Texas Vendor Drug Program

1.1 Drug Use Criteria: Substance P/Neurokinin1 Receptor Antagonists

Publication History

1. Developed December 2003.
2. Revised **September 2020;** September 2018; September 2016; May 2015; August 2013; June 2013; September 2011; October 2009; February 2006; January 2006.

Notes: 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.

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

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1 Dosage [*]

Current therapies for chemotherapy-induced nausea/vomiting (CINV) and post-operative nausea and vomiting (PONV) target corticosteroid, dopamine, and serotonin (5-HT3) receptors. In the central nervous system, tachykinins and neurokinins play a role in some autonomic reflexes and behaviors. Aprepitant is a selective human substance P/neurokinin 1 (NK1) antagonist with a high affinity for NK1 receptors and little, if any, attraction for corticosteroid, dopamine, or 5-HT3 receptors. Rolapitant (Varubi®), the newest substance P/NK1 antagonist, is FDA-approved to prevent delayed CINV with initial and repeat chemotherapy courses including, but not limited to, highly emetogenic chemotherapy in adults. Combination therapy including netupitant, a substance P/NK1 antagonist and palonosetron, a selective 5-HT3 receptor antagonist (Akynzeo®), is now available to prevent acute and delayed CINV with initial and repeat chemotherapy courses including, but not limited to, highly emetogenic chemotherapy in adults.

1.1 Adults

Aprepitant is FDA-approved for prevention of CINV due to high and moderate emetogenic agents including high dose cisplatin, as well as prevention for PONV. When used to prevent CINV with highly emetogenic chemotherapy, aprepitant is prescribed as triple therapy in combination with a 5-HT3 receptor antagonist and corticosteroids based on clinical trial data as well as data from available published anti-emetic guidelines showing more significant reductions in acute emesis on day 1 of chemotherapy and decreased incidence of delayed emesis with the addition of aprepitant. Rolapitant is indicated to manage delayed CINV seen with initial and repeat courses of chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Netupitant (substance P/NK1 receptor antagonist) and palonosetron (selective 5-HT3 receptor antagonist), as combination therapy, are FDA-approved to prevent acute and delayed CINV seen with initial and repeat courses of chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Palonosetron targets CINV in the acute phase while netupitant prevents CINV in both the acute and delayed phases. Maximum recommended adult dosages for substance P/NK1 receptor antagonists are summarized in Tables 1 & 2. Dosages exceeding those listed in Tables 1 & 2 will be reviewed.

Table 1. Maximum Recommended Adult Oral Substance P/Neurokinin 1 Receptor Antagonist Monotherapy Dosages

Drug Name	Treatment Indication	Dosage Form / Strength	Maximum Recommended Dosage
aprepitant (Emend®)	preventing CINV: *highly or moderately emetogenic chemotherapy:* • day 1 (one hour before chemotherapy)	40 mg, 80 mg, 125 mg capsules 125 mg/5 ml oral suspension	125 mg/day (as capsule or suspension)*
	preventing CINV: *highly or moderately emetogenic chemotherapy:* • days 2 and 3		80 mg/day (as capsule or suspension)+
	PONV: within 3 hours of anesthesia induction		40 mg as a single dose (as capsule)
rolapitant (Varubi®)	preventing delayed CINV seen with highly emetogenic chemotherapy	90 mg tablet	180 mg as a single dose 1 to 2 hours before chemotherapy on day 1 (2 x 90 mg tablets)^
	preventing delayed CINV seen with non-highly emetogenic chemotherapy		180 mg as a single dose 1 to 2 hours before chemotherapy on day 1 (2 x 90 mg tablets)#

**in conjunction with a 5-HT3 receptor antagonist plus dexamethasone*
+in conjunction with dexamethasone on days 2-3; dexamethasone also given on day 4
^in conjunction with dexamethasone and a 5-HT3 receptor antagonist on day 1, and dexamethasone on days 2-4
#in conjunction with dexamethasone and a 5-HT3 receptor antagonist on day 1, and a 5-HT3 receptor antagonist on days 1-4
CINV = chemotherapy-induced nausea and vomiting
PONV = postoperative nausea and vomiting

