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Subject: NK-1 receptor antagonist injectable therapy (Emend®, Cinvanti®, Varubi®)

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Chemotherapy-induced nausea and vomiting (CINV) can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy. The severity and incidence of CINV are affected by factors such as the selected agent and dose of chemotherapy, schedule and route of administration, and patient specific factors (e.g., age, sex, prior chemotherapy, history of alcohol use).

Neurokinin-1(NK-1) receptor antagonists block the binding of substance P at the NK-1 receptor in the central nervous system to prevent emesis. Fosaprepitant (Emend) injection is a prodrug of aprepitant that was the first injectable NK-1 receptor antagonist approved by the U.S. Food and Drug Administration (FDA) in 2008. Fosaprepitant is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy. In a randomized, double-blind study, fosaprepitant injection was shown to be non-inferior to a 3-day regimen of oral aprepitant in prevention of nausea and vomiting in patients receiving a highly emetogenic chemotherapy regimen that included cisplatin. Both treatment groups in the study received dexamethasone and ondansetron. Fosaprepitant injection is also FDA approved for prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. In a randomized, double-blind study, fosaprepitant injection, in combination with dexamethasone and ondansetron, was shown to more effectively control delayed nausea and vomiting as compared to ondansetron and dexamethasone alone in patients receiving a moderately emetogenic chemotherapy regimen. An injectable emulsion of aprepitant (Cinvanti) was FDA-approved in 2017 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly or moderate emetogenic chemotherapy. Aprepitant injectable emulsion demonstrated bioequivalence to fosaprepitant in healthy subjects in a cross-over study. An additional injectable NK-1 receptor antagonist, rolapitant (Varubi), was FDA approved in 2017 for the prevention of delayed nausea and vomiting associated with initial and repeat

courses emetogenic chemotherapy, including highly emetogenic chemotherapy. Rolapitant injectable emulsion demonstrated bioequivalence to the oral form of rolapitant in healthy subjects. In two separate randomized controlled trials, the oral form of rolapitant, in combination with granisetron and dexamethasone, demonstrated significantly more complete responses to control nausea and vomiting in the delayed phase following chemotherapy with moderate or high emetogenic potential as compared to granisetron and dexamethasone alone. National Comprehensive Cancer Network (NCCN) Guidelines for Antiemesis recommend NK1 receptor antagonist containing regimens (e.g., aprepitant, fosaprepitant, rolapitant, or netupitant) for acute and delayed emesis prevention in combination with dexamethasone and a serotonin antagonist with or without lorazepam, histamine-2 blockers, or proton pump inhibitors before intravenous antineoplastic therapy with high or moderate emetic risk. The use of fosaprepitant and aprepitant is also recommended in combination with olanzapine, dexamethasone, and a serotonin antagonist for high risk antineoplastic therapy. NCCN specifically states that use of NK1 receptor antagonists are for the prevention of CINV, not treatment of CINV.

POSITION STATEMENT:

- I. Fosaprepitant injection (Emend®) **meets the definition of medical necessity** when **ALL** of the following are met:
 1. Use is for prevention of acute or delayed chemotherapy-induced nausea and vomiting associated with initial or repeat courses of chemotherapy
 2. **ONE** of the following:
 - a. Chemotherapy has a moderate or high emetogenic potential (Table 1)
 - b. Chemotherapy has a low emetogenic potential (Table 1) and the member has an inadequate response or contraindication to use of a serotonin antagonist (i.e., ondansetron, dolasetron, granisetron, or palonosetron) to prevent chemotherapy-induced nausea and vomiting[‡]
 3. Use is in combination with a corticosteroid (i.e., dexamethasone) and a serotonin antagonist (i.e., ondansetron, dolasetron, granisetron, or palonosetron)* OR the member has a contraindication to corticosteroids or serotonin antagonist therapy
 4. The member is not receiving an additional NK1 receptor antagonist (e.g., aprepitant, rolapitant, netupitant)
 5. The dose does not exceed 150 mg and is given prior to chemotherapy

