NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	216686
Priority or Standard	Standard
Submit Date(s)	12/23/2021
Received Date(s)	12/23/2021
PDUFA Goal Date	10/23/2022
Division/Office	Division of Gastroenterology/Office of Immunology and Inflammation
Review Completion Date	10/4/2022
Established/Proper Name	Fosaprepitant injection
(Proposed) Trade Name	Focinvez
Pharmacologic Class	Substance P/neurokinin-1 (NK_1) receptor antagonist
Applicant	Spes Pharmaceuticals, Inc.
Dosage form	150 mg/50 mL (3 mg/mL) fosaprepitant dimeglumine ready-to-use sterile solution for injection
Applicant Proposed Dosing Regimen	Adults: 150 mg on Day 1 Pediatric Patients (6 months to 17 years): a single-day of fosaprepitant injection on Day 1 (for single dose chemotherapy regimens) or a 3-day regimen of fosaprepitant injection on Day 1 and aprepitant capsules or oral suspension on Days 2 and 3 (for single or multi-day chemotherapy regimens) Administer fosaprepitant injection on Day 1 as an intravenous infusion over 20 to 30 minutes (adults), 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years)
Applicant Proposed Indication(s)/Population(s)	Indicated in adults and pediatric patients 6 months of age and older, 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 Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Chemotherapy-induced nausea and vomiting (disorder), 18846006
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	n/a
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	n/a
Recommended Dosing Regimen	n/a

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Abbreviations: DEPI I, Division of Epidemiology I; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPMH, Division of Pediatrics and Maternal Health; DPV I, Division of Pharmacovigilance I; OMP, Office of Medical Policy; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology

Signatures

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Glossary

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
BLA	biologics license application
CFR	Code of Federal Regulations
CINV	chemotherapy-induced nausea and vomiting
CR	complete response
DP	drug product
DS	drug substance
FDA	Food and Drug Administration
HEC	highly emetogenic chemotherapy
ICH	International Conference on Harmonisation
IND	investigational new drug
IV	intravenous
LD	listed drug
LOQ	limit of quantitation
MEC	moderately emetogenic chemotherapy
NDA	new drug application
NF	National Formulary
NK_1	neurokinin-1
NMT	not more than
OPQ	Office of Pharmaceutical Quality
PDE	permitted daily exposure
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
SBEβCD	sulfobutyl ether β-cyclodextrin sodium
(b) (4)	(b) (4)
USP	United States Pharmacopeia

1. Executive Summary

1.1. Product Introduction

Nonproprietary (established) name and proposed proprietary/trade name: Fosaprepitant injection/Focinvez

Pharmacologic class: substance P/neurokinin-1 (NK_1) receptor antagonist

Proposed indication: Prevention of chemotherapy-induced nausea and vomiting (CINV) in adults and pediatric patients ages 6 months to 17 years

Route of administration, description, and formulation: Fosaprepitant injection is a 150 mg/50 mL (3 mg/mL) clear and colorless solution in a single-dose vial. Fosaprepitant injection is administered as an intravenous (IV) infusion.

Chemical name: 1-Deoxy-1-(methylamino)-D-glucitol[3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4triazol-1-yl]phosphonate (2:1) (salt)

Empirical formula: $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$

Molecular weight: 1004.83

New Drug Application (NDA) Submission

NDA 216686 seeks the approval of Focinvez (fosaprepitant injection) through the 505(b)(2) regulatory pathway. The Applicant has proposed to rely upon the Food and Drug Administration's (FDA) findings of safety and effectiveness for the listed drug (LD) Emend (fosaprepitant) for injection (NDA 22023, initial approval January 25, 2008), and has submitted information on the compositional similarity to the LD and data from nonclinical studies to support that the proposed reliance is scientifically appropriate. No new clinical studies were conducted to support this application.

The proposed product is fosaprepitant dimeglumine, a salt of fosaprepitant. Fosaprepitant is a water-soluble prodrug of aprepitant that is rapidly converted to aprepitant following IV administration. The pharmacologic effect of fosaprepitant is attributable to aprepitant, which is a substance P/NK_1 receptor antagonist.

The Applicant's fosaprepitant injection is formulated as a 150 mg/50 mL (3 mg/mL) ready-to-use sterile solution for injection. This differs from the LD, which is supplied as 150 mg sterile lyophilized powder for reconstitution. Preparation of fosaprepitant injection is different from the LD due to the differences in formulations.

The proposed indications are identical to the LD. The Applicant is seeking approval of fosaprepitant injection in adults and pediatric patients 6 months of age and older, 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 chemotherapy (HEC) including high-dose cisplatin.
- Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC).

The proposed dosages and instructions for administration are identical to the LD. For adults, the proposed dosage of fosaprepitant injection is 150 mg administered intravenously over 20 to 30 minutes as a single-dose regimen on Day 1 of chemotherapy. For pediatric patients, the proposed dosage and infusion time is dependent on the patient's age, weight, and the emetogenic risk of chemotherapy to be administered (i.e., HEC or MEC). Additionally, pediatric patients undergoing multiple-day chemotherapy may receive either a single-dose regimen with fosaprepitant injection on Day 1 or a 3-day regimen of fosaprepitant injection on Day 1 followed by either aprepitant capsules or aprepitant oral suspension on Days 2 and 3.

1.2. Conclusions on the Substantial Evidence of Effectiveness

No assessment of effectiveness is warranted for this application. NDA 216686 relies upon the FDA's findings of effectiveness for the LD (Emend for injection, NDA 22023), and no new clinical studies were conducted to support this application. The Applicant established that the proposed reliance is scientifically appropriate based on the similarity of the products and the submission of data from nonclinical studies to support that the differences between the product and the LD will not affect the efficacy of fosaprepitant injection for the sought indications of the prevention of CINV in adults and pediatric patients ages 6 months to 17 years.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Chemotherapy-induced nausea and vomiting (CINV) is a common and debilitating side effect of chemotherapy. CINV can be generally classified into acute phase (occurring within 24 hours of initiating chemotherapy) and delayed phase (occurring from 24 to 120 hours following initiation of chemotherapy). Chemotherapeutic drugs are classified based on their respective risk for causing emesis in patients in the absence of antiemetic prophylaxis. Highly emetogenic chemotherapy (HEC) is associated with a ≥90% incidence of nausea and vomiting, and moderately emetogenic chemotherapy (MEC) is associated with an incidence of nausea and vomiting of ≥30 to >90%. Approved products for the prevention of CINV are available from multiple drug classes (e.g., substance P/NK1 receptor antagonists, 5-HT3 receptor antagonists, cannabinoids) in various dosage forms and routes of administration (e.g., orally swallowed or orally disintegrating, intravenous, subcutaneous injection, transdermal). The administration of preventative antiemetic regimens consisting of drugs from multiple classes is considered to be the clinical standard of care for patients receiving HEC or MEC, as this is required to achieve adequate CINV prophylaxis (Hesketh et al. 2020).

No new clinical studies for efficacy were conducted to support this application. This Applicant has proposed to rely upon the FDA's findings of safety and effectiveness for the listed drug (LD) (Emend [fosaprepitant] for injection, NDA 22023) through the 505(b)(2) regulatory pathway.
Per the prescribing information for the LD (Merck&Co 2022), in a clinical study of 2,322 adult subjects receiving a HEC regimen that included cisplatin (≥70 mg/m2), the percentages of subjects with no vomiting and no use of rescue therapy (i.e., complete response [CR]) with Emend for injection (administered along with standard of care therapy [i.e., ondansetron and dexamethasone]) were 71.9% and 74.3% in the overall (0-120 h) and delayed (>24 to 120 h) phases of CINV, respectively. This rate was non-inferior by the prespecified margins of 7% in the overall phase and 7.3% in the delayed phase to the percentages of subjects with CR with Emend capsules (72.3% and 74.2% in the overall and delayed phases of CINV, respectively). This study was determined to be sufficient to support the approval of Emend for injection 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, as efficacy in the acute phase was demonstrated by the data from the overall phase.

