TEXAS Health and Human Services

Medicaid Drug Use Criteria

Serotonin 5-HT3 Receptor Antagonists for Nausea and Vomiting (Oral)

- Developed in September 1996.
- Revised September 2020; July 2018; September 2016; June 2015; October 2013; November 2011; September 2011; October 2009; December 2005; August 2003; July 2002; July 2001; August 2000; August 1999; July 1998; July 1997.

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; the prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

Prepared by:

- Drug Information Service, UT Health San Antonio
- The College of Pharmacy, the University of Texas at Austin

1 Dosage

1.1 Adults

Serotonin 5-HT_3 receptor antagonists are FDA-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea

and vomiting (RINV), and postoperative nausea and vomiting (PONV). Although not FDA-approved, these agents have also been utilized in the treatment of opioid-induced nausea, nausea and vomiting of pregnancy (hyperemesis gravidarum), and acute pediatric gastroenteritis. The American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the use of 5-HT_3 receptor antagonists in conjunction with dexamethasone, a neurokinin 1 (NK_1) receptor antagonist, and olanzapine to manage nausea and vomiting associated with highly emetogenic chemotherapy, and a 5-HT_3 receptor antagonist combined with dexamethasone and/or an NK_1 receptor antagonist for control of nausea and vomiting associated with moderately emetogenic chemotherapy. A single dose of a 5-HT_3 receptor antagonist or dexamethasone is recommended for use with low emetic risk chemotherapy regimens, while no antiemetic is recommended for use with chemotherapy regimens having minimal emetic risk. 5-HT_3 receptor antagonists are no longer recommended for use to control delayed emesis associated with highly emetogenic chemotherapy. ASCO also recommends 5-HT_3 receptor antagonist use—often in conjunction with dexamethasone—to manage nausea and vomiting associated with low, moderate, and high emetic risk radiation therapy. A combination product containing palonosetron, a serotonin 5-HT_3 receptor antagonist that prevents nausea in the acute phase, and netupitant, a selective substance P selective neurokinin 1 receptor antagonist, that prevents nausea and vomiting in both the acute and delayed phases, has been approved for use with both moderately and highly emetogenic chemotherapy in adults. Recommended FDA-approved dosage regimens for the available serotonin 5-HT_3 receptor antagonists are summarized in Tables 1 & 2. Dosages exceeding these recommendations will be reviewed.

Table 1. Maximum Recommended Oral Dosage Regimens for Serotonin 5-HT_3 Receptor Antagonist Monotherapy in Adults

Drug Name	Dosage Form / Strength	Recommended Dosage Regime - CINV	Recommended Dosage Regimen - PONV	Recommended Dosage Regimen - RINV
dolasetron	50 mg, 100 mg tablets (Anzemet®)	Moderately emetogenic: 100 mg*	---	---

Drug Name	Dosage Form / Strength	Recommended Dosage Regime - CINV	Recommended Dosage Regimen - PONV	Recommended Dosage Regimen - RINV
granisetron (generic)	1 mg tablet	Moderately or highly emetogenic: 2 mg daily (as a single dose or divided by 12 hours; only on days chemotherapy given)*	---	2 mg once daily*
granisetron	3.1 mg/24 hrs transdermal patch (Sancuso®)	Moderately or highly emetogenic: 3.1 mg/24 hrs (one patch) per seven days***	---	---
ondansetron	4 mg, 8 mg, 24 mg tablets (generic, Zofran®) 4 mg, 8 mg orally-disintegrating tablets (generic, Zofran® ODT) 4 mg/5 mL oral solution (generic, Zofran®) 4 mg, 8 mg oral film (Zuplenz®)	Moderately emetogenic: 8 mg twice daily* Highly emetogenic: 24 mg (single dose)†	16 mg (tablet or ODT)*	Usual: 8 mg three times daily Total body irradiation: 8 mg (on days radiotherapy given)** Single high-dose fraction to the abdomen: 8 mg**†† Daily fractions to the abdomen: 8 mg**†††

- * Doses should be administered within 1 hour before chemotherapy, radiation, or induction of anesthesia
- ** Doses should be administered within 2 hours before surgery or radiation
- *** Patch should be applied within 24 to 48 hours before chemotherapy begins and removed a minimum of 24 hours after therapy completion; patch can be worn for up to 7 days depending on the duration of chemotherapy
- † Doses should be given 30 minutes before the start of single-day therapy
- ≠ First dose should be given 30 minutes before the start of chemotherapy, with a second dose 8 hours after the first dose, followed by 8 mg twice daily (every 12 hours) continued for 1 to 2 days after completion of chemotherapy
- †† Subsequent doses should be given every 8 hours after the first dose and continued for 1 to 2 days after completion of radiotherapy

- ††† Subsequent doses should be given every 8 hours after the first dose each day radiotherapy is given

Table 2. Maximum Recommended Oral Dosage Regimens for Serotonin 5-HT$_3$ Receptor Antagonist Combination Therapy in Adults

Drug Name	Dosage Form / Strength	Recommended Dosage Regimen - CINV	Recommended Dosage Regimen - PONV	Recommended Dosage Regimen - RINV
netupitant/ palonosetron (Akynzeo®)	300 mg netupitant/ 0.5 mg palonosetron capsules	Moderate to highly emetogenic: 300 mg netupitant/ 0.5 mg palonosetron (1 capsule)*+	---	---

- * Doses should be administered within 1 hour before chemotherapy, radiation, or induction of anesthesia
- + For highly emetogenic chemotherapy, given concurrently with dexamethasone on days 1-4; with moderately emetogenic chemotherapy, given concurrently with dexamethasone on day 1