Duration of approval: 1 year

- II. Aprepitant injection (Cinvanti®) **meets the definition of medical necessity** when **ALL** of the following are met:
 1. Use is for prevention of acute or delayed chemotherapy-induced nausea and vomiting associated with initial or repeat courses of chemotherapy
 2. **ONE** of the following:
 - a. Chemotherapy has a moderate or high emetogenic potential (Table 1)
 - b. Chemotherapy has a low emetogenic potential (Table 1) and the member has an inadequate response or contraindication to use of a serotonin antagonist (i.e., ondansetron, dolasetron, granisetron, or palonosetron) to prevent chemotherapy-induced nausea and vomiting[‡]

3. Use is in combination with a corticosteroid (i.e., dexamethasone) and a serotonin antagonist (i.e., ondansetron, dolasetron, granisetron, or palonosetron)* OR the member has a contraindication to corticosteroids or serotonin antagonist therapy
4. The member is not receiving an additional NK1 receptor antagonist† (e.g., fosaprepitant, netupitant, rolapitant, oral aprepitant)
5. The dose does not exceed 130 mg and is given prior to chemotherapy

Duration of approval: 1 year

III. Rolapitant injection (Varubi®) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Use is for prevention of acute or delayed chemotherapy-induced nausea and vomiting associated with initial or repeat courses of chemotherapy
2. **ONE** of the following:
 - a. Chemotherapy has a moderate or high emetogenic potential (Table 1)
 - b. Chemotherapy has a low emetogenic potential (Table 1) and the member has an inadequate response or contraindication to use of a serotonin antagonist (i.e., ondansetron, dolasetron, granisetron, or palonosetron) to prevent chemotherapy-induced nausea and vomiting‡
3. Use is in combination with a corticosteroid (i.e., dexamethasone) and a serotonin antagonist (i.e., ondansetron, dolasetron, granisetron, or palonosetron)* OR the member has a contraindication to corticosteroids or serotonin antagonist therapy
4. The member is not receiving an additional NK1 receptor antagonist (e.g., aprepitant, fosaprepitant, netupitant, oral rolapitant)
5. The dose does not exceed 166.5 mg every 14 days and is given prior to chemotherapy

Duration of approval: 1 year

***Note:** Given with or without olanzapine, lorazepam, histamine-2 receptor blocker or proton pump inhibitor

†**Note:** Exception when aprepitant 100 mg IV is prescribed on day 1, followed by oral aprepitant on Day 2 and 3.

‡Step therapy requirement does not apply if the member was previously approved by Florida Blue or a prior health plan

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Emend

Fosaprepitant injection is indicated in adults, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin. It is also indicated in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Fosaprepitant has not been studied for the treatment of established nausea and vomiting.

The recommended dosing of fosaprepitant injection is 150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy in combination with dexamethasone and a 5HT3 antagonist.

Dose Adjustments

- There were no studies conducted in patients with severe hepatic impairment (Child-Pugh score greater than 9) thus additional monitoring for adverse reactions is recommended. No dose adjustment is necessary in patients with mild to moderate hepatic impairment.
- Drug Availability
- 150 mg single dose vial for reconstitution

Cinvanti

Aprepitant injectable emulsion is indicated in adults, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin. It is also indicated in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. It has not been studied for the treatment of established nausea and vomiting.

The recommended dosing of aprepitant injectable emulsion is the following:

- Highly emetogenic chemotherapy: 130 mg intravenously either by injection over 2 minutes or as an infusion (mixed with 100 ml of 0.9% sodium chloride) over 30 minutes on Day 1, completing the injection or infusion approximately 30 minutes prior to chemotherapy in combination with dexamethasone and a 5HT3 antagonist.
- Moderately emetogenic chemotherapy: 100 mg intravenously either by injection over 2 minutes or as an infusion (mixed with 100 ml of 0.9% sodium chloride) over 30 minutes on Day 1, completing the injection or infusion approximately 30 minutes prior to chemotherapy in combination with dexamethasone and a 5HT3 antagonist. Aprepitant capsules (80 mg) are given on day 2 and 3.