Also per the LD label (Merck&Co 2022), in a clinical study of 1,000 adult subjects receiving MEC, the CR rate for a single dose of Emend for injection given in combination with standard therapy (i.e., ondansetron and dexamethasone) was 78.9% for the delayed phase. This was superior to the observed CR rate for standard therapy alone (68.5%). This study was determined to be sufficient to support the approval of Emend for injection for the prevention of delayed nausea and vomiting associated with initial and repeat courses of MEC.

No new safety studies were conducted to support this application for fosaprepitant injection. Clinical trials conducted with the LD assessed the safety risks of a single dose of fosaprepitant given in combination with standard therapy (i.e., ondansetron and dexamethasone) versus standard therapy alone in subjects receiving either HEC or MEC. The most common adverse reactions (reported in ≥2% of subjects and at a greater incidence than standard therapy alone) for the LD were fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity, and infusion site reactions. The safety findings were generally similar across HEC and MEC studies.

Important warnings and precautions for the LD include the potential for drug-drug interactions with CYP3A4 substrates, inhibitors, or inducers (use with pimozide is contraindicated due to potential for QT prolongation), decreased prothrombin time (INR) when used with warfarin, reduced efficacy of hormonal contraceptives, and hypersensitivity reactions (including anaphylaxis). No new safety concerns were identified on either the Applicant's or the review team's evaluation of currently available literature describing the use of fosaprepitant/aprepitant products.

Through demonstration that reliance upon the FDA's findings of safety and effectiveness for the LD is scientifically appropriate, the Applicant has established a favorable benefit-risk profile for fosaprepitant injection for the indications sought. However, significant deficiencies were noted at the drug product manufacturing and testing facilities, as described in Section 4.2 of this review. As satisfactory resolution of these deficiencies has not been achieved during this review cycle, and a complete response action is recommended for NDA 216686.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	CINV is a common and debilitating side effect of chemotherapy. It is estimated that 80% of patients undergoing chemotherapy experience CINV. Although not inherently life-threatening, CINV adversely impacts the patient's quality of life and may adversely influence patient compliance with chemotherapy regimens, thus directly affecting prognosis.	Controlling CINV can prevent detrimental impacts to a patient's quality of life and their willingness or ability to complete chemotherapy.
Current Treatment Options	Current FDA-approved treatment options for prevention of CINV include drugs from the following classes: substance P/NK_1 receptor antagonists, 5-HT_3 receptor antagonists, and cannabinoids. Additionally, corticosteroids (e.g., dexamethasone) and dopamine receptor antagonists (e.g., olanzapine) are commonly used as off-label preventative therapy.	Multiple treatment options are available, but CINV is a debilitating side effect of chemotherapy that requires simultaneous use of multiple drugs to achieve adequate control of symptoms. Given the known burden and potentially serious implications of inadequately controlled CINV, there is a need for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Antiemetic drug regimens for patients receiving HEC or MEC commonly involve 2-4 drugs with differing mechanisms of action to address the multiple receptor pathways involved in the emetic reflex.	continued development of antiemetic drugs for prevention of CINV.
Benefit	No new efficacy studies were conducted to support this application. The Applicant is proposing to rely upon the FDA's findings of effectiveness for the LD. Per the approved prescribing information for the LD (Emend for injection; NDA 22023) (Merck&Co 2022), 2,322 adult subjects receiving HEC including cisplatin (≥70 mg/m^2), the percentages of subjects with no vomiting and no use of rescue therapy (i.e., CR) with Emend for injection (administered along with standard of care therapy [i.e., ondansetron and dexamethasone]) were 71.9% and 74.3% in the overall (0-120 h) and delayed (>24-120 h) phases of CINV, respectively. This rate was non-inferior to Emend capsules (72.3% and 74.2% in the overall and delayed phases of CINV, respectively) by the prespecified margins of 7% (overall phase) and 7.3% (delayed phase). This study was determined to be sufficient to support the approval of Emend for injection for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin, as efficacy in the acute phase was demonstrated by the data from the overall phase. In a clinical study of 1,000 adult subjects receiving MEC, the CR rate for a single dose of Emend for injection, given in combination with standard therapy (i.e., ondansetron and dexamethasone), was 78.9% for the delayed phase, and was superior to standard therapy alone (68.5%). This study was determined to be sufficient to support the approval of Emend for injection for the prevention of delayed nausea and vomiting associated with initial and repeat courses of MEC. To support that the proposed reliance upon the FDA's findings of effectiveness for the LD was scientifically appropriate, the Applicant submitted information to support the	The clinical effectiveness of fosaprepitant injection is established through reliance upon the FDA's findings of effectiveness for the LD. Reliance upon the FDA's findings of effectiveness for the LD is supported by the similarity of the product to the LD and submitted data from nonclinical studies to establish that differences from the LD will not affect the efficacy of fosaprepitant injection for the prevention of CINV.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	similarity of fosaprepitant injection to the LD and nonclinical data to justify that differences between the products would not affect the efficacy of the product.	
Risk and Risk Management	No new safety information was submitted with this application. The Applicant is proposing to rely upon the FDA's findings of safety for the LD. According to the prescribing information for the LD, the most common adverse reactions (reported in ≥2% of subjects and at a greater incidence than standard therapy alone) in clinical studies were fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity, and infusion site reactions. The safety profile was generally similar in both HEC and MEC studies. Important warnings and precautions include the potential for drug-drug interactions with CYP3A4 substrates, inhibitors, or inducers (use with pimozide is contraindicated due to potential for QT prolongation), decreased prothrombin time (INR) when used with warfarin, reduced efficacy of hormonal contraceptives, and hypersensitivity reactions (including anaphylaxis). The Applicant submitted information of the similarity of fosaprepitant injection to the LD and nonclinical data to support the differences would not affect the safety of the product for the proposed indication to establish that the proposed reliance upon the FDA's findings of safety for the LD was scientifically appropriate. No new safety concerns were identified on either the Applicant's or the review team's evaluation of currently available literature describing the use of fosaprepitant/aprepitant products.	The clinical safety of fosaprepitant injection is established through reliance upon the FDA's findings of safety for the LD. Reliance upon the FDA's findings of safety for the LD is supported by the similarity of the product to the LD and submitted data from nonclinical studies to establish that differences will not affect the safety of fosaprepitant injection for the prevention of CINV. No additional or new safety concerns were identified upon review of currently available literature describing the use of fosaprepitant/aprepitant products. As no new safety concerns were identified, routine pharmacovigilance is appropriate.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

CINV has been identified by cancer patients as the adverse effect of treatment with the highest impact on their quality of life. An estimated 80 percent of patients undergoing chemotherapy experience CINV. CINV can cause decreased appetite, compromised nutrition, and dehydration that can progress to metabolic derangements. Inadequate control of CINV can lead to patient noncompliance or withdrawal from antineoplastic therapies, directly impacting overall prognosis.

With the known burden and potential implications of these symptoms, providing preventative treatment for CINV is the standard of care for patients undergoing chemotherapy with moderately or highly emetogenic agents. A combination of drugs from multiple therapeutic classes is generally required to achieve optimal prevention of CINV, and recommendations for preventative treatment regimens are available from several professional organizations, including the American Society of Clinical Oncology (Hesketh et al. 2020).

American Society of Clinical Oncology guidelines define chemotherapy regimens (including combination regimens) associated with a 90 percent or higher incidence of nausea and vomiting in the absence of antiemetic prophylaxis as highly emetogenic chemotherapy (HEC) and regimens associated with a 30 to 90 percent incidence of vomiting as moderately emetogenic chemotherapy (MEC) (Hesketh et al. 2020).

CINV is further classified by the onset of symptoms relative to the timing of chemotherapy administration into acute phase (onset 0 through ≤24 hours) and delayed phase (onset >24 through ≤120 hours). The overall phase of CINV is defined as symptoms that are present from 0 to 120 hours following chemotherapy administration.

2.2. Analysis of Current Treatment Options

Current FDA-approved treatments for the prevention of CINV include drugs from the following classes: substance P/NK_1 receptor antagonists, 5-HT_3 receptor antagonists, and cannabinoids. Additional drugs recommended in clinical practice guidelines for off-label use include dexamethasone and olanzapine (Hesketh et al. 2020). Of the FDA-approved drugs for the prevention of CINV, options are available in various dosage forms and routes of administration (e.g., orally swallowed or orally disintegrating, intravenous, subcutaneous, transdermal). Antiemetic drug regimens for patients receiving HEC or MEC commonly involve 2-4 drugs with differing mechanisms of action to address the multiple receptor pathways involved in the emetic reflex and provide adequate prophylaxis.