Table 2. Maximum Recommended Adult Oral Substance P / Neurokinin 1 Receptor Antagonist Combination Therapy Dosages

Drug Name	Treatment Indication	Dosage Form / Strength	Maximum Recommended Dosage
netupitant/ palonosetron (Akynzeo®)	preventing acute and delayed CINV seen with chemotherapy (highly emetogenic)	300 mg netupitant/ 0.5 mg palonosetron capsules	1 capsule on day 1 (one hour before chemotherapy)**
	preventing acute and delayed CINV seen with chemotherapy (NOT highly emetogenic)	300 mg netupitant/ 0.5 mg palonosetron capsules	1 capsule on day 1 (one hour before chemotherapy)++

**in conjunction with dexamethasone 30 minutes before chemotherapy on day 1, and dexamethasone once daily on days 2-4*
++*in conjunction with dexamethasone 30 minutes before chemotherapy on day 1*
CINV = chemotherapy-induced nausea and vomiting

1.2 Pediatrics

Aprepitant capsules are FDA-approved for use in children and adolescents 12 years of age and older to prevent nausea and vomiting associated with initial and repeat courses of moderately to highly emetogenic chemotherapy (includes high-dose cisplatin). Aprepitant oral suspension is FDA-approved to prevent acute and delayed nausea and vomiting seen with initial and repeat courses of highly emetogenic chemotherapy (includes high-dose cisplatin) as well as nausea and vomiting associated with moderately emetogenic chemotherapy in pediatric patients 6 months of age and to 11 years of age weighing at least 6 kg or pediatric patients of any age weighing at least 6 kg who cannot swallow capsules. Rolapitant is not yet approved for use in pediatric patients as safety and efficacy have not been established. Combination therapy with netupitant and palonosetron is not FDA-approved in patients < 18 years of age as safety and efficacy have not been established in this patient population. Pediatric aprepitant dosages are summarized in Table 3. Aprepitant dosages exceeding these recommendations in pediatric patients will be reviewed.

Table 3. Maximum Recommended Oral Aprepitant Dosages in Pediatric Patients

Treatment Indication	Patient Characteristics	Usual Dosage/Dosage Form	Maximum Recommended Dosage
CINV: Moderate **to highly** emetogenic chemotherapy – day 1	6 months to < 12 years (at least 6 kg)	3 mg/kg on day 1 (as suspension)*+	125 mg on day 1
CINV: Moderate **to highly** emetogenic chemotherapy – days 2 and 3	6 months to < 12 years (at least 6 kg)	2 mg/kg on days 2 and 3 (as suspension)*+	80 mg on days 2 and 3
CINV: Moderate **to highly** emetogenic chemotherapy – day 1	pediatric patients any age (at least 6 kg) unable to swallow capsules	3 mg/kg on day 1 (as suspension)*+	125 mg on day 1
CINV: Moderate **to highly** emetogenic chemotherapy – days 2 and 3	pediatric patients any age (at least 6 kg) unable to swallow capsules	2 mg/kg on days 2 and 3 (as suspension)*+	80 mg on days 2 and 3
moderately to highly emetogenic chemotherapy – day 1	> 12 years of age	125 mg on day 1 one hour before chemotherapy (as capsule)*+	125 mg on day 1
moderately to highly emetogenic chemotherapy – days 2 and 3	> 12 years of age	80 mg on days 2 and 3 (as capsule)*+	80 mg on days 2 and 3

**in conjunction with a 5-HT3 receptor antagonist plus dexamethasone on day 1*
+in conjunction with dexamethasone on days 2-3; dexamethasone also given on day 4

2 Duration of Therapy

The maximum treatment duration for aprepitant is three days per chemotherapy cycle for moderately or highly emetogenic chemotherapy regimens. The maximum treatment duration for rolapitant and netupitant/palonosetron is one day for each chemotherapy cycle in conjunction with corticosteroids; 5-HT3 receptor antagonists are also administered concurrently with rolapitant. Chemotherapy regimens are administered for one to several days within a 30-day time period and repeated in

cycles. The number of cycles varies based on the type of cancer being treated. Unless otherwise specified, aprepitant treatment regimens continuing for greater than three days per chemotherapy cycle and rolapitant and netupitant/palonosetron treatment regimens continuing for longer than one day per chemotherapy cycle will be reviewed for appropriateness of use.

