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Cinvanti

Ambulatory Care Pharmacy Newsletter

Article I – June 2018

Adherence Packaging[1]

In the United States, medication nonadherence can account for up to 25% of hospitalizations and 50% of treatment failures. Adherence rates of at least 80% are recommended to see optimal therapeutic effect. However, recent research is showing that adherence rates to chronic medications is only 50%, which poses an issue for healthcare providers. There are a variety of different methods for increasing patient adherence, such as utilization of pill boxes, 90-day refills, and medication compliance packaging.

XXXX Pharmacy offers medication compliance packaging at no additional cost for the patient. The pharmacy organizes medications into convenient blister packs, filled every 30 days. Each blister pack contains medications which are separated by each day of the week (Sunday-Saturday) and then further subdivided into morning, noon, evening, and bedtime dosing pockets. The pharmacy provides home delivery of the medications free of charge as an added service. If interested, your patient can contact XXXX Pharmacy at XXX-XXX-XXXX or stop by the pharmacy and request pill packaging. It is conveniently located in the XXXXXX at XXX XXXXX Street in downtown XXXXXXX.

"Each capsule contains your medication, plus a treatment for each of its side effects."

Antimicrobial Stewardship – UTI's[2]

Uncomplicated urinary tract infection (UTI), or acute cystitis, is frequently seen and inappropriately treated in the outpatient setting. Rising rates of bacterial resistance can be associated with overtreatment, incorrect antibiotic selection, and incorrect duration of therapy. Ciprofloxacin is one of the most misused antibiotics for uncomplicated UTI's. Guidelines recommend ciprofloxacin be reserved for more complicated infections due to increasing resistance and a poor side effect profile.

The Infectious Diseases Society of America (IDSA) treatment guidelines for uncomplicated cystitis recommend treatment with Bactrim DS (sulfamethoxazole/trimethoprim) twice daily for 3 days, Nitrofurantoin monohydrate 100 mg twice daily for 5 days, or a one-time dose of fosfomycin 3 grams. When selecting treatment options, patient specific factors that must be taken into account include: allergies, culture sensitivities, antibiotic history, renal function, and community resistance. XXXXXXX publishes a community antibiogram annually which can be found on the intranet InfoWeb homepage under 'Reference'. The antibiogram is a summary of the susceptibilities from the previous year and is separated for systemic and urinary pathogens. This allows providers to make informed empiric antibiotic selections based off community susceptibility patterns. Based upon the 2017 antibiogram, we are experiencing increasing resistance with some of the first line agents such as Bactrim. Our infectious diseases team has recommended the use of Cephalexin 500 mg BID to TID (adjusted for renal function) for 5 to 7 days as an alternative to other first line agents.

ACC/AHA Hypertension Guidelines – 2017[3]

Hypertension (HTN) guidelines continue to keep health care practitioners on their toes as the experts have changed the blood pressure (BP) categories once again. The 2017 guidelines from the ACC/AHA committee now use four BP categories:

1. **Normal BP:** systolic < 120 mmHg and diastolic < 80 mmHg
2. **Elevated BP:** systolic 120 – 129 mmHg and diastolic < 80 mmHg
3. **Stage 1 HTN:** systolic 130 – 139 mmHg or diastolic 80 – 89 mmHg
4. **Stage 2 HTN:** systolic > 140 mmHg or diastolic > 90 mmHg

The new goal BP of a patient with HTN is < 130/80 mmHg regardless of comorbidities or age. However, it is recommended to use clinical judgement when more strict BP goals would be inappropriate (e.g., frail elderly adults).