Table 1 describes FDA-approved products indicated for the prevention of CINV.

Table 1. Summary of FDA-Approved Drugs for CINV

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
5-HT$_3$ Receptor Antagonists				
Ondansetron (Zofran) NDA 20103: Oral tablets 4 mg, 8 mg Approved 1991 ANDAs available NDA 20605: Oral solution 4 mg/5 mL Approved 1997 ANDAs available NDA 20781: Orally disintegrating tablets 4 mg, 8 mg Approved 1999 ANDAs available	Prevention of CINV from HEC (adults) and MEC (adults and pediatric patients age ≥4 years)	Adults HEC: 24 mg 30 mins before chemo Adults MEC:8 mg 30 mins before chemo, then 8 mg 8 hrs after 1st dose; then 8 mg BID for 1-2 days after end of chemo Pediatric patients MEC:12-17 yrs: same as adult MEC 4-11 yrs: 4 mg 30 mins before chemo, then 4 mg 4-8 hrs after 1st dose; then 4 mg TID for 1-2 days after the end of chemo	Contraindications: hypersensitivity to drug or components; concomitant apomorphine Warnings: hypersensitivity reactions; QT prolongation and TdP; serotonin syndrome; myocardial ischemia; masking of progressive ileus and/or gastric distension; phenylketonuria with ODT Special Populations: do not exceed 8 mg/day in severe hepatic impairment	Prevention of RINV (adults); prevention of PONV (adults)
Ondansetron (Zofran) NDA 20007: Solution for injection 40 mg/20 mL Approved 1991 Brand discontinued ANDAs available	Prevention of CINV (adults and pediatric patients age ≥6 months)	Adults and pediatric patients: 0.15 mg/kg/dose for 3 doses (max 16 mg/dose) infused over 15 mins beginning 30 min before chemo; then repeat 4 and 8 hrs after 1st dose	Same as Zofran tablets or solution	Prevention of PONV (adults and pediatric patients age ≥1 month)

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Ondansetron (Zuplenz) NDA 22524: Oral soluble film 4 mg, 8 mg Approved 2010 Brand discontinued No ANDAs available	Prevention of CINV from HEC (adults) and MEC (adults and pediatric patients age ≥4 years)	Same as Zofran oral tablets/solution/ODT	Same as Zofran oral tablets/solution/ODT	Prevention of RINV (adults); prevention of PONV (adults)
Dolasetron (Anzemet) NDA 20623: Oral tablet 50 mg, 100 mg Approved 1997 Brand 100 mg discontinued No ANDAs available NDA 20624: Solution for injection 500 mg/25 mL, 100 mg/5mL, 12.5 mg/0.625 mL Approved 1997 Brand discontinued No ANDAs available	Prevention of CINV from MEC (adults and pediatric patients age ≥2 years)	Adults: 100 mg <1 hr before chemo Pediatric patients: 2-16 years: 1.8 mg/kg <1 hr before chemo (max 100 mg) IV solution can be mixed into apple juice for oral dosing in pediatrics	Contraindications: hypersensitivity to drug Warnings: QT, PR, QRS prolongation and TdP; serotonin syndrome Interactions: caution with drugs that prolong ECG intervals or cause hypokalemia or hypomagnesemia	

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Granisetron (Kytril) NDA 20305: Oral tablet 1 mg, 2 mg Approved 1995 Brand discontinued ANDAs available	Prevention of CINV (adults)	Adults: 2 mg QD <1 hr before chemo, OR 1 mg BID (1 mg <1 hr before chemo then 1 mg 12 hrs later)	Contraindications: hypersensitivity to drug or components Warnings: masking of progressive ileus and/or gastric distension	Prevention of RINV (adults)
Granisetron (Kytril) NDA 20239: - Solution for injection 0.1 mg/mL or 1 mg/mL - Approved 1993 - ANDAs available	Prevention of CINV (adults and pediatric patients ages 2-16 years)	Adults: 10 mcg/kg infused 30 mins before chemo Pediatric patients 2-16 yrs: same as adults	Same as Kytril tablets	Prevention and treatment of PONV (adults)
Granisetron (Sancuso) NDA 22198: ER transdermal system 3.1 mg/24h Approved 2008 No ANDAs available	Prevention of CINV from HEC and MEC for up to 5 consecutive days (adults)	Adults: one transdermal system worn for 24-48 hrs before chemo and for 24-120 hrs after end of chemo	Same as Kytril tablets and solution Warnings: avoid direct exposure to sunlight to avoid potential skin reaction Interactions: serotonergic drugs (serotonin syndrome)	

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Granisetron (Sustol) NDA 22445: ER suspension for SubQ injection 10 mg/0.4 mL single-dose syringe Approved 2016 No ANDAs available	Prevention of CINV from MEC or anthracycline and cyclophosphamide combination regimens (adults)	Adults: 10 mg SubQ injection >30 min before chemo on day 1; no more frequently than every 7 days Requires slow, sustained injection over 20-30 sec due to viscosity Use of SUSTOL with successive emetogenic chemotherapy cycles for more than 6 months is not recommended	Contraindications: hypersensitivity to drug or components Warnings: injection site reactions; constipation and ileus; hypersensitivity; serotonin syndrome Interactions: serotonergic drugs (serotonin syndrome) Special Populations: avoid in severe renal impairment; use no more than once every 14 days in moderate renal impairment	
Palonosetron (Aloxi) NDA 21372: Solution for injection 0.25 mg/5 mL or 0.075 mg/1.5 mL Approved 2003 Brand discontinued ANDAs available	Prevention of acute and delayed CINV from MEC; prevention of acute CINV from HEC (adults) Prevention of acute CINV (pediatric patients ages 1 month to <17 years)	Adults: 0.25 mg infused over 30 secs, 30 minutes prior to chemo Pediatric patients: 1 mo - <17 yrs: 20 mcg/kg (max 1.5 mg) infused over 15 min, 30 min prior to chemo	Contraindications: hypersensitivity to drug or components Warnings: hypersensitivity; serotonin syndrome	Prevention of PONV for up to 24 hrs following surgery (adults)
Palonosetron (Aloxi) NDA 22233: Oral capsules 0.5 mg Approved 2008 Brand discontinued No ANDAs available	Prevention of acute CINV from MEC (adults)	Adults: 0.5 mg 1 hr before chemo	Same as Aloxi solution	

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Substance P/NK$_1$ Receptor Antagonists				
Aprepitant (Emend) NDA 21549: Oral capsules 40, 80, 125 mg Approved 2003 Brand 40 mg discontinued ANDAs available	Prevention of acute and delayed CINV from HEC; prevention of MEC (adults and pediatric patients age ≥12 years) In combination with other antiemetic agents	Adults and pediatric patients (at least 30 kg BW): 125 mg on day 1; 80 mg on days 2 and 3; administer 1 hr before chemotherapy	Contraindications: Hypersensitivity; pimozide Interactions: CYP3A4; hormonal Contraceptives (risk of decreased efficacy); warfarin (risk of decreased INR)	
Aprepitant (Emend) NDA 207865: Oral suspension 125 mg Approved 2015	Prevention of acute and delayed CINV from HEC; prevention of MEC (adults and pediatric patients age ≥6 months) In combination with other antiemetic agents	Pediatrics or adults unable to swallow oral capsules: 6 mo or older: Day 1: 3 mg/kg (max 125 mg); day 2: 2 mg/kg (max 80 mg); day 3: 2 mg/kg (max 80 mg); do not dose in BW <6 kg	Same as Emend capsules	
Aprepitant (Cinvanti) NDA 209296: Injectable emulsion	Prevention of acute and delayed CINV from HEC; prevention of delayed CINV from MEC; CINV from MEC as 3-day regimen (adults) Part of regimen with corticosteroid and 5-HT$_3$ antagonist	Adults (single dose for HEC and MEC): 130 mg on Day 1 Adults (3-day regimen for MEC): 100 mg on Day 1 followed by aprepitant capsules (80 mg) orally on Days 2 and 3	Same as Emend capsules and suspension, plus warning for hypersensitivity reactions	
Fosaprepitant (Emend) for injection NDA 22023: Powder for IV Approved 2008 ANDAs available	Prevention of acute and delayed CINV from HEC; prevention of delayed CINV from MEC (adults and pediatric patients age ≥6 months) In combination with other antiemetic agents	Adults: 150 mg on day 1 as IV infusion over 20-30 min, ~30 min prior to chemo Pediatrics: 12-17 yrs: 150 mg over 30 mins; 2 yrs to <12 yrs: 4 mg/kg over 60 mins; 6 mo to <2 yrs: 5 mg/kg over 60 mins	Same as Emend capsules and suspension, plus warnings for hypersensitivity and infusion site reactions	

