CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207534Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS-DISCIPLINE TEAM LEADER REVIEW

Date	June 1, 2017
From	Lydia Gilbert-McClain, MD Deputy Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Subject	Summary Review
NDA#	207-534
Applicant Name	Adamis Pharmaceuticals Corp
Date of Submission/Receipt Date	December 16, 2016
PDUFA Goal Date	June 15, 2016
Proprietary Name/Established (USAN) Name	SYMJEPI (epinephrine injection, USP)
Dosage forms/Strength	Prefilled syringe (PFS) with solution for injection /1 mg/mL
Proposed Indication (s)	Emergency treatment of allergic reactions (Type I) including anaphylaxis, and anaphylactic
Recommended Action	Approval

1. Introduction

Adamis Pharmaceuticals Corporation (Adams) submitted a 505(b)(2) application for epinephrine injection, USP 1 mg/mL (b) (4) for marketing approval for epinephrine injection for the emergency treatment in the unsupervised medical setting (self or care-giver administration) of allergic reactions including anaphylaxis in patients who weigh ≥ 30 kg. The dosage form is a pre-filled syringe (PFS) with solution for injection. The product was previously illegally marketed and the applicant submitted an NDA seeking regulatory approval for the same product. The reference product for this 505(b) (2) application is EpiPen ®, an epinephrine auto-injector product marketed by Mylan Specialty L.P. for the emergency treatment of allergic reactions including anaphylaxis in the unsupervised medical setting. The NDA was given a Complete Response on March 27, 2015 for CMC reasons. The applicant submitted a complete response on December 04, 2015 with device changes and a human factors validation study to support the device change (b) (4) there were critical errors noted in the human factors validation study which the sponsor was unable to address in that review cycle. The application was given a second complete response action on June 3, 2016. The sponsor submitted a complete response on December 16, 2016 to address the second complete response. The PDUFA date for this complete response is June 15, 2017

2. Background

Adamis (the applicant) submitted the NDA to support marketing of epinephrine solution for injection in a pre-filled syringe (PFS) for the emergency treatment of the signs and symptoms of anaphylaxis in the non-supervised medical setting. This is the third review cycle for this application. In the first cycle, the application was given a complete response because of CMC issues regarding the delivered volume, unacceptable impurity specifications ([(b) (4)] specifically), and the residual solvent [(b) (4)] limit [(b) (4)] The applicant satisfactorily addressed those CMC issues. To address the delivered volume, the applicant redesigned the device [(b) (4)] During the second review cycle, the Applicant submitted the results of human factors studies that they had performed to evaluate this new design. Notably, the Applicant did not submit these human factor results with the submission of the complete response. The Human Factors protocol and results were reviewed and several deficiencies were noted which led to another complete response action. The Applicant has since addressed the human factors deficiencies and submitted a complete response on December 16, 2016.

3. Chemistry Manufacturing and Controls

There were no CMC issues to be addressed in this cycle. The Applicant had adequately addressed the CMC issues in the second complete response. In addition the applicant adequately addressed biocompatibility issues that were identified by CDRH during the second review cycle. One remaining issue regarding device reliability is outstanding but this can be handled as a post-marketing commitment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies were not conducted nor required to support approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The applicant did not conduct any clinical pharmacology studies to support the application. In the original submission the applicant requested a biowaiver from conducting an in vivo bioavailability study and this request was reviewed by the ONDQA/Biopharmaceutics team. Based on the similarity of the formulation composition and the route of administration, no difference in physic-chemical and pharmacokinetic characteristics is expected between the proposed product and the reference product. Therefore, a biowaiver was granted for the applicant's product.

6. Clinical Microbiology

A clinical microbiology review was not needed for this application. The product quality microbiology assessment was adequate.

7. Clinical/Statistical- Efficacy

Clinical trials were not performed for this application. The applicant made modifications to the device labeling to address the human factors deficiencies identified in the last review cycle. The human factors testing was reviewed by OSE/DMEPA and found to be acceptable.

8. Safety

No new safety data on epinephrine was submitted with the complete response. The safety profile of epinephrine is well established as this moiety is over 100 years old and has been in use for the treatment of signs and symptoms of anaphylaxis for decades.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

The applicant is not required to address the regulatory requirements of the Pediatric Research Equity Act (PREA) (21 U.S.C 355c) as there is no new ingredient, dosage form, dosing regimen, route of administration, or new indication proposed. However, although PREA does not apply to this application, the Division has encouraged applicants of approved epinephrine products for the proposed indication to develop a product for use in lower weight patients (i.e. < 15 kg) as anaphylaxis can occur in very young children and there is an unmet medical need for a product for that patient population.

11. Other Relevant Regulatory Issues

Data Quality, Integrity, and Financial Disclosure

Not applicable. The applicant did not conduct any clinical trials for this NDA

12. Labeling

Proprietary name

The applicant's proposed proprietary name SYMJEPI® was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and it was found to be acceptable.

Physician labeling Carton and Immediate Container Labels/ Patient labeling

The labeling was revised to ensure consistency (as appropriate) with the other epinephrine products approved for the emergency treatment of the signs and symptoms of anaphylaxis. There is agreed upon labeling with the Applicant and the Division.

13. Action and Risk Benefit Assessment

Regulatory action

The recommended regulatory action for the application is approval. The Applicant has agreed to address the outstanding device reliability issues as a post marketing commitment.

Risk Benefit Assessment

Epinephrine is the drug of choice for the emergency treatment of anaphylaxis. It has been in use for over 100 years. As a sympathomimetic catecholamine, epinephrine has a narrow therapeutic index and serious adverse reactions including cardiovascular and cerebrovascular reactions can be associated with its use. Nevertheless, the use epinephrine for this indication is life saving and the benefits of using it outweigh the potential safety risks.

Postmarketing Risk Management Activities

None

Postmarketing Study Commitments/Requirements

The applicant will be asked to submit data to address the reliability specification for delivery volume for the product as a post-marketing commitment. The Applicant has agreed in principle to this commitment and the final language of the commitment was communicated to the sponsor via FAX on 5/31/2017

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/s/

LYDIA I GILBERT MCCLAIN
06/01/2017