Lifestyle modification is first line for all patients while drug therapy is recommended when BP is >140 mmHg systolic or >90 mmHg diastolic. However, pharmacotherapy can also be started if BP is <140/90 mmHg and the patient has established cardiovascular disease or an estimated 10-year ASCVD risk of ≥10%. One agent should be used for Stage 1 HTN, and two agents for Stage 2 HTN. ACEis, ARBs, thiazide diuretics, and CCBs remain as first line agents to treat BP, while beta-blockers are reserved for patients with heart failure or a history of myocardial infarction. If a patient has resistant HTN, defined as a BP above goal while on 3 anti-HTN medications including a thiazide diuretic or taking 4 or more anti-HTN medications, then spironolactone should be recommended as long as the creatinine clearance is greater than 30 mL/min and serum potassium is within normal limits. Although the stages of hypertension have been redefined, these guidelines have attempted to streamline the BP goals and treatment options involving a wide array of patient populations.

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Patient Case #1 – MDD

Chief Complaint

"I just feel down and tired"

HPI

A 42-year-old man comes to his outpatient psychiatrist with complaints of a depressed mood, which he states is identical to depression he has experienced previously and feels tired often throughout the day making it hard for him to stay awake at work. He was diagnosed with major depression for the first time 20 years ago. At that time, he was treated with imipramine, up to 150 mg/day, with good results. During a second episode, which occurred 15 years ago, he was treated with imipramine, and once again his symptoms remitted after 4 to 6 weeks. He denies illicit drug use or any recent traumatic events. The man states that although he is sure he is experiencing another major depression, he would like to avoid imipramine this time because it produced unacceptable side effects such as dry mouth, dry eyes, and constipation.

PMH

Hypertension (uncontrolled)

GERD

Obesity (BMI >30)

Irritable Bowel Syndrome (IBS)

Allergies

NKDA

Social History

Denies alcohol, no illicit drug use, non-smoker

Medications

Lisinopril 10mg 1 PO Daily

Ranitidine 150mg 1 PO Daily

Hydrochlorothiazide 25mg 1 PO Daily

Physical Exam

Unremarkable

Labs

Within normal limits

Questions

1. What pharmacologic treatment would you recommend for this patient?
2. What information should be provided to this patient to enhance adherence, ensure successful therapy, and what adverse effects to monitor for?

Patient Case #1 – MDD Answers

1. First-line options are generally going to be SSRI or SNRI.
    a. SSRI – going to be the best option in this patient
        i. Could do sertraline, fluoxetine, escitalopram, or citalopram.
            1. All SSRI's are associated with insomnia, but could choose fluoxetine since it is more activating
        ii. May want to avoid fluvoxamine (lots of DI), paroxetine (weight gain (pt has history of obesity))
    b. SNRI – may not be the best choice due to patient history of hypertension
2. Education points for the patient
    a. Adherence, Adherence, Adherence!!!
        i. Educate patient on importance of taking medication every day not PRN. Just because they feel it is working does not mean you can stop the medication.
    b. Successful therapy
        i. Educate patient that they will not see the full effect of the medication for at least 4 weeks. It is important to continue therapy even when they feel it may not be working
    c. Adverse effects of SSRI
        i. GI – nausea, vomiting, diarrhea (should subside with continued treatment)
        ii. Insomnia or agitation
        iii. Sexual dysfunction
        iv. Migraines, tension headaches
        v. Some weight gain

Summary:

A 42-year-old man complains of symptoms of major depression identical to two prior episodes he experienced in the past. Previously, he was successfully treated with a tricyclic antidepressant (TCA), although this class of medication often produces anticholinergic side effects such as dry mouth, dry eyes, and constipation, of which this patient complains. The question becomes what medication should be used to treat recurrent major depression when tricyclics are not an option.

Although the patient has been successfully treated with a TCA (imipramine) two times in the past, these medications are no longer considered first-line treatments because of their side effect profiles and their potential lethality in overdose (cardiac arrhythmias). For a patient such as this one, one might consider using imipramine again. However, the patient specifically requests another type of medication because of his previous discomfort with the side effects. Current first-line treatments for patients with major depression, SSRIs, SNRIs, bupropion, and mirtazapine, are thus logical choices; they have fewer side effects and are safer.