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Rolapitant (Varubi) NDA 206500: Oral tablets 90 mg Approved 2015 No ANDAs available	Prevention of delayed CINV (adults) In combination with other antiemetic agents	Adults: 180 mg approximately <2 hr prior to chemo	Contraindications: thioridazine Warnings: CYP2D6 substrates with narrow therapeutic index Interactions: BCRP and P-gp substrates with narrow therapeutic index; strong CYP3A4 inducers	
Rolapitant (Varubi) NDA 208399: Emulsion for injection 166.5 mg/92.5 mL single-dose vial Approved 2017 Discontinued No ANDAs available	Prevention of delayed CINV (adults) In combination with other antiemetic agents	Adults: 166.5 mg infused over 30 mins <2 hr prior to chemo	Same as Varubi tablets, plus: Contraindications: contraindicated in pediatric patients <2 years of age Interactions: warfarin (increased INR)	
Combination Substance P/NK_1 Receptor Antagonist and 5-HT_3 Receptor Antagonists				
Netupitant and palonosetron (Akynzeo) NDA 205718: Oral capsule Approved 2014 No ANDAs available	Prevention of acute and delayed CINV (adults)	One capsule (300/0.5 mg) ~1 hr prior to chemo	Contraindications: None Warnings: Hypersensitivity; serotonin syndrome Interactions: CYP3A4 Other: Avoid in severe hepatic or renal impairment	

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Fosnetupitant and palonosetron (Akynzeo) for injection NDA 210493: Powder for IV; solution for IV; approved 2018	Prevention of acute and delayed CINV from HEC (adults) In combination with dexamethasone Limitation of use: Not studied for CINV from anthracycline + cyclophosphamide regimen	One vial (235/0.25 mg) diluted and infused over 30 mins, 30 mins prior to chemo	Same as Akynzeo capsules	
Cannabinoids				
Dronabinol (Marinol) NDA 18651: Oral capsule 2.5 mg, 5 mg, 10 mg Approved 1985 ANDAs available	Treatment of CINV in adults with failed response to conventional antiemetics	Starting dosage of 5 mg/m^2, administered 1-3 hr prior to chemo, then every 2-4 hr after chemo, for a total of 4-6 doses/day Administer first dose on empty stomach >30 min prior to eating; subsequent doses can be taken without regard to meals	Contraindications: hypersensitivity to drug or sesame oil Warnings: neuropsychiatric effects; hemodynamic instability; seizures; substance abuse; paradoxical NV Interactions: CYP3A4; CYP2C9; highly protein-bound drugs Specific Populations: avoid breastfeeding; consider lower starting dose in elderly	
Dronabinol (Syndros) NDA 18651: Oral solution 5 mg/mL Approved 2016 No ANDAs available	Treatment of CINV in adults with failed response to conventional antiemetics	Starting dosage of 4.2 mg/m^2, administered 1-3 hr prior to chemo, then every 2-4 hr after chemo, for a total of 4-6 doses/day Administer first dose on empty stomach >30 min prior to eating; subsequent doses can be taken without regard to meals	Contraindications: sensitivity to drug or alcohol; hypersensitivity to alcohol; disulfiram or metronidazole in past 14 days Warnings: Same as Marinol Interactions: Same as Marinol Specific Populations: same as Marinol	

Drug Information	Relevant Indication	Dosing Information	Safety and Tolerability Issues	Other NV Indications
Nabilone (Cesamet) NDA 18677: Oral capsule 1 mg Approved 1985 No ANDAs available	Treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments	Adults: 1-2 mg BID, initial dose given 1-3 hrs before chemo; max recommended dose 6 mg/day in 3 divided doses; may be given BID-TID during entire course of each chemo cycle and for 48 hrs after last dose of each cycle	Contraindications: hypersensitivity to any cannabinoid Warnings: psychiatric and CNS effects Interactions: highly protein-bound drugs	

Source: Reviewer's table
Abbreviations: 5-HT3, 5-hydroxytryptamine (serotonin) subtype 3; ANDA, abbreviated new drug application; BCRP; breast cancer resistance protein; BID, twice a day; CINV, chemotherapy-induced nausea and vomiting; CNS, central nervous system; CYP, cytochrome P450; ER, extended release; HEC, highly emetogenic chemotherapy; INR, prothrombin time; IV, intravenous; MEC, moderately emetogenic chemotherapy; NDA, new drug application; NK1, neurokinin-1; NV, nausea and vomiting; ODT, orally disintegrating tablet; P-gp, p-glycoprotein; PONV, postoperative nausea and vomiting; QD, once a day; RINV, radiotherapy-induced nausea and vomiting; TdP, torsades de pointes; TID, three times a day

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Focinvez is not currently marketed in the United States.

NDA 22023 for the LD (Emend [fosaprepitant] for injection) was initially approved in 2008. Support for the approval was based on:

- Demonstration of noninferiority to Emend (aprepitant) capsules when both treatments were administered with standard therapy (i.e., ondansetron and dexamethasone) for the prevention of acute and delayed CINV in patients receiving HEC,
- Demonstration of superiority to standard therapy (i.e., ondansetron and dexamethasone) for the prevention of CINV in the delayed phase in patients receiving MEC, and
- Referenced data submitted to NDA 21549 for Emend (aprepitant) capsules (initially approved in 2006 and owned by the same Applicant).

Fosaprepitant dimeglumine continues to be marketed in the US through the innovator product (Emend for injection), an additional formulation of fosaprepitant approved through the 505(b)(2) regulatory pathway (NDA 210054), and multiple ANDA products that relied on the FDA's findings of safety and effectiveness for Emend for injection as the reference listed drug .

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-NDA communication occurred under investigational new drug (IND) 140555. A summary of relevant regulatory activity is described in Table 2.

Table 2. Summary of Presubmission/Submission Regulatory Activity

Communication	Summary
September 28, 2018: Type B Pre-IND Written Response	• FDA agreed the proposal to rely upon Emend for injection appeared acceptable. • FDA stated a "bridge" should be established between the proposed drug and each LD. • FDA stated an in vitro hemolysis potential study was needed, in addition to the proposed local irritation study in rabbits. • FDA agreed there were no novel excipients in the proposed formulation. • FDA stated that leachability and extractability studies were needed. • FDA could not agree with granting a biowaiver and requested additional information regarding differences between the proposed drug and LD.
October 11, 2018: Type B Pre-IND Written Response	• FDA agreed with the proposed plan for registration batch manufacturing and scale-up for future commercial production but stated that additional information would need to be submitted in the NDA, or as a pre-approval supplement, once a manufacturer is identified. • FDA stated that an iPSP must be submitted, as the proposed product is a new dosage form, which triggers the requirement for a pediatric assessment under PREA.

