CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210064Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	210064
Applicant	Teva Pharmaceuticals USA, Inc.
Date of Submission	December 16, 2016; TA 10/12/2017; resubmission 4/5/2019
PDUFA Goal Date	September 5, 2019
Proprietary Name	
Established or Proper Name	Fosaprepitant for Injection
Dosage Form(s)	150 mg vial
Applicant Proposed Indication(s)/Population(s)	in combination with other antiemetic agents in ADULTS 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)
Action or Recommended Action:	*Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	*As above*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sandhya Apparaju/ Preeti Venkataraman
Pharmacology Toxicology Review	Sushanta Chakder
OPQ Review	(Multiple) review dated 5/9/2019
Clinical Pharmacology Review	Dilara Jappar
OPDP	Metta Patel
OSE	Kimberly Swank
/CDTL Review	Hitesh Shroff
OSE/DEPI	Nabila Sadiq
OSE/DMEPA	Sherly Abraham
DPMH	Amy Taylor
DMPP	Kelly Jackson

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DPMH= Division of Pediatric and Maternal Health
CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP= Division of Medical Policy Programs

1. Benefit-Risk Assessment

Refer to the clinical review by Sandhya Apparaju (9/8/2017) for complete findings and BR framework table for the use of Fosaprepitant for intravenous use in ADULT patients. This 505(b)(2) submission relies on the safety and efficacy of Emend as the listed drug (LD). The differences in impurities will be discussed in the safety section below.

2. Background

This is a 505(b)(2) application for fosaprepitant, a phosphorylated prodrug of aprepitant, which is a substance P/neurokinin 1 (NK1) receptor antagonist. The proposed formulation is a sterile lyophilized powder in a single dose glass vial for reconstitution and administration as an intravenous injection. The Applicant's proposed indications and dosing regimen are identical to the referenced drug EMEND® for Injection:

"Fosaprepitant for Injection, in combination with other antiemetic agents, is proposed for use in adults for the prevention of:

- *Acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin.*
- *Delayed nausea and vomiting associated with initial and repeat courses of MEC."*

The proposed dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy. No new clinical trials have been conducted in support of this 505(b)(2)NDA. The applicant is primarily relying upon the safety and efficacy of the listed drug (LD) EMEND® (fosaprepitant) for Injection, NDA 22023. The proposed and listed drug products are identical with respect to the active pharmaceutical ingredients (API), dosage form, route of administration, and dosing regimen. The products differ only with respect to inactive ingredients.

This application was originally submitted on December 16, 2016. On October 12, 2017 a tentative approval letter was sent to the Applicant. The listed drug upon which the application relies is subject to a period of patent and exclusivity protection and therefore final approval of this application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired. The expiry date is 9/5/2019.

On April 5, 2019 this Application was submitted as a complete response to the tentative approval letter and included additional updates for chemistry and manufacturing. Previously the review team worked on the final labeling with the Applicant. During the current review cycle, DPMH and OCC were involved with the development of the final pediatric wording for the label, as additional issues regarding the reformulated innovator product with lower levels of EDTA compared to those in this Application were also considered (see safety discussion below and clinical review by S. A.).

3. Nonclinical Pharmacology/Toxicology

Dr. Sushanta Chakder concluded in his review dated 9/7/2017 that no nonclinical approvability issues have been identified for NDA 210064. In his review, Dr. Sushanta Chakder concluded absence of safety concerns regarding the proposed excipients. Specifically, Dr. Chakder noted, "The safety of the exposure levels for Providone K12 and meglumine, are justified by clinical experience and/or nonclinical safety data with these two excipients."

Regarding EDTA, Dr. Chakder concluded, "The level of EDTA (18.8 mg/vial) present in fosaprepitant dimeglumine injection is present in FDA approved products indicated for adult patients, and there are no safety concerns for the EDTA levels in the fosaprepitant dimeglumine injection formulation".

4. Clinical Pharmacology

No new Clinical Pharmacology information was included in this 505(b)(2) NDA. The Office of Clinical Pharmacology deemed the application acceptable. See the final Clinical Pharmacology review by Dr. Dilara Jappar in DARRTS, dated 07/14/2017.

5. OPQ review

The final OPQ review (5/9/2019) recommended approval of this product for its intended use.

A biowaiver for *in vivo* BA/BE studies under 21 CFR 320.24(b)(6) was granted because the proposed drug product contains the same active ingredient in the same concentration as the listed drug, Emend for injection, and adequate justification was provided supporting the relative bioavailability of the proposed drug product to the reference drug to establish a *biobridge* to the Agency's finding of safety and efficacy of the listed drug.