Clinical Pearls:

- It is important to rule out an underlying substance (eg, alcohol and cocaine withdrawal), medication (eg, antihypertensives, steroids), or medical condition causing depression (eg, hypothyroidism, multiple sclerosis), especially if the patient does not have a prior history of depression.
- More than 50% of patients who have had one episode of major depression will have recurrent episodes.
- The risk of further episodes of major depression increases with the number of prior episodes, the occurrence of residual symptoms of depression between episodes, and any comorbid psychiatric or chronic medical illnesses.
- The treatment that was successful for prior episodes of major depression has a higher likelihood of achieving remission in future episodes.
- Selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors as well as bupropion, and mirtazapine, are all first-line treatment options for major depressive disorder.

Patient Case #2 – Bipolar Disorder

Chief Complaint

Unable to obtain

HPI

A 29-year-old man is brought to the emergency center in a drunken stupor. He is accompanied by his wife, who states that he hasn't been himself at all for the past few months. According to his wife, he was evaluated for depression by his personal physician about 3 months ago and started on an SSRI. He responded quite well to this therapy over the subsequent 2 months. He started feeling so good and so energetic that he stopped taking his medication. He found that he needed less and less sleep, to the point where he is now only sleeping 2 to 3 hours a day. He has been showering his wife with very expensive gifts and has hit the maximum limit on all of their credit cards. He has been extremely romantic and more interested in sexual relations than at any time before. He has also started drinking heavily and has passed out drunk more than once. His work has suffered, and his boss said that he was in danger of being fired if things didn't straighten out. Other than being drunk, his physical examination and blood tests are normal. He is admitted to the psychiatric unit with a diagnosis of bipolar disorder and started on lithium.

PMH

Depression

Allergies

NKDA

Social History

Drinks several beers daily and recently has been passing out drunk, no illicit drug use, non-smoker

Medications

None

Physical Exam

Unremarkable

Labs

Within normal limits

Questions

1. Do you agree with the pharmacologic treatment?
2. What information should be provided to this patient to enhance adherence, ensure successful therapy, and what adverse effects to monitor for?

Patient Case #2 – Bipolar Disorder Answers

1. Acute Treatment – Manic or mixed
    a. Severe
        i. Lithium + antipsychotic
        ii. Valproate + antipsychotic
    b. Less Severe
        i. Lithium
        ii. Valproate
        iii. Atypical antipsychotic
2. Education points for the programs
   Adverse Effects:
    a. Dose related – polyuria (can resolve by changing to a once daily dose at bedtime), polydipsia, weight gain, cognitive problems (dulling, impaired memory, poor concentration, confusion, mental slowness), tremor, sedation or lethargy, impaired coordination, GI distress (nausea, vomiting, dyspepsia, diarrhea – can decrease incidence if administered with meals), hair loss, benign leukocytosis, acne and edema
    b. Side effects that persist despite dose adjustment – can manage with other medications (beta blockers for tremor, diuretics for polyuria, polydipsia, or edema
    c. Hypothyroidism – tends to appear after 6-18 months of lithium treatment and may be associated with rapid cycling → this is not a contraindication to lithium therapy, just treat with levothyroxine!
    d. >1.5 meq/liter – marked tremor, nausea and diarrhea, blurred vision, vertigo, confusion, and increased deep tendon reflexes
    e. >2.5 meq/liter – may experience more severe neurological complications and eventually experience seizures, coma, cardiac dysrhythmia, and permanent neurological impairment
        i. Hemodialysis is the only method of removing excess lithium from the body

   Educate patients on potential side effects and the need to avoid salt-restricted diets or concomitant medications that could elevate serum lithium levels (diuretics, ACE, NSAIDS)

   Monitoring of lab values generally recommended on the bases of pathophysiological knowledge. Decision to recommend a test based on the probability of finding that would alter treatment. Recommended tests are as follows:

    - Baseline measures – ECG, CBC
    - Tests to determine conditions requiring different additional treatments (pregnancy, TSH)