October 8, 2021: Type B Pre-NDA Written Response	• FDA stated that the acceptance criteria for tests in the proposed drug product specification would be a matter of NDA review but that the endotoxins specification should be lowered to be appropriate for pediatric dosing. • FDA stated that the extractability and leachability studies appeared reasonable and provided advice regarding additional information to include in the NDA. • FDA stated that modification of manufacturing facilities during the NDA review cycle may change the PDUFA goal date and provided advice regarding CMC information to include in the NDA. • (b) (4) • FDA stated that expiration of the drug product would be determined during NDA review based on the stability data. • FDA stated that the results of the in vitro assessment of human blood pH appeared to address concerns regarding effects of the highly alkaline formulation. • FDA agreed that the submitted information provided evidence to demonstrate that the differences between the two formulations in terms of inactive ingredients and physicochemical properties would not affect in vivo pharmacokinetic performance. • FDA did not agree with the biowaiver request because the proposed drug product is not qualitatively and quantitatively the same as the LD but stated that bridging may be possible. • FDA stated that the proposed content of the ISS appeared reasonable, provided that a bridge is established between the proposed product and the LD, and that determination of a necessary risk management approach would be determined during NDA review. • FDA stated that assessment of the acceptability of a request for waiver or deferral of pediatric studies and contents of eventual prescribing information, would be determined during NDA review.
November 10, 2021: Pediatric Study Plan – Initial Agreement	• FDA agreed with the Agreed iPSP dated November 9, 2021 and had no further comments.

Source: reviewer generated table
Abbreviations: CMC, chemistry, manufacturing, and controls; FDA, United States Food and Drug Administration; IND, investigational new drug application; iPSP, initial pediatric study plan; ISS, integrated safety summary; LD, listed drug; NDA, new drug application; PDUFA, Prescription Drug User Fee Act; PREA, Pediatric Research Equity Act

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

No clinical studies were conducted to support this 505(b)(2) application. Therefore, the Office of Scientific Investigations inspection was not needed.

4.2. Product Quality

The drug product (DP) manufacturing and testing facilities (FEI 3006503102 and FEI 1000513101, Pharmaceutics International, Inc.; Hunt Valley, Maryland) were considered inadequate upon inspection and deficiencies were not resolved during the review cycle of this application. The Applicant has not designated an alternate drug product manufacturing facility; therefore, the drug product manufacturing facilities are inadequate to support approval of this application. For further information, refer to the Manufacturing chapter of the Office of Pharmaceutical Quality (OPQ) review.

4.3. Biopharmaceutics

The Applicant is seeking approval to market fosaprepitant injection, 150 mg/50 mL (3 mg/mL) (in 50 mL vials), a ready-to-use sterile solution for injection, following the 505(b)(2) regulatory pathway. The Applicant is relying upon the FDA's findings of safety and effectiveness of the LD (Emend [fosaprepitant dimeglumine] injection, powder, lyophilized, for solution, 150 mg/vial marketed by Merck & Co., Inc. [NDA 022023]). The proposed drug product contains the same active ingredient as the LD (fosaprepitant dimeglumine), is intended for the same indications in the same patient population, uses the route of intravenous administration, and follows the same dosing regimen. The proposed product is a ready-to-use aqueous solution formulation containing 3 mg/mL of fosaprepitant, 0.108 mg/mL of edetate disodium (b) (4), and 160 mg/mL of Betadex sulfobutyl ether sodium (i.e., sulfobutyl ether β-cyclodextrin sodium; SBEβCD) (b) (4) in water for injection. The LD is a lyophilized powder (150 mg/vial). As per the approved labeling, the LD is diluted with 0.9% NaCl solution in the vial to a concentration of 1 mg/mL before adding to the IV infusion bag. The proposed drug product is a ready-to-use solution with a concentration of 3 mg/mL and does not require dilution before adding to the IV infusion bag. The development strategy of the proposed product, therefore, is focused on bridging the difference between the proposed drug product and the LD.

The Applicant submitted a formal request to bridge the proposed drug product and the LD based on 21 CFR 320.24(b)(6). The Biopharmaceutics review focused on the waiver request for fosaprepitant injection, 150 mg/50 mL. A scientific bridge between the LD and the proposed drug product has been established under 21 CFR 320.24(b)(6) due to the following reasons:

1. The proposed drug product and the LD are both administered by IV infusion.
2. The proposed undiluted drug product and the reconstituted LD are compositionally similar and have comparable physicochemical properties.
3. Although the proposed product has a higher pH and osmolarity than the LD, nonclinical studies demonstrated that administration of the proposed fosaprepitant injection product results in comparable absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetics (PK) profiles when compared to administration of the LD.

The adequacy of the nonclinical data to support acceptance of the excipient SBEβCD at its proposed concentration, and to demonstrate that the differences between the proposed

product and the LD will not impact the safety of fosaprepitant injection for the prevention of CINV, was reviewed by the Pharmacology/Toxicology group as described in Section 5.

From a Biopharmaceutics perspective, NDA-216686-ORIG-1 for fosaprepitant injection, 150 mg/50 mL is recommended for approval. For further information, refer to the Biopharmaceutics chapter of the OPQ review.

4.4. Microbiology

The data submitted in support of the microbiology review were determined to be adequate. For further information, refer to the Microbiology chapter of the OPQ review.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

NDA 216686 seeks approval of fosaprepitant injection, 150 mg/50 mL (3 mg/mL) through the 505(b)(2) regulatory pathway, referencing Emend (fosaprepitant) for injection (NDA 22023) as the LD. The proposed product and the LD have the same active ingredient, fosaprepitant dimeglumine**.** Fosaprepitant dimeglumine is a phosphorylated prodrug of aprepitant. Fosaprepitant is rapidly converted to aprepitant in vivo following intravenous administration. Aprepitant is a selective antagonist of human substance P/NK_1 receptors. The proposed fosaprepitant injection product is intended for the same indications in the same patient population, using the same (intravenous) route of administration, and following the same dosing regimen as the LD. However, it has a different dosage form with different inactive ingredients than the LD. Emend (fosaprepitant) for injection is a lyophilized powder that requires reconstitution to solution prior to injection, whereas the proposed fosaprepitant injection is a ready-to-use solution. No novel excipients are used in the DP formulation.

Fosaprepitant and aprepitant have been extensively studied and have a long history of clinical use. The Applicant is proposing to rely upon the FDA's findings of safety and effectiveness for the LD based on the compositional similarity of their product. In addition, the Applicant has conducted the following nonclinical studies to support that the differences between the proposed product and the LD will not affect its safety or effectiveness for the proposed indications and to establish that the proposed bridge to the LD is scientifically appropriate: PK, local tolerance, hemolytic potential, and effects on blood pH and electrolyte balance.

The IV PK study (Study B20A30A) in male beagle dogs showed that fosaprepitant was rapidly converted to aprepitant after IV administration of either the proposed fosaprepitant injection product or the LD. There were no significant differences in the PK parameters between both products, and the plasma concentration-time profiles of formed aprepitant were comparable between both products. Similarly, in human liver microsomes, fosaprepitant was rapidly converted to aprepitant from both products. In the local tolerance study, IV or perivascular

injection of the proposed fosaprepitant injection product caused minimal irritation that was comparable to observations after administration of either the LD or the vehicle control. Additionally, the proposed fosaprepitant injection product did not cause hemolysis of dog or human blood in vitro.

Overall, based on the available nonclinical information, no safety concerns or approvability issues are noted for the Applicant's fosaprepitant injection.

5.2. Referenced NDAs, BLAs, DMFs

This application references NDA 22023 (Emend [fosaprepitant] for injection) as the LD.

5.3. ADME/PK

A summary of the Applicant's conducted assessments of ADME and PK are shown in Table 3 below.

Table 3. Summary of ADME and PK Assessments

Type of Study	Major Findings
Absorption	
Study Title: Pharmacokinetic Study of Fosaprepitant in Male Beagle Dogs in Two Formulations Study Number: B20A30A	The objective of this study was to compare the PK profiles of fosaprepitant, and its metabolite aprepitant, following a single IV dose of fosaprepitant in male beagle dogs of two formulations, the Applicant's fosaprepitant injection, 3 mg/mL and Emend for injection (powder, lyophilized for solution). Fosaprepitant was found to be rapidly converted to aprepitant after IV dosing of fosaprepitant in these two formulations. Plasma concentration-time profiles of aprepitant appeared approximately the same between these two formulations. The C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and $T_{1/2}$ were 2103 ng/mL, 0.083 min, 19974 ng.h/mL, 21280 ng.h/mL and 11 h, respectively, for Spes' fosaprepitant injection, and 2023 ng/mL, 0.104 min, 19939 ng.h/mL, 21442 ng.h/mL, and 12 h, respectively, for Emend for injection. There was no significant difference in these PK parameters between these two formulations. The ratios of aprepitant C_{max}, AUC_{0-t} and AUC_{0-inf} between fosaprepitant injection and Emend for injection were 1.06, 1.00, and 0.99, respectively. Overall, based on the results of this study, differences in formulation compositions between these two test products did not appear to affect the PK profile and conversion of fosaprepitant to aprepitant in vivo.