3 Duplicative Therapy [*]

Aprepitant is the first medication in the class of selective human substance P/NK1 antagonists. Fosaprepitant, the injectable aprepitant formulation, was indicated for use on day 1 of the chemotherapy cycle as the 115 mg dose with oral aprepitant administered on days 2 and 3; however, the 115 mg vial is no longer commercially available. Fosaprepitant 150 mg injection is not administered with oral aprepitant on any treatment days. Dosage regimens incorporating concurrent use of fosaprepitant 150 mg and aprepitant will be reviewed. Concurrent administration of selective human substance P/NK1 receptor antagonists is not supported in the literature and may result in enhance adverse pharmacologic effects. Additionally, combined use of oral rolapitant or netupitant/palonosetron is not indicated and may result in increased adverse effects. Combined use of substance P/NK1 receptor antagonists or adjunctive use of oral and parenteral substance P/NK1 receptor antagonist formulations is not recommended and will be reviewed.

4 Drug-Drug Interactions [*]

Patient profiles will be monitored to identify regimens that may have clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for substance P/NK1 receptor antagonists are summarized in Table 4. Only those interactions classified as clinical significance level 1, contraindicated, or life threatening which have not been classified will be reviewed.

Table 4. Substance P/NK1 Receptor Antagonist Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
aprepitant	CYP3A4 inducers (e.g., carbamazepine, rifampin)	adjunctive use may induce aprepitant metabolism and potential for reduced aprepitant serum levels and decreased aprepitant efficacy; CYP3A4 inducer activity may also be reduced, as aprepitant is also a CYP3A4 inducer	monitor patients for aprepitant efficacy; if needed, modify aprepitant dose or choose alternative anti-emetic without CYP3A4 inducer interaction; monitor CYP3A4 inducer activity and adjust dose as necessary	moderate (DrugReax) 3-moderate (CP)
aprepitant	CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, nefazodone, clarithromycin, ritonavir)	combined use may result in reduced aprepitant metabolism, increased serum aprepitant levels, and the potential for adverse effects; however, aprepitant appears to be tolerated over a wide dosage range and is prescribed for short time periods	clinical significance of interaction not well defined; observe patients for increased aprepitant adverse effects and adjust dose if necessary	major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
aprepitant	CYP3A4 substrates (e.g., aripiprazole, colchicine, diltiazem, phenytoin, ranolazine, ziprasidone)	combined use may result in elevated substrate plasma levels and potential for toxicity or loss of efficacy, as aprepitant is known CYP3A4 inhibitor and inducer and may interfere with metabolism of medications metabolized by CYP3A4	use aprepitant cautiously with compounds metabolized by CYP3A4; monitor patients carefully for signs/ symptoms of substrate toxicity or loss of efficacy and adjust substrate dose as necessary	major (DrugReax) 2-major, 3-moderate (CP)
aprepitant	oral contraceptives (OC)	adjunctive use may result in reduced OC efficacy as AUC for both estrogen and progestin components may be reduced	alternative or back-up methods of contraception recommended during time that aprepitant is prescribed and for one month following last aprepitant dose	moderate (DrugReax) 2-major (CP)
aprepitant	pimozide (Orap®)	co-use may result in elevated plasma pimozide levels and increased risk for cardiac arrhythmias, QT interval prolongation, as aprepitant inhibits CYP3A4 (enzyme for pimozide metabolism)	adjunctive use contraindicated	contraindicated (DrugReax) 1-severe (CP)
aprepitant	phenytoin	combined use may result in reduced phenytoin levels and potential loss of seizure control as aprepitant induces CYP2C9, the enzyme that metabolizes phenytoin	administer cautiously together; observe for loss of seizure control	moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