- Tests to determine conditions requiring alteration of the standard dosage regimen of lithium (CrCl every 2-3 months during first 6 months of treatment once stable every 6 months to a year)

*Initiation – general medical history, physical exam, BUN and CrCl, pregnancy test, thyroid function evaluation (once or twice during the first 6 months once stable every 6 months to a year), and if >40 years ECG monitoring with a rhythm strip

Initiation of lithium – start in low, divided doses to minimize side effects (300mg TID or less, depending on patient weight and age). Titrate dose upward to serum concentrations of 0.5-1.2 meq/liter according to response and side effects. Check levels after each dose increase and before the next. Css reached 5 days after dose adjustment. Monitor levels every 6 months.

Clinical Pearls

When a patient admitted with acute mania is taking an antidepressant, the antidepressant should be tapered and withdrawn. In some patients, antidepressants may activate mania or increase the rate of cycling, and potentially delay response to antimanic/mood stabilizers. Antidepressants can always be added back, if needed, to the regimen after the patient is more stable.

Question:

Can Prolia be used to treat osteoporosis in patients with chronic kidney disease stage 2 and chronic gastritis.

Answer:

Gastrointestinal effects are not common adverse effects seen with Prolia. Prolia is advantageous over bisphosphonates for patients with gastrointestinal disorders and impaired renal function.

Evidence:

Per the Prolia package insert the gastrointestinal adverse effects mentioned are upper abdominal pain, flatulence, gastroesophageal reflux disease occurring in ≥2% of patients with osteoporosis.

In a review, titled "*Can denosumab be a substitute, competitor, or complement to bisphosphonates?"* It was found that denosumab has better compliance, strong inhibition of osteoclastic activity, reversibility of its action after discontinuance and advantages to patients with gastrointestinal issues and renal impairment. In those patients experiencing severe renal impairment (CrCl <30mL/min or receiving dialysis) were at higher risk for hypocalcemia.

There was no data available for chronic gastritis specifically.

Recommendation:

Prolia seems to be the preferred medication, if not contraindicated, in patients experiencing gastrointestinal issues and impaired renal function than that of bisphosphonates. Even though this patient has CKD type 2 it is still important to monitor for hypocalcemia as this is commonly seen in patients taking Prolia especially those having severe renal impairment. However, if the patient was initially taking a PPI for GERD, there is a chance this could be exacerbated do to Prolia's adverse effect profile.

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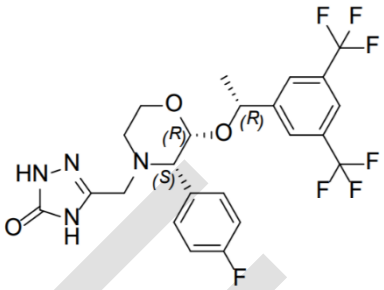
Kim SY, Ok HG, Birkenmaier C, Kim KH. Can denosumab be a substitute, competitor, or complement to bisphosphonates?. Korean J Pain. 2017;30(2):86-92.

Cinvanti® Injectable Emulsion (aprepitant)
Heron Therapeutics



Generic Name[1,2]
Aprepitant

Brand Name[1,2]
Cinvanti®

Similar Agents[3]
Aprepitant (Emend®), fosaprepitant (Emend®), and rolapitant (Varubi®)

Classification[1,2]
Substance P/neurokinin-1 (NK1) receptor antagonist

Indication[1,2]
Aprepitant 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 (HEC) including high-dose cisplatin, and nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). The limitations of use include treatment of established nausea and vomiting due to the lack of studies.

Pharmacology[1,2,4,5,6]
Aprepitant is an injectable emulsion containing the active ingredient, aprepitant. It is a substance P/neurokinin 1 (NK1) receptor antagonist with little to no affinity for serotonin (5-HT_3), dopamine, and corticosteroid receptors.

Aprepitant is the first and only polysorbate 80-free intravenous NK1 receptor antagonist approved for acute and delayed CINV prevention. Polysorbate 80 is a synthetic surfactant used to solubilize injectable chemotherapy and supportive care drugs. This compound has been linked to adverse events in oncology patients, such as hypersensitivity, anaphylaxis, and infusion site reactions.