Type of Study	Major Findings
Metabolism	
Study Title: Metabolic Conversion of Fosaprepitant to Aprepitant in Human Liver Microsomes in Vitro with Two Formulations Study Number: B20A46A	In vitro $T_{1/2}$ of fosaprepitant was estimated to be 2.4 min and 2.3 min for fosaprepitant injection and Emend for injection, respectively. In vitro intrinsic clearance (CLint) of fosaprepitant was estimated to be 0.58 mL/min/mg and 0.60 mL/min/mg for fosaprepitant injection and Emend for injection, respectively. There was no substantial difference in microsomal clearance of fosaprepitant between these two formulations. Approximately 100% of fosaprepitant was converted to aprepitant following 10 min of incubation for both formulations. The formation rate was 3.42 and 3.53 nmol/mg/min for fosaprepitant injection and Emend for injection, respectively. There was no substantial difference in the formation of aprepitant in human liver microsomes between the two formulations.

Source: Reviewer's generated table
Abbreviations: ADME, absorption, distribution, metabolism, excretion; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IV, intravenous; PK, pharmacokinetics; $T_{1/2}$, half-life; T_{max}, time to C_{max}

5.4. Toxicology

5.4.1. Other Toxicology Studies

Study Title: Fosaprepitant Injection (3 mg/ mL): Vascular and Perivascular Tolerance Study in Rabbits (Study No. 54871)

An assessment of local tolerance and irritation potential of the undiluted and diluted fosaprepitant injection product compared to the LD (i.e., the control article) and 0.9% sodium chloride injection, United States Pharmacopeia (USP) (i.e., normal saline [NS], the vehicle control) was conducted in New Zealand white rabbits following a single IV or perivascular injection, respectively.

Minimal dermal edema and erythema of the same incidence and severity were observed at the IV injection sites of animals that received either the control article (Group 2) or diluted test article (Group 4). IV administration of undiluted (Group 3) test article resulted in a slight increase in the incidence and severity of dermal edema and erythema compared to the vehicle control (Group 1) and the control article (Group 2). However, no microscopic evidence of necrosis or fibrosis was observed in the examined sections of IV dosing sites. No microscopic evidence of thrombus, necrosis, or fibrosis was observed in the examined sections of perivascular administration. Overall, IV or perivascular administration of fosaprepitant injection (3 mg/mL) caused minimal irritation that was comparable to the control article (Emend for injection) and vehicle control (NS).

Study Title: Effect of Fosaprepitant Injection on the pH of Human Blood In Vitro (Study No. B21A16)

This in vitro study was conducted using human blood to mimic adult and pediatric in vivo situations, based on the estimated total blood volumes (TBV). The pH was measured before and after the addition of the test article.

The pH of the blood was 7.15 before the addition of the Applicant's fosaprepitant injection. After the addition of fosaprepitant injection, the pH values were 7.15, 7.16, and 7.16 for lot # 001, lot # 002, and lot # 003 for adult situations (1:100, v/v). For pediatric situations (1:46.5, v/v), the pH values after the addition of fosaprepitant injection were 7.16, 7.13, and 7.14. The minor differences among the groups were within the normal variations of pH measurement. Overall, the pH of human blood was not affected by the addition of fosaprepitant injection, 150 mg/50 mL (3 mg/mL). Based on these results, the higher pH of fosaprepitant injection, as compared to the LD, is unlikely to cause alkalemia in either adult or pediatric patients when administered at the proposed doses.

Study Title: Determination of Hemolysis Potential by Fosaprepitant Injection and Emend for Injection in Human and Beagle Dog Whole Blood (Study No. BGUA-0002-DV-SB)

The purpose of this study was to examine the hemolysis potential of fosaprepitant injection and the LD in beagle dog whole blood and human whole blood. In this study, stock and serially diluted solutions of fosaprepitant injection and the LD were spiked into whole blood. The final assay concentrations of fosaprepitant in blood ranged from 0.0195 to 30.0 µg/mL for fosaprepitant injection and 0.0195 to 10.0 µg/mL for the LD. Saponin and warfarin were used as positive and negative controls, respectively.

In beagle dog whole blood, fosaprepitant injection, over a concentration range of 0.0195 to 30.0 µg/mL, caused no hemolysis. The LD did not cause hemolysis over a concentration range of 0.0195 to 10.0 µg/mL. In human whole blood, neither fosaprepitant injection nor the LD caused hemolysis over a concentration range of 0.0195 to 30.0 µg/mL and 0.0195 to 10.0 µg/mL, respectively. Overall, no hemolysis was observed with fosaprepitant injection or the LD.

Excipients

The proposed fosaprepitant injection product is a ready-to-use solution of fosaprepitant (as fosaprepitant dimeglumine salt). Each 50 mL vial contains 150 mg (3 mg/mL) of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine), 5.4 mg of edetate disodium, USP (0.108 mg/mL), and 8.0 g (160 mg/mL) of Betadex sulfobutyl ether sodium (i.e., sulfobutyl ether β-cyclodextrin sodium [SBEβCD]), USP in Water for Injection, USP. In addition, sodium hydroxide, National Formulary (NF) (b) (4) used for pH modification. All excipients in the DP met compendia (USP-NF) monograph specifications and have been used in FDA approved DPs as listed in the FDA inactive ingredient database (FDA

2022). The levels of all excipients used were within those used in the FDA-approved injection products.

Edetate Disodium

Edetate disodium is a commonly used [redacted] in parenteral formulations. The concentration of edetate disodium in the proposed fosaprepitant injection formulation is approximately 0.108 mg/mL. The expected daily exposure of 5.4 mg of edetate disodium from the DP is well below the daily maximum exposure to edetate disodium from FDA approved intravenous DP (19 mg/day) per the inactive ingredient database.

Betadex Sulfobutyl Ether Sodium, USP

Betadex sulfobutyl ether sodium, or SBEβCD, is widely used [redacted] in pharmaceutical products including parenteral injection products. The inactive ingredient database lists the usage of SBEβCD at up to 40% or 400 mg/mL as the maximum potency in intravenous, intramuscular, and subcutaneous injection products. SBEβCD is included at a concentration of 160 mg/mL in the proposed fosaprepitant injection formulation [redacted]. The maximum daily exposure of SBEβCD from the proposed DP is 8.0 g/day, which is less than the maximum daily exposure of SBEβCD in other FDA-approved drug products such as Carnexiv (carbamazepine) injection (i.e., 28 g/day). Thus, the amount of SBEβCD used in the proposed DP is acceptable from the nonclinical standpoint.

Impurities

[redacted] ([redacted] was controlled at a limit of not more than (NMT) [redacted]% as an "unspecified impurity" in the drug substance (DS). Per the FDA/CDER Computational Toxicology Consultation Service report dated March 29, 2022, [redacted] was predicted to be negative for bacterial mutagenicity. Based on this, the specification for [redacted] at NMT [redacted]% is acceptable from the nonclinical standpoint.

The major degradation product identified in the DP was [redacted]. The Applicant's proposed acceptance limit of [redacted] (NMT [redacted]%) in the DP is acceptable, [redacted]

Potential Genotoxic Impurities

Three potential genotoxic materials (i.e., [redacted] were used or generated during the manufacturing process of the DS. The levels of the potential genotoxic impurities are acceptable as the maximum daily exposure of each impurity will be below the acceptable daily intake (ADI) of [redacted] µg per day [redacted]ppm based on the maximum daily fosaprepitant dimeglumine dose of 245.3 mg; [redacted] and the total

exposure for the three impurities will be (b) (4) µg per day (b) (4)), which is below the ADI for multiple Class 3 impurities (60 µg/day) for treatment durations of 1-12 months per the International Conference on Harmonisation (ICH) M7 guidance (March 2018).