6. Clinical/Statistical-Efficacy

No assessment of effectiveness is warranted for the proposed drug product, as this 505(b)(2) NDA relies upon the findings of efficacy for the listed drug [EMEND® (fosaprepitant) for Injection, NDA 22023]. Consistent with 21 CFR 320.24 (b)(6) the applicant submitted a justification for the differences in the inactive ingredients, and in the physiochemical properties between the proposed and LD products thus providing a biobridge to the FDA's previously established findings of safety and efficacy for the LD.

7. Safety

On 12/02/2016, a formulation change was approved for the LD as a CMC supplement. The amount of the chelating agent EDTA was reduced from 18.8 mg to 5.4 mg. This change was made in response to the unknown safety impact in pediatrics and the LD Sponsor's intent to study EMEND® for Injection in pediatric patients (under PREA PMRs). The proposed 505(b)(2) NDA formulation contains 18.8mg EDTA and is not planned for pediatric use. The active drug, aprepitant, is approved as EMEND® capsules [initial approval on 03/26/2003, NDA 021549, Merck]. Oral aprepitant is now approved for CINV in both adults and pediatric patients. An oral suspension was approved on 12/17/2015 under NDA 207865 (Merck) to allow dosing in patients ≥ 6 months of age and older.

The safety implications of the amount of EDTA were investigated by the clinical reviewer (see Dr. Sandhya Apparaju's review for complete details) and it was concluded that EDTA exposures from potential clinically relevant doses of fosaprepitant for injection are unlikely to produce a clinically meaningful hypocalcemia in pediatric CINV patients. EDTA in this formulation did not result in clinically relevant electrolyte changes in vulnerable adult patients. Evaluation of approved products e.g. Amphotec, Depacon, Aloxy etc. for pediatric CINV provide EDTA dose up to 11 mg in pediatric patients <12 y/o. These EDTA exposures are comparable to that anticipated at pediatric relevant doses of fosaprepitant IV of 3 mg/kg. It is not known what the exact effect of this level of EDTA might be in pediatric patients as the LD studied product with lower levels of EDTA. This may be of theoretical concern only if this product is used off label in pediatric patients.

A review of published literature and FAERS database identified several cases of anaphylaxis/ anaphylactic shock with additional symptoms, as well as an increased incidence of infusion site reactions. Overall, the proposed drug product is deemed safe for its intended use in the proposed adult CINV population.

8. Advisory Committee Meeting

Not required for this 505(b)(2) Application as the safety profile is similar to that of the approved referenced product.

9. Pediatrics

This Application requests use in ADULT patients only. Since the Applicant is not proposing a new active ingredient, a new dosage form, a new dosing regimen, or a new route of administration, per Section 505(a)(1) of the Food, Drug and Cosmetic Act, the Pediatric Research Equity Act (PREA) does not apply to this application.

Based upon extensive calculations and review of data in other drug products, the clinical reviewer concluded that "EDTA exposures from potential clinically relevant doses of fosaprepitant IV are unlikely to produce a clinically meaningful hypocalcemia in pediatric CINV patients. EDTA at anticipated exposure is estimated to reduce 1-2 % reduction of serum free calcium levels based on the dose. According to published ranges of serum calcium, reduction of ~ 30 % from low normal baseline is considered critically low in pediatric patients, with a more than 50 % reduction resulting in life-threatening complications. In addition, previously reviewed literature supporting the safety of EDTA as an excipient in propofol did not indicate an adverse effect on calcium homeostasis. While this information was not from pediatric patients, it is nevertheless reassuring that EDTA in IV formulations did not result in clinically relevant electrolyte changes in vulnerable adult populations."

Final agreed upon pediatric labeling is listed below.

10. Other Relevant Regulatory Issues

- *No exclusivity issues preclude the approval of this 505(b)(2) application.*

11. Labeling

The majority of the label was agreed upon with the Applicant during the first review period. Regarding pediatric labeling and EDTA the following was agreed upon by DPMH and OCC:

8.4 Pediatric Use
This Fosaprepitant for Injection product is not approved for use in pediatric patients.

This Fosaprepitant for Injection product contains 18.8 mg of edetate disodium (EDTA) per vial [see Description (11)]. Edetate disodium is a chelator of metal ions, including calcium. Other fosaprepitant for injection products may contain less edetate disodium.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None required

- Other Postmarketing Requirements and Commitments

None required.

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/

JOYCE A KORVICK
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