimen.	
NK_1 Receptor Antagonist Emend® (aprepitant)*	MEC and HEC: 125 mg PO 1 hour prior to chemotherapy and 80 mg on Day 2, 3 Emend 115 mg IV may be substituted for Emend 125 mg PO 30 minutes prior to chemotherapy on day 1 only if the CINV regimen as an infusion administered over 15 minutes.	1 x 125 mg capsule (or 1 x 115mg IV) and 2 x 80 mg capsules per cycle
NK_1 Receptor Antagonist Emend® (aprepitant)*	Prevention of PONV: 40 mg PO within 3 hours prior to induction of anesthesia	Prevention of postoperative nausea and vomiting: One day
Oral Corticosteroids Dexamethasone (Decadron®)	20 mg PO (pre-chemotherapy) and 8 mg PO daily on Day 2, 3 various chemotherapy dosage regimens	40mg/day
Phenothiazines Promethazine (Phenergan®)	Oral, Rectal, IM: 12.5 mg-25 mg q4-6 hours prn	100 mg/day
Phenothiazines Prochlorperazine (Compazine®)	Oral: 5-10 mg PO q 6-8 hours Rectal: 25 mg q12 hours IM: 5-10 mg initially, repeat q 3-4 hours prn	40 mg/day
Benzodiazepines Lorazepam (Ativan®)	0.5-2 mg PO or IV q 4-6 hours prn various chemotherapy dosage regimens	10mg/day

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.
*****Requires prior authorization

V. Dosage and Administration

Zofran		
Indication	**Dosing Regimen**	**Maximum Dose**
moderately emetogenic cancer chemotherapy (MEC)	Adults and children 12 years and older: 8 mg PO BID administered 30 minutes before the start of chemotherapy, with a subsequent dose 8 hours after the first dose; continue 8 mg BID for 1 to 2 days after completion of chemotherapy Adults: Three 0.15 mg/kg IV doses up to a maximum of 16 mg per dose. The first dose is infused over 15 minutes beginning 30 minutes before the start of chemotherapy and subsequent doses are administered 4 and 8 hours after the first dose. Children 4-11 years: 4 mg PO TID administered 30 minutes before the start of chemotherapy, with subsequent doses 4 and 8 hours after the first dose; continue 4 mg TID for 1 to 2 days after completion of chemotherapy Children 6 months-18 years: Three 0.15 mg/kg IV doses up to a maximum of 16 mg per dose. The first dose is administered 30 minutes before the start of chemotherapy, with subsequent doses 4 and 8 hours after the first dose. Each dose is infused IV over 15 minutes.	Adults: 24 mg/day PO; 0.45 mg/kg/day IV (in 3 divided doses, max single dose = 16 mg IV) Children: *< 4 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). Safety and efficacy have not been established for PO formulation. *4—11 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). 12 mg/day PO. *>= 12 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). 16 mg/day PO.

highly emetogenic cancer chemotherapy (HEC)	Adults: 24 mg (given as three 8 mg tablets) PO administered 30 minutes before the start of single-day chemotherapy. Use for multi-day, single-dose administration of 24 mg not established. Adults: Three 0.15 mg/kg IV doses up to a maximum of 16 mg per dose. The first dose is infused over 15 minutes beginning 30 minutes before the start of chemotherapy and subsequent doses are administered 4 and 8 hours after the first dose. Children 6 months-18 years: Three 0.15 mg/kg IV doses up to a maximum of 16 mg per dose. The first dose is administered 30 minutes before the start of chemotherapy, with subsequent doses 4 and 8 hours after the first dose. Each dose is infused IV over 15 minutes.	Adults: 24 mg/day PO; 0.45 mg/kg/day IV (in 3 divided doses, max single dose = 16 mg IV) Children: *< 4 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). Safety and efficacy have not been established for PO formulation. *4—11 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). 12 mg/day PO. *>= 12 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). 16 mg/day PO.
nausea and vomiting associated with radiotherapy (RINV)	Total body irradiation: Adults: 8 mg PO given 1 to 2 hours before each fraction of radiotherapy administered each day. Single high dose fraction radiotherapy to the abdomen therapy: Adults: 8 mg PO given 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose; continue 1 to 2 days after completion of radiotherapy. Daily fractionated radiotherapy to the abdomen	24 mg/day PO

	therapy: Adults: 8 mg PO given 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given	
Prevention of postoperative nausea and/or vomiting (PONV)	Adults: 16 mg (given as two 8-mg tablets) PO 1 hour before induction of anesthesia Adults: 4 mg undiluted IV infused over 2 to 5 minutes immediately before induction of anesthesia or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively, 4 mg undiluted may be administered intramuscularly as a single injection. Children 1 month–12 years: 0.1 mg/kg IV dose (for patients weighing 40kg or less) or 4 mg IV dose (for patients weighing more than 40 kg) infused over 2 to 5 minutes immediately before or following induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery.	Adults: 24 mg/day PO; 0.45 mg/kg/day IV (in 3 divided doses, max single dose = 16 mg IV) Children: *< 4 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). Safety and efficacy have not been established for PO formulation. *4—11 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). 12 mg/day PO. *>= 12 years:* 0.15 mg/kg/dose IV (Max: 16 mg/dose). 16 mg/day PO.
Hyperemesis due to pregnancy	8 mg PO every 8 hours as needed	24 mg/day PO

Zuplenz		
Indication	**Dosing Regimen**	**Maximum Dose**
highly emetogenic cancer chemotherapy (HEC)	Adults and children 12 years and older: One 8 mg PO film 30 minutes before chemotherapy followed by an 8mg PO dose 8 hours later. Administer one 8mg PO film BID (every 12 hours) for 1 to	24 mg/day PO

	2 days after completion of chemotherapy Children 4-11 years: one 4 mg PO film TID. Administer the first dose 30 minutes before chemotherapy, with subsequent doses of 4 and 8 hours later. Administer one 4mg PO film TID (every 8 hours) for 1 to 2 days after completion of chemotherapy	
highly emetogenic cancer chemotherapy (HEC)	Adults: 24mg PO given successively as three 8mg films 30 minutes before the start of chemotherapy	24 mg/day PO
nausea and vomiting associated with radiotherapy (RINV)	Adults: one 8mg PO film TID	24 mg/day PO
Prevention of postoperative nausea and/or vomiting (PONV)	Adults:16mg PO given successfully as two 8mg films 1 hour before anesthesia	24 mg/day PO

Ondansetron ODT		
Indication	**Dosing Regimen**	**Maximum Dose**
Pediatric gastroenteritis	Gastroenteritis - Vomiting: (body weight 8 to 15 kg) 2 mg, (body weight 15 to 30 kg) 4 mg, and (body weight over 30 kg) 8 mg (0.13 to 0.26 mg/kg), dissolved orally on the tongue usually as a single dose	8 mg/day

VI. Product Availability

Drug	Availability
Zofran	Tablet: 4 mg, 8 mg Orally disintegrating Tablet (ODT): 4 mg, 8 mg Oral Solution: 4 mg/5 ml (50 ml bottle) Injection: 2 mg/ml (20 ml multidose vial)
Zuplenz	Oral soluble film: 4 mg, 8 mg (package size 10)

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Minor changes to verbiage and grammar. References updated.	01.11.17	11.17

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.