Elemental Impurities

(b) (4) was used as a (b) (4) during manufacturing of the DS and was controlled at NMT (b) (4) ppm per the ICH Q3D guidance (September 2022). Other elements listed in ICH Q3D were not intentionally added and were considered not likely to be present in the DS based on the risk assessment per the ICH Q3D guidance.

Residual Solvents

The limit of each residual solvent (b) (4)) in the DS was set per the ICH Q3C guidance and were below the acceptable limits and are acceptable. The above solvents are Class 2 solvents except (b) (4), which is a Class 3 solvent (less toxic) per the ICH Q3C guidance (December 2021).

(b) (4) **Risk Assessment**

The Applicant submitted a (b) (4) assessment report which evaluated the potential risk of (b) (4) forming and carryover from starting materials per FDA guidance (September 2020). The Applicant stated that (b) (4) were used in the manufacturing process of fosaprepitant dimeglumine (b) (4) Additionally, (b) (4) was used in the manufacturing process (b) (4) However, as no (b) (4) were used in the manufacturing process of fosaprepitant dimeglumine there was no potential risk of (b) (4) formation or carryover. Based on the Applicant's risk assessment, there is no risk for potential (b) (4) formation in the active pharmaceutical ingredient .

Extractable/Leachable Evaluation

The primary packaging components or the container closure components for the proposed fosaprepitant injection product consists of a (b) (4) glass vial and a (b) (4) rubber stopper (b) (4) The Applicant submitted results from the following extractable/leachable studies:

- Extractable and Leachable Analysis for Glass Vial
- Extractables Screening of (b) (4) Rubber Stoppers for Fosaprepitant Injection, 3 mg/mL (Report No. 20-76518-A)

- Safety Evaluation-Extractables from [redacted] (Report No. R-19-5293-RISKL)
- Leachable Study (Report No. 20-76518-C)

Extractable and Leachable Analysis for Glass Vial

Based on the continuous monitoring and testing results for the USP <660>Glass Grain test, extractable heavy metal, and arsenic extraction, and tests using stressed (after storage at 25°C for more than 8 months) samples from all three registration batches of the DP, potential leachables from the glass vials were considered negligible and no further testing for glass extractables was warranted.

Extractables Screening of [redacted] Rubber Stoppers for Fosaprepitant Injection, 3 mg/mL (Report No. 20-76518-A)

An extractables study with the stopper for the proposed fosaprepitant injection product, a [redacted] 20 mm grey [redacted] rubber stopper [redacted] was performed using water at pH 11, isopropyl alcohol (IPA), 50% IPA, and 2% nitric acid as extraction solvents. The safety of each extractable was evaluated as a possible leachable by a worst-case extrapolation of extractables data to potential leachable behavior in the proposed fosaprepitant injection product. Three potential leachables were considered to have levels that could go above the threshold of toxicological concern (1.5 µg/day) but remain well below the ADI of 20 µg/day (per ICH M7 guidance) (March 2018) based on the intermittent treatment duration or less than lifetime exposure of 1-12 months. It should be noted that the extraction study was conducted using aggravated conditions that do not represent actual use/storage conditions.

A study assessing safety of leachables from the DP was conducted using stability samples. As discussed below under **Leachable Study (Report No. 20-76518-C)** (i.e., the leachable study conducted with the final DP), three non-volatile and five volatile/semi-volatile leachables were detected above the limit of quantitation (LOQ) [redacted] µg/day, respectively); however, these were well below the ADI of 20 µg/day and do not raise significant safety concerns.

Safety Evaluation-Extractables from [redacted] (R-19-5293-RISKL)

The Applicant submitted an extractables safety evaluation report for potential leachables from [redacted] In the extractables study, [redacted]. Potential risk of extractables was evaluated by comparing the toxicological profiles of the substances with the exposure scenario based on available data from the literature or structural considerations (quantitative structure activity relationship/QSAR). The permitted daily exposure

(PDE) values were calculated by applying appropriate safety factors (F1-F6) per the ICH Q3C guidance (December 2021) using 50 kg body weight. Eighteen substances were identified in this extractable study, (b) (4) However, the potential daily exposure for each of these nine identified extractables was well below their respective PDE values. The objective of this extractable study was to identify potential leachables from the final DP and did not reflect actual user/storage conditions; rather, the conditions used in this extractables study represented exaggerated (worst-case) conditions. The safety assessment of leachables should ultimately be based on the results of the leachable study conducted with the final DP stability batches. As discussed below under **Leachable Study (Report No. 20-76518-C)** (i.e., the leachable study conducted with the final DP), three non-volatile and five volatile/semi-volatile leachables detected above the LOQ (b) (4) µg/day, respectively) were well below the ADI of 20 µg/day and do not raise significant safety concerns.

Leachable Study (Report No. 20-76518-C)

A worst-case potential leachable analysis was conducted using three registration batches of stability samples (i.e., the final DP) stored inverted at 25°C/60% relative humidity (RH) under accelerated conditions for 8-9 months. (b) (4) ll detected leachables were well below the ADI of 20 µg/day. Overall, from the nonclinical standpoint, the results of the leachable study with the DP stability batches do not raise significant safety concerns.

6. Clinical Pharmacology

6.1. Executive Summary

NDA 216686 seeks approval of fosaprepitant injection, 150 mg/50 mL or 3 mg/mL through the 505(b)(2) regulatory pathway, referencing Emend (fosaprepitant) for injection (NDA 22023), as LD. The proposed fosaprepitant injection product is a ready-to-use sterile solution for injection compared to Emend for injection, which is a sterile lyophilized powder for solution that requires reconstitution prior to administration. The same indications and dosage regimens as the LD are proposed. The infusion rate is also the same (i.e., 150 mg over 20-30 min for adult patients), although the drug concentration of the proposed product (3 mg/mL) is higher than

Emend for injection after reconstitution (1 mg/mL). As the proposed product is for intravenous infusion, the Applicant established a scientific bridge to the LD through the similarity of fosaprepitant injection to the LD, and an in vivo relative bioavailability study was deemed unnecessary. See Section 4.2, and refer to the Biopharmaceutics chapter of the OPQ review for more details. No additional clinical pharmacology studies were conducted to support this 505(b)(2) application. The proposed labeling for clinical pharmacology information is consistent with the labeling of the LD and is acceptable.

Recommendation

The Office of Clinical Pharmacology found the application acceptable from a clinical pharmacology standpoint.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

None.

7.2. Review Strategy

No clinical studies were conducted to support this 505(b)(2) application. The Applicant proposes to rely upon the FDA's findings of safety and effectiveness for the LD (Emend [fosaprepitant] for injection, NDA 22023). Therefore, the determination of effectiveness for fosaprepitant injection for the prevention of CINV is based on the establishment of a scientific bridge to the LD. This bridge is based on the similarity of the product to the LD and submitted data from nonclinical studies. For details on adequacy of the bridge to support that reliance upon the FDA's findings of safety and effectiveness for the LD is scientifically appropriate, refer to Section 4.2 and Section 5.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

No clinical efficacy studies were conducted to support this 505(b)(2) application. The Applicant proposes to rely upon the FDA's findings of effectiveness for the LD (Emend [fosaprepitant] for injection, NDA 22023).

8.2. Review of Safety

8.2.1. Safety Review Approach

No clinical safety studies were conducted to support this 505(b)(2) application. The Applicant proposes to rely upon the FDA's findings of safety for the LD (Emend [fosaprepitant] for injection, NDA 22023). In addition to information on the compositional similarity of the products, the Applicant submitted nonclinical data to justify that the differences between fosaprepitant injection and the LD (i.e., the addition of SBEβCD as an excipient and the higher pH of the proposed product) would not impact its safety to support that reliance upon the FDA's findings of safety for the LD is scientifically appropriate.

In the NDA, the Applicant also submitted the following information to support the evaluation of safety for fosaprepitant injection:

- Summary of scientific literature published between 2008 to July 2021 regarding clinical safety of fosaprepitant.
- Summary of adverse events potentially related to fosaprepitant reported to the FDA Adverse Event Reporting System between 2008 to August 2021.