1.2 Pediatrics

Table 3 summarizes the current pediatric FDA-approved indications and dosages of the available serotonin 5-HT$_3$ receptor antagonists. In the pediatric population, aprepitant is the recommended NK$_1$ receptor antagonist for highly and moderately emetogenic chemotherapy, while ondansetron is the recommended oral 5-HT$_3$ receptor antagonist for low emetogenic chemotherapy. Dolasetron and ondansetron are the only oral serotonin 5-HT$_3$ receptor antagonists FDA-approved for the prevention of CINV in children. Currently, there are no oral 5-HT$_3$ receptor antagonists approved for preventing PONV in children. Dolasetron is approved for use in children greater than 2 years of age; safety and efficacy in children less than 2 years of age have not been established. Ondansetron is approved for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in children 4 years of age and older. There are no data available addressing the use of 24 mg ondansetron tablets for highly emetogenic chemotherapy in children. The safety and efficacy of granisetron in children less than 18 years of age have not been established. Netupitant/palonosetron combination therapy is not approved in pediatric patients as safety and efficacy data are not available for this agent in this patient population. No data are available

evaluating serotonin 5-HT_3 receptor antagonists for the use of RINV in pediatric patients.

Table 3. Maximum Recommended Oral Pediatric Dosages for Serotonin 5-HT_3 Receptor Antagonists

Drug Name	Dosage Form / Strength	Recommended Dosage Regimen - CINV	Recommended Dosage Regimen - PONV	Recommended Dosage Regimen - RINV
dolasetron	50 mg, 100 mg tablets (Anzemet®)	Moderately emetogenic: 2-17 years old: 1.8 mg/kg, not to exceed 100 mg*	---	---
ondansetron	4 mg, 8 mg, 24 mg tablets (generic, Zofran®) 4 mg, 8 mg orally-disintegrating tablets (generic, Zofran® ODT 4 mg/5 mL oral solution (generic, Zofran®) 4 mg, 8 mg oral film (Zuplenz®)	Moderately emetogenic: Greater than or equal to 12 years old: 8 mg twice daily** 4-11 years old: 4 mg three times daily†	---	---

- * Doses should be administered within 1 hour before chemotherapy.
- ** The first dose should be given 30 minutes before the start of chemotherapy, with a second dose 8 hours after the first dose, followed by 8 mg twice daily (every 12 hours) continued for 1 to 2 days after completion of chemotherapy
- † The first dose should be given 30 minutes before the start of chemotherapy, with subsequent doses 4 and 8 hours after the first dose, followed by 4 mg three times daily (every 8 hours) continued for 1 to 2 days after completion of chemotherapy

2 Duration of Therapy

Nausea and vomiting are common side effects of cancer-chemotherapy and radiation therapy. Treatment is usually intermittent and dependent on the emetogenicity of the scheduled therapy. Patient profiles documenting the use of oral serotonin 5-HT_3 receptor antagonists without concurrent antineoplastic therapy will be reviewed. Patient profiles documenting the use of more than one transdermal granisetron (Sancuso®) patch per 7 days will be reviewed. The maximum duration for most cancer chemotherapy regimens is 30 days, although some chemotherapy protocols may last longer. Radiation therapy protocols for some patients may last for six to seven weeks. Unless otherwise specified, 5-HT_3 receptor antagonist treatment regimens continuing for greater than 49 days will be reviewed for the appropriateness of use. Approximately one-third of surgical patients experience nausea and vomiting after receiving general anesthesia. A single dose of a serotonin 5-HT_3 receptor antagonist is usually administered one to two hours before the induction of anesthesia.

3 Duplicative Therapy [*]

The use of two or more serotonin 5-HT_3 receptor antagonists concurrently is not justified due to the potentially increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest). There are no additional therapeutic benefits when serotonin 5-HT_3 receptor antagonists are used in combination. Patient profiles documenting receipt of multiple serotonin 5-HT_3 receptor antagonists will be reviewed.

4 Drug-Drug Interactions [*]

Patient profiles will be reviewed to identify those drug regimens which may result in clinically significant drug-drug interactions. The following drug-drug interactions summarized in Table 4 are considered clinically relevant for serotonin 5-HT_3 receptor antagonists. Only those drug-drug interactions classified as clinical

significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 4. Major Drug-Drug Interactions for Serotonin $5HT_3$ Receptor Antagonists

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
dolasetron, granisetron, ondansetron, palonosetron	QTc interval-prolonging medications (e.g., class Ia anti-arrhythmic agents†, class III anti-arrhythmic agents††, erythromycin, gemifloxacin, ziprasidone, tricyclic antidepressants, phenothiazines, pimozide)	increased risk of cardiotoxicity (QTc prolongation, torsades de pointes, cardiac arrest) due to the potential for additive QT interval prolongation	monitor for interaction; alternative drug therapy may be preferred	contraindicated, major (DrugReax) 1-severe, 2-major (CP)
dolasetron, granisetron, ondansetron, palonosetron	apomorphine	potential for profound hypotension and loss of consciousness due to additive hypotensive effects	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)
dolasetron, granisetron, ondansetron, palonosetron	serotonergic agents	potential for serotonin syndrome with combined therapy due to additive serotonergic effects	monitor for signs/ symptoms of serotonin syndrome (e.g., hyperthermia, hypertension, rigidity) and discontinue combined therapy, if symptoms present	major (DrugReax) 2-major (CP)

- † Class Ia anti-arrhythmic agents include quinidine, disopyramide, procainamide
- †† Class III anti-arrhythmic agents include amiodarone, sotalol, dofetilide
- * CP = Clinical Pharmacology

5 References

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