Joint Summary Clinical Review

Division of Gastroenterology
Office of Immunology and Inflammation / Office of New Drugs
Center for Drug Evaluation and Research

Application Type	NDA
Application Number(s)	216686
Submit Date(s)	February 28, 2023 (Class 2 Resubmission)
PDUFA Goal Date	August 28, 2023
Division/Office	Division of Gastroenterology/Office of Immunology and Inflammation
Review Completion Date	August 9, 2023
Established/Proper Name	Fosaprepitant injection
(Proposed) Trade Name	Focinvez
Pharmacologic Class	Substance P/neurokinin-1 (NK1) 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: 1) Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin 2) Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Applicant Proposed SNOMED CT Indication	Chemotherapy-induced nausea and vomiting (disorder), 18846006
Recommended 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: 1) Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin 2) Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Recommended SNOMED CT Indication	Chemotherapy-induced nausea and vomiting (disorder), 18846006
Recommendation on Regulatory Action	Approval

Review Team- Division of Gastroenterology and Collocates

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Abbreviations: DIIP, Division of Inflammation and Immune Pharmacology; DPT, Division of Pharmacology and Toxicology; DRO II, Division of Regulatory Operations II; OCP, Office of Clinical Pharmacology; ORO, Office of Regulatory Operations; OTS, Office of Translational Sciences

Additional Reviewers of Application Resubmission

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OPQ Drug Product	Zhengfang Ge; Hong Cai
OPQ Drug Substance	Sharon Kelly; Laurence Perez; Donna Christner
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DPMH/Maternal Health	Christos Mastroyannis; Tamara Johnson
DPMH/Pediatric Health	Sonaly McClymont; Shetarra Walker; Shamir Tuchman

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

Executive Summary

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) Resubmission

NDA 216686 seeks the approval of Focinvez (fosaprepitant injection) through the 505(b)(2) regulatory pathway. This resubmission was received on February 28, 2023 in response to the issuance of a complete response action for the original NDA submission. In the original submission of NDA 216686 (received December 23, 2021), the Applicant 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).

During review of the original submission of NDA 216686, the review team determined that the Applicant adequately established a scientific bridge between the proposed product and the LD. This bridge was established through the demonstration of compositional similarity between the products 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. The review team determined that the information contained in the Application was adequate to justify that the proposed reliance upon the FDA's previous findings of safety and effectiveness for the LD was scientifically appropriate.

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 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 a Complete Response letter was issued on October 19, 2022. The letter communicated the following deficiencies.

1. During a recent inspection of the Pharmaceutics International, Inc. (FEI 3006503102) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. During a recent inspection of the Pharmaceutics International, Inc. (FEI 1000513101) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

For details of the prior review, including discussion of the therapeutic context and additional regulatory background, see the October 13, 2022 Multi-Disciplinary Review and Evaluation (Unireview) in Darrts (Reference ID: 5060107). In this resubmission, the Applicant has provided a response to the above deficiencies, revisions to the proposed prescribing information and patient labeling in accordance with FDA recommendations communicated in the Complete Response letter, and a safety update of available clinical information from the use of fosaprepitant in accordance with 21 CFR 314.50(d)(5)(vi)(b).

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:

1. Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC) including high-dose cisplatin.
2. 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.

Conclusions on the Substantial Evidence of Effectiveness

As with the review of the original submission of NDA 216686, no assessment of effectiveness is warranted for this resubmission. 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.

Updated Regulatory Background

The original submission of NDA 216686 received a complete response action on October 19, 2022. On January 12, 2023, the Applicant submitted a Type A end of review meeting request; however, this request was withdrawn upon receipt of the meeting preliminary comments (issued by FDA on February 7, 2023 [Reference ID: 5122300]). The current resubmission was received on February 28, 2023.

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

Product Quality

On repeat inspection post-remediation, the drug product (DP) manufacturing and testing facilities (FEI 3006503102 and FEI 1000513101, Pharmaceutics International, Inc.; Hunt Valley, Maryland) were assessed to have adequately resolved the deficiencies identified during the original review of the NDA and as communicated in the October 19, 2022 Complete Response letter. Accordingly, these facilities are considered to be adequate to support approval of this Application. For further information, refer to the Manufacturing chapter of the Office of Pharmaceutical Quality (OPQ) review, dated July 22, 2023 (Reference ID: 5213649).

Nonclinical Pharmacology/Toxicology

No new nonclinical/toxicology information was included in this resubmission. For details of the prior review, see the October 13, 2022 Multi-Disciplinary Review and Evaluation (Unireview) in Darrts (Reference ID: 5060107).