According to animal and human Positron Emission Tomography (PET) studies, aprepitant has been shown to cross the blood brain barrier. Animal studies have shown that aprepitant inhibits emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin through central actions. Additionally, human and animal studies show that aprepitant augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and dexamethasone as well as inhibits acute and delayed phases of cisplatin-induced emesis.

Drug	Indication	Adverse Effects
Aprepitant (Cinvanti®) Injectable Emulsion	- For 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 (HEC) including high-dose cisplatin, and nausea	- In the 3-day oral aprepitant in conjunction with MEC group the most common adverse effect (≥1%) was fatigue and eructation - Single-dose intravenous fosaprepitant in conjunction with HEC showed a similar safety profile to that seen in the 3-day

	and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). The limitations of use include treatment of established nausea and vomiting due to the lack of studies.	oral aprepitant regimen as mentioned above. However, infusion site reactions occurred at a higher incidence in the intravenous fosaprepitant group (3%) compared to oral aprepitant group (0.5%) - Most common adverse effect with single dose Cinvanti was (≥2%) headache and fatigue.
Aprepitant (Emend®) Capsule Suspension	- In combination with other antiemetic agents ≥6 months of age (suspension)/ ≥12 years of age (capsules) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high dose cisplatin and nausea and vomiting associated with initial and repeat courses of MEC. - For the prevention of post-operative nausea and vomiting (PONV) in adults (capsules)	CINV: - Adults (≥3%): fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, ↓ WBC count, dehydration, ↑ alanine aminotransferase - Pediatrics (≥3%): neutropenia, headache, diarrhea, ↓ appetite, cough, fatigue, ↓ hemoglobin, dizziness, hiccups PONV: - Adults (≥3%): constipation and hypotension
Fosaprepitant (Emend®) Intravenous Injection	- 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 HEC and delayed nausea and vomiting associated with initial and repeat courses of MEC	- Most common (≥2%): fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremities
Rolapitant (Varubi®) Injectable Emulsion Tablet	- In combination with other antiemetic agents in adults for the prevention of delayed nausea associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC	Most common (≥5%) - Cisplatin based HEC: neutropenia and hiccups - MEC and combinations of anthracycline and cyclophosphamide: ↓ appetite, neutropenia, dizziness

Pharmacokinetics[1,2,7]

Absorption

Pharmacokinetic parameters following administration of a single intravenous 100mg or 130mg dose of aprepitant administered as a 30-minute infusion to healthy subjects is summarized below.

Aprepitant Pharmacokinetic Parameters (After single dose IV administration of aprepitant over 30 minutes)		
	Aprepitant 130mg (Mean (± Std Dev))	Aprepitant 100mg (Mean (± Std Dev))
$AUC_{0\text{-}72hr}$ (mcg/hr/mL)	43.9 (± 12.7)	27.8 (± 6.5)
C_{max} (mcg/mL)	6.1 (± 1.5)	4.3 (± 1.2)

Distribution
Aprepitant is >99% bound to plasma proteins and the mean apparent volume of distribution at steady state (VD_{ss}) was approximately 70L in humans. It crosses the blood brain barrier in humans.

Metabolism
In vitro it is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

In healthy young adults it accounts for ~24% of radioactivity in plasma over 72 hours following a single oral 300mg dose of [14C]-aprepitant, indicating a substantial presence of metabolites in plasma. There have been 7 weakly active metabolites of aprepitant identified in humans

Excretion
Aprepitant is eliminated primarily by metabolism and it is not renally excreted. The terminal half-life ranged from 9 to 13 hours.

Clinical Efficacy[1,2,7,8,9]
Safety and efficacy of aprepitant have been established based on adult studies of a single-dose of intravenous fosaprepitant (prodrug of aprepitant) and a 3-day regimen of oral aprepitant in chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC).

"Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol – EASE"
In a randomized, double-blind, active-control study, patients receiving HEC regimen that included cisplatin ≥70 mg/m^2 for the first time received ondansetron and dexamethasone with a standard aprepitant regimen (125mg on day 1, 80mg on day 2, 80mg on day 3) or a single-dose fosaprepitant regimen (150mg on day 1). The primary endpoint was complete response (no vomiting, no rescue medication) during overall phase (0-120 hours). Secondary endpoints were complete response during delayed phase (25-120 hours) and no vomiting during overall phase. A total of 2,322 patients were stratified by sex and were randomly assigned into one of the two treatment arms. Each treatment group had similar baseline demographics. The majority of patients were men (63.3%), were >55 years (58.4%), and were white (56.1%). Results of the primary endpoint of complete response in the overall phase, 71.9% (95% CI, 69.1% to 74.5%) of patients in the fosaprepitant group reported complete response in comparison to 72.3% (95% CI, 69.6% to 74.9%) in the oral aprepitant group. Secondary endpoint of complete response during the delayed phase resulted in 74.3% (95% CI, 71.6% to 75.9%) of patients in the fosapreptiant group reporting complete response compared with 74.2% (95% CI, 71.6% to 76.8%) in the oral aprepitant group. In regard to the secondary endpoint of no vomiting during overall phase, 72.9% (95% CI, 70.2% to 75.5%) of patients in the fosaprepitant group reported no vomiting compared with 74.6% (95% CI, 71.9% to 77.1%) in the oral aprepitant group. The study indicates that a trip-

antiemetic regimen containing a single dose of IV fosaprepitant is noninferior to a triple antiemetic regiment containing 3 days of oral aprepitant. Although both regimens were well tolerated, more frequent infusion site reactions was seen with fosaprepitant in comparison to that of aprepitant (2.7% vs 0.3%).

"Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy"
In a multicenter, randomized, double-blind, parallel-group, clinical study, breast cancer patients were randomly assigned to either an aprepitant regimen (day 1, aprepitant 125mg, ondansetron 8mg, and dexamethasone 12mg before chemotherapy and ondansetron 8mg 8 hours later; days 2-3, aprepitant 80mg daily) or a control regimen in patients receiving MEC (day 1, ondansetron 8mg and dexamethasone 20mg before chemotherapy and ondansetron 8mg 8 hours later; days 2-3, ondansetron 8mg BID). The primary endpoint was the proportion of patients with a complete response (no vomiting, no use of rescue therapy) during 120 hours after initiation of chemotherapy in cycle 1. The secondary endpoint was the proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis (FLIE) questionnaire. A total of 866 patients were randomized to either the aprepitant regimen (N=438) or control regimen (N=428). Treatment groups were similar with respect to baseline characteristics. The majority of patients were white (78.6%) and female (99.8%). There was a statistically significantly higher proportion of patients receiving the oral aprepitant regimen in cycle 1 and had a complete response during the overall phase compared with patients receiving the control regimen (51% vs 42% p=0.015). On the FILE questionnaire, significantly more patients taking the oral aprepitant regimen reported minimal or no impact on daily living. Overall, the addition of oral aprepitant to an anti-emetic regimen of ondansetron and dexamethasone resulted in significantly better prevention of CINV than ondansetron and dexamethasone alone in patients receiving MEC.