aprepitant	warfarin	co-administration may result in significant decreases in warfarin serum levels, INR and warfarin efficacy, as aprepitant induces CYP2C9, the enzyme involved in warfarin metabolism	monitor clotting status closely within 2-week period (especially 7 to 10 days) after each 3-day chemotherapy regimen or following single-dose therapy for PONV	major (DrugReax) 2-major (CP)
netupitant/ palonosetron (palonosetron component)	apomorphine (Apokyn®)	adjunctive administration may result in hypotension and loss of consciousness due to additive hypotensive effects	avoid combined use	contraindicated (DrugReax) 1-severe (CP)
netupitant/ palonosetron (netupitant component), rolapitant	strong CYP3A4 inducers (e.g., rifampin)	concurrent use may reduce netupitant, rolapitant efficacy with reduced serum levels due to CYP3A4-induced netupitant, rolapitant metabolism	avoid co-administration	major (DrugReax) 2-major (CP)
netupitant/ palonosetron (netupitant component)	CYP3A4 inhibitors	combined administration with strong CYP3A4 inhibitors may increase serum netupitant levels as netupitant is metabolized by CYP3A4; netupitant is CYP3A4 inhibitor and may increase concentrations of other medications	no netupitant dosage adjustment necessary due to single dose therapy; monitor for enhanced pharmacologic/ adverse effects and adjust dosages of other medications as necessary	3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
netupitant/ palonosetron (netupitant component)	CYP3A4 substrates	adjunctive use may result in enhanced substrate pharmacologic/ adverse effects as netupitant is CYP3A4 inhibitor and may increase concentrations of other medications	use cautiously together; monitor for enhanced pharmacologic/ adverse effects and adjust substrate dosages as necessary	moderate (DrugReax) 2-major, 3-moderate (CP)
netupitant/ palonosetron (netupitant component)	flibanserin (Addyi®)	combined use may lead to significant hypotension and syncope due to increased flibanserin serum levels as netupitant is moderate CYP3A4 inhibitor and flibanserin is CYP3A4 substrate	avoid concurrent use for 1 week, if possible; if combined use necessary, consider CYP3A4 substrate dose reduction	major (DrugReax) 1-severe (CP)
netupitant/ palonosetron (palonosetron component)	serotonergic agents	potential for serotonin syndrome with combined therapy due to additive serotonergic effects with palonosetron	monitor for signs/ symptoms of serotonin syndrome (e.g., hyperthermia, hypertension, rigidity) and discontinue combined therapy, if symptoms present	major (DrugReax) 2-major (CP)
rolapitant	breast cancer resistant protein (BCRP) substrates with narrow therapeutic index (e.g., methotrexate, topotecan)	combined use may increase BCRP substrate levels and potential for adverse effects as rolapitant is BCRP inhibitor	avoid use, if possible; if adjunctive use necessary, monitor for BCRP substrate adverse events	2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
rolapitant	p-glycoprotein substrates with narrow therapeutic index (e.g., digoxin)	combined use may increase p-glycoprotein substrate levels and potential for adverse effects as rolapitant is p-glycoprotein inhibitor	avoid use, if possible; if adjunctive use necessary, monitor for p-glycoprotein substrate adverse events	major (DrugReax) 3-moderate (CP)
rolapitant	pimozide	concurrent administration may increase risk of pimozide-associated QT interval prolongation/ torsades de pointes as pimozide metabolized by CYP2D6 and rolapitant is CYP2D6 inhibitor	avoid combined use, if possible; if concomitant use necessary, monitor for pimozide adverse effects	major (DrugReax) 1-severe (CP)
rolapitant	other CYP2D6 substrates	combined use may increase CYP2D6 substrate levels and potential for adverse effects as rolapitant is CYP2D6 inhibitor	use cautiously together; monitor for enhanced pharmacologic/ adverse effects and adjust substrate dosages as necessary	major (DrugReax) 2-major, 3-moderate (CP)
rolapitant	thioridazine	combined administration may increase risk of QT interval prolongation/ torsades de pointes with thioridazine as rolapitant CYP3A4 inhibitor and thioridazine CYP3A4 substrate	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)

**CP = Clinical Pharmacology*

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