Dose Adjustments

- There were no studies conducted in patients with severe hepatic impairment (Child-Pugh score greater than 9) thus additional monitoring for adverse reactions is recommended. No dose adjustment is necessary in patients with mild to moderate hepatic impairment.

Drug Availability

- 130 mg single dose vial. See product label for dilution instructions.

Varubi

Rolapitant injectable emulsion is indicated in adults, in combination with other antiemetic agents, for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy, including, but not limited to, highly emetogenic cancer chemotherapy. It has not been studied for the treatment of established nausea and vomiting.

The recommended dosing of rolapitant injectable emulsion is 166.5 mg intravenously over 30 minutes within 2 hours prior to chemotherapy in combination with dexamethasone and a 5HT3 antagonist. Do not give more frequently than every 2 weeks.

Dose Adjustments

- There are no studies in patients with severe hepatic impairment (Child-Pugh score C) and use should be avoided. If use cannot be avoided, additional monitoring for adverse reactions is recommended. No dose adjustment is necessary in patients with mild to moderate hepatic impairment.

Drug Availability

- 166.5 mg/92.5 ml single dose vial

PRECAUTIONS:

Emend and Cinvanti

Contraindications

- Should not be administered to patients with known hypersensitivity to any component of the product.
- Should not be administered concurrently with pimozide due to a drug interaction that may result in increased plasma concentrations of pimozide and potentially life-threatening reactions, including QT prolongation.

Precautions/Warnings

- **Clinically Significant CYP3A4 Drug Interactions**— Fosaprepitant, a prodrug of aprepitant, is a weak inhibitor of CYP3A4, and aprepitant is a substrate, inhibitor, and inducer of CYP3A4. Use with other drugs that are CYP3A4 substrates, may result in increased plasma concentration of the concomitant drug. Use with strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, diltiazem) or strong CYP3A4 inducers (e.g., rifampin) may alter the plasma concentrations of aprepitant.
- **Hypersensitivity Reactions** – reactions including flushing, erythema, dyspnea, and anaphylaxis have been reported. Discontinue and do not reinitiate the infusion in patients who experience these symptoms.
- **Decrease in INR with Concomitant Warfarin** –Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant injection with each chemotherapy cycle
- **Risk of Reduced Efficacy of Hormonal Contraceptives** –the efficacy of hormonal contraceptives may be altered.
- **Infusion site reactions (Emend)** – reactions including thrombophlebitis, necrosis and vasculitis have occurred with the majority of reactions in patients receiving vesicant chemotherapy. Avoid infusion into small veins.

Varubi

Contraindications

- Should not be administered to patients with known hypersensitivity to any component of the product (including soybean oil).
- Should not be administered concurrently with CYP2D6 substrates with a narrow therapeutic index (e.g., thioridazine, pimozide) due to a drug interaction that may result in increased plasma concentrations and potentially life-threatening reactions, including QT prolongation and Torsades de Pointes.

Precautions/Warnings

- **Anaphylaxis, Anaphylactic Shock and other Hypersensitivity Reactions** – May occur during or soon after infusion. Discontinue and do not reinitiate the infusion in patients who experience these symptoms.
- **CYP2D6 substrates**— Rolapitant is a moderate inhibitor of CYP2D6 and increases the plasma concentrations of CYP2D6 substrates for at least 28 days following single dose administration of rolapitant. Avoid use with thioridazine and pimozide and see prescribing information for information regarding interactions with other CYP2D6 substrates.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0185	Injection, aprepitant, 1 mg
J1453	Injection, fosaprepitant 1mg
J2797	Injection, rolapitant, 0.5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

R11.0	Nausea
R11.10 – R11.12	Vomiting, unspecified
R11.2	Nausea with vomiting, unspecified
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs, subsequent encounter
T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs, sequela
T45.95XA	Adverse effect of unspecified primarily systemic and hematological agent, initial encounter
T50.905A	Adverse effect of unspecified drugs, medicaments and biological substances
Z51.11	Encounter for antineoplastic chemotherapy
Z51.12	Encounter for antineoplastic immunotherapy

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the guideline creation.