Clinical Pharmacology

No new clinical pharmacology data was included in this resubmission. For details of the prior review, see the October 13, 2022 Multi-Disciplinary Review and Evaluation (Unireview) in Darrts (Reference ID: 5060107).

Sources of Clinical Data and Review Strategy

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 the October 13, 2022 Multi-Disciplinary Review and Evaluation (Unireview) in DARRTS (Reference ID: 5060107).

Review of Safety

Safety Review Approach

During the original submission of NDA 216686, the review team determined that Applicant successfully demonstrated that the proposed reliance upon the FDA's findings of safety for the LD (Emend [fosaprepitant] for injection, NDA 22023) for the prevention of CINV was scientifically appropriate. For additional details, see the October 13, 2022 Multi-Disciplinary Review and Evaluation (Unireview) in DARRTS (Reference ID: 5060107).

FDA review of safety for this Application resubmission focused on the Applicant's updated integrated summary of safety. The Applicant's summary was updated to include information on adverse events reported to the FDA Adverse Event Reporting System (FAERS) Public Dashboard from the approval of the LD (Emend [fosaprepitant] for injection, NDA 22023) in 2008 through

September 30, 2022 and new clinical safety information for fosaprepitant available in the published literature through December 6, 2022. FDA review confirmed that this summary was accurate and representative of the known safety profile of fosaprepitant. No new safety signals were identified during review of this resubmission.

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 was been established between fosaprepitant injection and Emend (fosaprepitant) for injection during review of the original submission of NDA 216686. This scientific bridge remains 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:

1. Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
2. 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 resubmission. The identified risks can be mitigated through labeling and routine pharmacovigilance is recommended. No additional risk management strategies are recommended at this time.

Pediatrics

This Application included a requested indication for pediatric patients ages 6 months to 17 years that is 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.

With establishment of a scientifically appropriate bridge to the LD, fosaprepitant injection is eligible to receive the pediatric indications granted to the LD. However, this will 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 to IND 140555 prior to the original 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.

The following PREA postmarketing requirement (PMR) will be issued upon approval of the Application.

> *A study to evaluate pharmacokinetics, safety, and tolerability of a single dose of Fosaprepitant Injection 150 mg/50 mL (3 mg/mL) for prevention of chemotherapy-induced nausea and vomiting in pediatric patients 0 to 6 months of age undergoing highly emetogenic cancer chemotherapy (HEC) or moderately emetogenic cancer chemotherapy (MEC).*

This PMR was discussed with the Pediatric Review Committee (PeRC) during the review of the original Application. See the September 20, 2022 PeRC Meeting Minutes in DARRTS for full details (Reference ID: 5067145, date of submission October 26, 2022).

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 resubmission.

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 updated labeling has adequately addressed FDA's prior recommendations communicated in the October 19, 2022 Complete Response letter. For additional details, see the June 5, 2023 Label and Labeling Review from the Division of Medication Error Prevention and Analysis 1 in DARRTS (Reference ID: 5184773).

> *As agreed during review of the original Application the following statement was included in the prescribing information to acknowledge the exclusivity held by the LD.*

> *Additional pediatric use information is approved for Merck Sharp $ Dohme LLC's EMEND (fosaprepitant) for injection. However, due to Merck Sharp &Dohme LLC's marketing exclusivity rights, the drug product is not labeled with that information.*

The prescribing information includes similar information to that found in the prescribing information for the LD (Emend [fosaprepitant] for injection). For full details, see the approved prescribing information.

Risk Evaluation and Mitigation Strategies

No risk revaluation and mitigation strategies are recommended.

Postmarketing Requirements and Commitment

A PMR will be issued for studies under PREA. See Pediatrics above.

Division Director (Clinical – Designated Signatory Authority) Comments

I concur with the recommendation of the review team to issue a approval letter for NDA 216686 for fosaprepitant injection. 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.

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.

The deficiencies identified on prior inspection of the drug product manufacturing and testing facilities (FEI 30006503102 and FEI 100513101, Pharmaceutics International, Inc.) have been adequately resolved, and the facilities have been established to be acceptable to support the approval of NDA 216686.

NDA 216686 is subject to PREA requirements as a new formulation. The following PREA PMR will be issued at the time of approval.

A study to evaluate pharmacokinetics, safety, and tolerability of a single dose of Fosaprepitant Injection 150 mg/50 mL (3 mg/mL) for prevention of chemotherapy-induced nausea and vomiting in pediatric patients 0 to 6 months of age undergoing highly emetogenic cancer chemotherapy (HEC) or moderately emetogenic cancer chemotherapy (MEC).

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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