"Bioequivalence of HTX-019 (aprepitant IV) and fosaprepitant in healthy subjects: a Phase I, open-label, randomized, two-way crossover evaluation"
An open-label, single-dose, randomized, two-way crossover bioequivalence study compared the pharmacokinetics and safety of aprepitant emulsion (HTX-09) and fosaprepitant. Healthy subjects received a single-dose of HTX-019 130mg or fosaprepitant 150mg IV over 30 minutes, with at least a 7-day washout period between doses. The primary objective was to determine bioequivalence, based on area under the curve (AUC) from time 0 to time of last measurable plasma concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity (AUC_{0-inf}), and plasma concentration at 12 h (C_{12h}) of IV infusions of single doses of HTX-019 130mg compared with fosaprepitant 150mg. Secondary objectives assessed safety and tolerability of HTX-019 130mg and fosaprepitant infusions. One hundred healthy subjects were enrolled and randomly assigned to treatment sequence one (HTX-019 x 4 days then fosaprepitant x 4 days separated by a 7-day washout period) or two (fosaprepitant x 4 days then HTX-019 x 4 days separated by a 7-day washout period). Baseline characteristics were similar among groups. Results showed that a single dose of HTX-019 130mg was bioequivalent to a single dose of fosaprepitant 150mg with 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{12h} were all within the bioequivalence bounds (80%-125%). The most common treatment-emergent adverse events (TEAE) overall were headache and infusion-site pain. Of the adverse effects reported 15% were from patients receiving HTX-019 and 28% receiving fosaprepitant. Overall, HTX-019 was shown to be generally well tolerated and bioequivalent to commercially available fosaprepitant for patients with CINV without the risk of polysorbate 80 surfactant-associated systemic hypersensitivity.

Contraindications/Warnings/Precautions[1,2,5]

Aprepitant is contraindicated in patients who are hypersensitive to any component of the product. Hypersensitivity and anaphylactic reactions have been reported with fosaprepitant and oral aprepitant. Symptoms that have been reported include, flushing, erythema, dyspnea, hypotension, and syncope. It is recommended to monitor patients during and after infusion and if hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate aprepitant in patients who experience these symptoms after first-time use. Additionally, it is contraindicated in patients taking pimozide, a CYP3A4 substrate. Concomitant administration could result in elevated plasma concentrations of pimozide causing serious or life-threatening reactions, such as QT prolongation.

Drug Interactions[1,2,5]

- Aprepitant is a CYP3A4 substrate, inducer, weak-to-moderate (dose dependent) inhibitor and CYP2C9 inducer.
- Some substrates of CYP3A4 are contraindicated with aprepitant and dosage adjustments may be warranted with use of some CYP3A4 and CYP2C9 substrates.

CYP3A4 Substrates	
Pimozide *(use contraindicated)*	Increased pimozide exposure
Benzodiazepines	Increased exposure to benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam, midazolam) may increase risk for adverse reactions
Dexamethasone	Increased dexamethasone exposure
Methylprednisolone	Increased methylprednisolone exposure
Chemotherapeutic agents metabolized by CYP3A4	Increased exposure of chemotherapeutic agent may increase risk of adverse reactions
Hormonal contraceptives	Decreased estrogen and progestin exposure during administration of and for 28 days after last dose of aprepitant
Moderate to Strong CYP3A4 Inhibitors	
Moderate – diltiazem Strong – ketoconazole, intraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with Cinvanti
Strong CYP3A4 Inducers	
Rifampin, carbamazepine, phenytoin	Substantially decreased exposure of aprepitant in patients chronically taking a strong CYP3A4 inducer may decrease the efficacy of Cinvanti
CYP2C9 Substrates	
Warfarin	Decreased warfarin exposure and prolongation of prothrombin time
Other Antiemetic Agents	
5-HT3 Antagonists	No change in exposure of the 5-HT3 antagonist

Adverse Effects[1,2,5]

The safety of Cinvanti® was evaluated from both a single-dose and from studies of intravenous fosaprepitant and/or oral aprepitant.

The most common adverse effects with 3-day oral aprepitant regimen in conjunction with MEC (≥1% and greater than standard therapy) were fatigue and eructation. In studies with single-dose intravenous fosaprepitant regimen in conjunction with HEC the adverse effects were similar to prior studies seen with oral aprepitant. Additionally, infusion site reactions (infusion site pruritus, infusion site pain, infusion site induration and infusion site thrombophlebitis) occurred at a higher incidence in patients receiving intravenous fosaprepitant (3%) compared to those who received oral aprepitant (0.5%). Of the 200 healthy subjects who received a single dose of Cinvanti® 130mg as a 30-minute infusion the most common adverse effects reported were headache and fatigue.