FDA review of safety for this application focused on the Applicant's demonstration of the similarity of the proposed fosaprepitant injection product to the LD (Section 4.2), the submitted data from nonclinical studies to support the safety of the formulation differences between the proposed drug product and the LD (Section 5), and review of available literature and post-marketing safety data from the clinical use of fosaprepitant/aprepitant products for the prevention of CINV.

8.2.2. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety concerns were identified through review postmarket experience with the use of fosaprepitant/aprepitant products for the prevention of CINV. Additionally, review of the currently available scientific literature regarding clinical safety of fosaprepitant/aprepitant products did not reveal new safety concerns.

Of note, in July 2021, the Division of Pharmacovigilance-I completed a review of FDA Adverse Event Reporting System reports for fosaprepitant in pediatric patients from January 25, 2008 (the date of initial approval for Emend [fosaprepitant] for injection) to April 30, 2021. Division of Pharmacovigilance-I did not identify any unlabeled pediatric adverse events and did not identify any new pediatric safety concerns for fosaprepitant. See the July 22, 2021 review under NDA 22023 for details.

Expectations on Safety in the Postmarket Setting

The review team anticipates that routine pharmacovigilance will be adequate to ensure safe use of fosaprepitant injection.

8.2.3. Integrated Assessment of Safety

No clinical studies were conducted to support this 505(b)(2) application. The Applicant proposes to rely upon the FDA's findings of safety for the LD (Emend [fosaprepitant] for injection, NDA 22023).

To support the proposed reliance, the Applicant submitted information to demonstrate the similarity of fosaprepitant injection to the LD and data from nonclinical studies to support that the safety of their product will not be impacted by the differences from the LD. The review team has determined that Applicant has successfully demonstrated that the proposed reliance upon the FDA's findings of safety for the LD for the prevention of CINV is scientifically appropriate.

Additionally, no new safety concerns were identified during the review of available post-marketing safety data from the clinical use of fosaprepitant or aprepitant products for the prevention of CINV or based on the review of the currently available scientific literature regarding clinical safety of fosaprepitant or aprepitant products.

8.3. Conclusions and Recommendations

Based on the demonstration of the similarity of fosaprepitant injection to the LD (Emend [fosaprepitant] for injection, NDA 22023) and the data from nonclinical studies submitted to support that the formulation differences between the proposed product and the LD would not impact the safety or effectiveness of fosaprepitant injection relative to the LD, a scientific bridge has been established between fosaprepitant injection and Emend (fosaprepitant) for injection. This scientific bridge is adequate to justify the Applicant's proposed reliance upon the FDA's findings of safety and effectiveness for the LD for the sought indications. Accordingly, the overall benefit-risk for fosaprepitant injection for the indications listed below is favorable.

Indicated in adults and pediatric patients 6 months of age and older, 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
- Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

No new safety signals were identified during review of this application. The identified risks can be mitigated through labeling and routine pharmacovigilance is recommended. No additional risk management strategies are recommended at this time.

The review team, however, is unable to recommend approval for this NDA due to identified issues with the DP manufacturing and testing facilities (FEI 30006503102 and FEI 100513101, Pharmaceutics International, Inc.; Hunt Valley, Maryland). As described in Section 4.1, the facilities were considered inadequate upon inspection and the identified deficiencies were not resolved during the review cycle of this application. Therefore, the DP manufacturing and testing facilities are inadequate to support approval of this application. For further information, refer to the Manufacturing Review Chapter of the OPQ review.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was needed for this 505(b)(2) NDA.

10. Pediatrics

This application included a requested indication for pediatric patients ages 6 months to 17 years that was consistent with the indication granted to the LD (Emend [fosaprepitant] for injection).

Under the Pediatric Research Equity Act (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. This NDA triggered PREA as a new formulation.

Although with establishment of a scientifically appropriate bridge to the LD, should the NDA be approved, fosaprepitant injection is eligible to receive the pediatric indications granted to the LD, this would not fulfill the PREA requirement for a pediatric assessment in pediatric patients ages birth to 6 months.

The Applicant submitted an initial pediatric study plan pediatric to IND 140555 prior to NDA submission, and initial agreement was reached on November 10, 2021. The agreed initial pediatric study plan included a plan to conduct a study to evaluate the pharmacokinetics, safety, and tolerability of a single dose of fosaprepitant injection for prevention of chemotherapy-induced nausea and vomiting in pediatric patients 0 to less than 6 months of age undergoing HEC or MEC. Because a complete response (CR) is recommended for NDA 216686, no PREA postmarketing requirements (PMRs) will be issued. If NDA 216686 is resubmitted, then PREA would apply. PMRs will be determined upon receipt of a subsequent submission to address the deficiencies noted during the review of this application.

Of note, on May 2, 2022, NDA 22023/S-021 for the LD (Emend [fosaprepitant] for injection) was approved to add an additional 3-day dosing regimen consisting of Emend for injection on Days 1, 2, and 3 for pediatric patients ages 6 months to 17 years. As this regimen is currently protected by pediatric exclusivity, it was not requested by the Applicant nor considered for during review of this application.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant's proposed labeling was reviewed, and recommended revisions and comments have been communicated to the Applicant during the review of this NDA.

The prescribing information includes similar information to that found in the prescribing information for the LD (Emend [fosaprepitant] for injection). However, as this application will receive a CR letter, no labeling will be approved.

12. Risk Evaluation and Mitigation Strategies

No risk revaluation and mitigation strategies are recommended.

13. Postmarketing Requirements and Commitment

None at this time.

14. Division Director (Clinical – Designated Signatory Authority) Comments

I concur with the recommendation of the review team to issue a CR letter for NDA 216686 for fosaprepitant injection due to unresolved deficiencies with the drug product manufacturing and testing facilities. NDA 216686 is a 505(b)(2) application that relies upon the FDA's previous findings of safety and effectiveness for the LD, Emend for injection (NDA 22023).

The proposed fosaprepitant injection product is a 150 mg/50 mL (3 mg/mL) ready-to-use solution for injection. Preparation and concentration of the proposed product differs from the LD, which is supplied as a lyophilized powder for reconstitution to a final concentration of 1 mg/mL.

I agree with the review team that the Applicant has adequately established a scientific bridge between the proposed product and the LD through the demonstration of compositional similarity and submitted nonclinical studies to support that the differences between the products will not impact the safety or effectiveness of fosaprepitant injection for the prevention of CINV. This bridge is adequate to justify the proposed reliance upon the FDA's previous findings of safety and effectiveness for the LD.

However, during the pre-approval inspection of the drug product manufacturing and testing facilities (FEI 30006503102 and FEI 100513101, Pharmaceutics International, Inc.) significant deficiencies were identified which resulted in a facility assessment recommendations of inadequate and withhold status based on current good manufacturing practice regulations.

Therefore, the facilities were determined to be unacceptable to support the approval of NDA 216686, and an approval action cannot be taken until the Applicant satisfactorily resolves the deficiencies.

NDA 216686 is subject to PREA requirements as a new formulation. Because a CR is recommended, no PREA PMRs will be issued. Postmarketing requirements and commitments, if deemed appropriate, will be communicated at the time of resubmission of the application.

15. Appendices

15.1. References

Guidance for Industry *Q3C(R8) Impurities: Guidance for Residual Solvents Guidance for Industry* (December 2021)

FDA, 2022, Inactive Ingredients Database Download, accessed, https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download.

Hesketh, PJ, MG Kris, E Basch, K Bohlke, SY Barbour, RA Clark-Snow, MA Danso, K Dennis, LL Dupuis, SB Dusetzina, C Eng, PC Feyer, K Jordan, K Noonan, D Sparacio, and GH Lyman, 2020, Antiemetics: ASCO Guideline Update, J Clin Oncol, 38(24):2782-2797.

Guidance for Industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018)

Merck&Co, 2022, EMEND (fosaprepitant) IV USPI, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022023s021lbl.pdf.

(b) (4)

Draft Guidance for Industry *Q3D(R2) – Guideline for Elemental Impurities* (September 2022)

15.2. Financial Disclosure

Not applicable, as no new clinical studies were conducted to support this 505(b)(2) NDA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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