DEFINITIONS:

Acute chemotherapy-induced nausea and vomiting – nausea and/or vomiting that occurs within a few minutes to several hours after drug administration and commonly resolves within the first 24 hours.

Delayed chemotherapy-induced nausea and vomiting – nausea and/or vomiting that occurs 24 hours after drug administration.

RELATED GUIDELINES:

[Palonosetron Hydrochloride \(Aloxi®\), 09-J0000-87](#)

OTHER:

Table 1

Emetogenic Potential of Antineoplastic Agents		
	High emetic risk (>90% frequency of emesis)	Moderate emetic risk (30-90% frequency of emesis)
IV	AC combination (doxorubicin or epirubicin with cyclophosphamide) Carboplatin AUC > 4 Carmustine (>250 mg/m ²) Cisplatin Cyclophosphamide (> 1500 mg/m ²) Dacarbazine Doxorubicin (>60 mg/m ²) Epirubicin (>90 mg/ m ²) Ifosfamide (≥2 g/ m ²) Methotrexate Streptozocin	Aldesleukin (>12-15 million IU/m ²) Amifostine (>300 mg/m ²) Arsenic trioxide Azacitidine Bendamustine Busulfan Carboplatin AUC < 4 Carmustine (≤250 mg/m ²) Clofarabine Cyclophosphamide (≤1500 mg/m ²) Cytarabine (>200 mg/m ²) Dactinomycin Daunorubicin Dual-drug liposomal encapsulation of cytarabine and daunorubicin Dinutuximab Doxorubicin (<60 mg/m ²) Epirubicin (≤90 mg/m ²) Idarubicin

		Ifosfamide (< 2g/m ²) Interferon alfa (≥10 million IU/m ²) Irinotecan Irinotecan (liposomal) Melphalan Methotrexate (≥250 mg/m ²) Oxaliplatin Temozolomide Trabectedin
IV	Low emetic risk (10 – 30% frequency of emesis)	
	Ado-trastuzumab emtansine Aldesleukin <12 million international units/m ² Amifostine <300 mg/m ² Axicabtagene ciloleucel Belinostat Brentuximab vedotin Cabazitaxel Carfilzomib Copanlisib Cytarabine (low dose) 100 – 200 mg/m ² Docetaxel Doxorubicin (liposomal) Eribulin Etoposide 5-FU Floxuridine Gemcitabine Gemtuzumab ozogamicin Inotuzumab ozogamicin Interferon alfa >5 -<10 million international units/m ² Ixabepilone Methotrexate > 50 mg/m ² - <250 mg/m ² Mitomycin Mitoxantrone Necitumumab Olaratumab Omacetaxine Paclitaxel Paclitaxel-albumin Pemetrexed Pentostatin Pralatrexate Romidepsin Talimogene laherparepvec Thiotepa Tisagenlecleucel Topotecan Ziv-aflibercept	

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

06/15/16	New Medical Coverage Guideline.
06/15/17	Review and revision to guideline consisting of updating position statement and references.
03/15/18	Review and revision to guideline consisting of updating position statement, description, dosing, coding and references.
04/01/18	Addition of HCPCS codes C9463 and C9464
05/15/18	Review and revision to guideline consisting of updating position statement and references.
01/01/19	Revision: HCPCS code updates. Added J0185 and J2797, and removed C9463, C9464, and J3490.
05/15/19	Review and revision to guideline consisting of updating Table 1 and references.
01/01/20	Revision to guideline; consisting of updating the position statement.