Pregnancy/Lactation[1,2,5]

Currently, there is insufficient data on the use of aprepitant in pregnant women in order for a drug-associated risk of developmental outcomes to be established. Since aprepitant contains alcohol, use should be avoided in pregnant women.

No data is available on the presence of aprepitant in human milk, the effects on breastfed infants, or the effects on milk production. Risk versus benefit must be considered.

Dosing[1,2]

Recommended Dose of Aprepitant for Prevention of Nausea and Vomiting Associated with HEC (Single Dose Regimen)				
Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Aprepitant	130mg intravenously over 30-minutes, approximately 30 minutes prior to chemotherapy	None	None	None
Dexamethasone[a]	12mg orally	8mg orally	8mg orally BID	8mg orally BID
5-HT2 antagonist	See prescribing information for specific 5-HT3 antagonist	None	None	None

[a] Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2-4. Additionally, administer dexamethasone in the evenings on Days 3-4 (50% dose reduction of dexamethasone on Day 1-2 is recommended to account for drug interaction with aprepitant).

Recommended Dose of Aprepitant for Prevention of Nausea and Vomiting Associated with MEC (3-Day Regimen with Oral Aprepitant on Days 2-3)			
Drug	**Day 1**	**Day 2**	**Day 3**
Aprepitant	100mg intravenously over 30 minutes approximately 30 minutes prior to chemotherapy	None	None
Oral Aprepitant	None	80mg orally	80mg orally
Dexamethasone	12mg orally	None	None
5-HT3 antagonist	See prescribing information for specific 5-HT3 antagonist	None	None

[a] Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 (50% dose reduction of dexamethasone is recommended to account for drug interaction with aprepitant).

There is no information regarding the treatment of overdose. However, it is known that aprepitant is not removed by hemodialysis.

How Supplied[1,2]

Supplied as a 130mg/18mL single-dose injectable emulsion

Cost Comparison

Drug	How Supplied	Acquisition Cost/Unit*
Aprepitant (Cinvanti®)	130mg/18mL vial	$157.69
Aprepitant (Emend®) Trifold Kit	125mg x 1, 80mg x 2 capsules	$141.34
Aprepitant (Emend®) Bifold	80mg x 2 capsules	$87.41
Fosaprepitant (Emend® IV)	150mg injection (5mL)	$192.62
Rolapitant (Varubi®)	100mL vial	$174.05
	90mg x 2 tablets	$354.05

*Cost is reflective of 340B pricing from Amerisource Bergen

Storage[1,2]

Refrigeration of vials is required, store at 2-8°C (36-46°F) but can remain at room temperature up to 60 days. Do not freeze. Diluted aprepitant solution is stable at ambient room temperature for 6 hours in 0.9% sodium chloride injection, USP or 12 hours in 5% dextrose injection, USP.

Conclusion/Recommendations[5,6,11,12]

Aprepitant (Cinvanti®) is one of several NK1 receptor antagonists available, including oral aprepitant (Emend®), intravenous fosaprepitant (Emend IV®), and rolapitant (Varubi®). Of this class of medications, aprepitant is the first and only polysorbate 80-free intravenous NK1 receptor antagonist approved for acute and delayed CINV prevention. The absence of polysorbate 80 results in a lower risk for hypersensitivity and infusion site reactions. Additionally, it has been found that Cinvanti® when compared to fosaprepitant, is generally well tolerated and bioequivalent to that of fosaprepitant.

In January of 2018, the FDA issued a safety alert regarding anaphylaxis, anaphylactic shock, and other hypersensitivity reactions after administration with rolapitant injectable emulsion, most of which occurring within the first few minutes of administration.

Aprepitant remains an attractive option for the treatment of acute and delayed CINV prevention due to its lower risk for hypersensitivity and infusion site reactions, affordable cost, and comparable efficacy to that of fosaprepitant.

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