



# Texas Medicaid/CHIP Vendor Drug Program

## Drug Utilization Criteria For Outpatient Use Guidelines

### Oral Serotonin 5-HT<sub>3</sub> Receptor Antagonists for Nausea and Vomiting

#### About

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; 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.

#### Publication History

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#### 1. Dosage [\*]

##### *Adults*

Serotonin 5-HT<sub>3</sub> receptor antagonists are FDA-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea and vomiting (RINV), and post-operative 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<sub>3</sub> receptor antagonists in conjunction with aprepitant and dexamethasone to manage nausea and vomiting associated with highly emetogenic chemotherapy, and a 5-HT<sub>3</sub> receptor antagonist combined with dexamethasone for control of nausea and vomiting associated with moderately emetogenic chemotherapy. 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<sub>3</sub> receptor antagonists are no longer recommended for use to control delayed emesis associated with highly emetogenic chemotherapy. ASCO also recommends 5-HT<sub>3</sub> receptor antagonist use to manage nausea and vomiting associated with low, moderate, and high emetic risk radiation therapy. **A combination product containing palonosetron, a serotonin 5-HT<sub>3</sub> 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<sub>3</sub> receptor antagonists are summarized in Table 1. Dosages exceeding these recommendations will be reviewed.



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**Table 1: Maximum Recommended Oral Dosage Regimens for Serotonin 5-HT<sub>3</sub> Receptor Antagonists in Adults**

Drug	Dosage Form	Recommended Dosage Regimen		
		CINV	PONV	RINV
<b>Monotherapy</b>				
dolasetron	tablets (Anzemet®) - 50 mg, 100 mg	<i>moderately emetogenic:</i> 100 mg*	--	---
granisetron	tablets (generic) - 1 mg	<i>moderately or highly emetogenic:</i> 2 mg* daily (as a single dose or divided by 12 hours; only on days chemotherapy given)	---	2 mg once daily*
	transdermal patch (Sancuso®) - 3.1 mg/24 hrs	<i>moderately or highly emetogenic:</i> 3.1 mg/24 hrs*** (one patch per 7 days)	---	---
ondansetron	tablets (Zofran®, generic) - 4 mg, 8 mg, 24 mg orally-disintegrating tablets (Zofran® ODT, generic) - 4 mg, 8 mg oral solution (Zofran®, generic) - 4 mg/5mL oral film (Zuplenz®) - 4 mg, 8 mg	<i>highly emetogenic:</i> 24 mg <sup>†</sup> (single dose) <i>moderately emetogenic:</i> 8 mg twice daily <sup>‡</sup>	16 mg as tablet or ODT*	<i>usual:</i> 8 mg three times daily <i>total body irradiation:</i> 8 mg** (on days radiotherapy given) <i>single high-dose fraction to the abdomen:</i> 8 mg*** <i>daily fractions to the abdomen:</i> 8 mg****
<b>Combination Therapy</b>				
netupitant/ palonosetron	300 mg netupitant/ 0.5 mg palonosetron capsules (Akynzeo®)	<i>moderate to highly emetogenic:</i> 1 capsule**	--	--

\*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

\* For highly emetogenic chemotherapy, given concurrently with dexamethasone on days 1-4; with moderately emetogenic chemotherapy, given concurrently with dexamethasone on day 1



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*Pediatrics*

Table 2 summarizes the current pediatric FDA-approved indications and dosages of the available serotonin 5-HT<sub>3</sub> receptor antagonists. Dolasetron and ondansetron are the only serotonin 5-HT<sub>3</sub> receptor antagonists FDA-approved for the prevention of CINV in children, and dolasetron is the only agent approved for use in prevention of 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. 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<sub>3</sub> receptor antagonists for the use of RINV in pediatric patients.

Table 2: Maximum Recommended Oral Pediatric Dosages for Serotonin 5-HT <sub>3</sub> Receptor Antagonists			
Drug	Recommended Dosage Regimen		
	CINV	PONV	RINV
dolasetron	<i>moderately emetogenic:</i> 2-17 years of age: <b>1.8 mg/kg*</b>	100 mg**	---
ondansetron	<i>moderately emetogenic:</i> ≥ 12 years of age: 8 mg twice daily*** 4-11 years of age: 4 mg three times daily†	---	---

\*Doses should be administered within 1 hour before chemotherapy or induction of anesthesia.

\*\*Doses should be administered within 2 hours before surgery.

\*\*\*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<sub>3</sub> 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<sub>3</sub> receptor antagonist treatment regimens continuing for greater than 49 days will be reviewed for 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<sub>3</sub> receptor antagonist is usually administered one to two hours before the induction of anesthesia.



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**3. Duplicative Therapy [\*]**

The use of two or more serotonin 5-HT<sub>3</sub> 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<sub>3</sub> receptor antagonists are used in combination. Patient profiles documenting receipt of multiple serotonin 5-HT<sub>3</sub> 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 3 are considered clinically relevant for serotonin 5-HT<sub>3</sub> 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 3: Major Drug-Drug Interactions for Serotonin 5-HT<sub>3</sub> Receptor Antagonists**

Target Drug	Interacting Drug	Interaction	Recommendations	Clinical Significance*
dolasetron, granisetron, ondansetron, <b>palonosetron</b>	QTc interval-prolonging medications (e.g., class Ia anti-arrhythmic agents <sup>†</sup> , class III anti-arrhythmic agents <sup>††</sup> , erythromycin, gemifloxacin, ziprasidone, tricyclic antidepressants, phenothiazines, pimozone)	increased risk of cardiotoxicity (QTc prolongation, torsades de pointes, cardiac arrest) due to 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	apomorphine	potential for profound hypotension and loss of consciousness due to additive hypotensive effects	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)

\*Clinical Pharmacology

<sup>†</sup>Class Ia anti-arrhythmic agents include quinidine, disopyramide, procainamide

<sup>††</sup>Class III anti-arrhythmic agents include amiodarone, sotalol, dofetilide

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**Prepared by**

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