CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207534Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW FOR REGULATORY ACTION

Date	June15, 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 15, 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

Materials reviewed include the action package and the following reviews:

Reviews	Names of Discipline reviewers
Medical Officer Review	Peter Starke, Janet Maynard (CDTL previous review cycles)
CMC Review	Craig Bertha, Julia Pinto, Venkateswara Pavuluri, Ying Wang,
CDRH Consult review	Kathleen FitzGerald, Nurse consultant Alan Stevens
OSE/Division of Medication Error Prevention and Analysis	Lisa Owens, Mishale Mistry, Lubna Merchant

1. Introduction

Adamis Pharmaceuticals Corporation (Adamis) submitted a 505(b)(2) application on May 23, 2014 (received May 28, 2014) 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 to address the CMC issues [redacted] there were critical errors noted in a human factors validation study which the applicant had conducted when the changed the device. The applicant was unable to address the human factors issues in the review cycle. The application was again given a complete response action on June 3, 2016. The sponsor submitted a complete response on December 14, 2016 to address the second complete response. The PDUFA date for this complete response is June 15, 2017

2. Background

Adamis (the applicant) submitted this 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 ([redacted] specifically), and the residual solvent [redacted] limit [redacted] The applicant satisfactorily addressed those CMC issues in the second review cycle. To address the delivered volume, the applicant redesigned the device [redacted] This device change [redacted] raised questions regarding the need for human factors testing. 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 the second complete response action. The Applicant has since addressed the human factors deficiencies and submitted a complete response on December 14 (received December 15), 2016.

3. Chemistry Manufacturing and Controls

There were no CMC issues to be addressed in this the 3rd review cycle. The drug substance (DS) in the drug product is epinephrine base (sourced from [redacted] [DMF [redacted]]). The proposed drug product contains epinephrine injection, USP in a sterile solution at a labeled concentration of 1 mg/mL. The formulation includes epinephrine USP, sodium metabisulfite, sodium chloride HCl [redacted] to adjust the pH to 2.2 – 5 and water for injection.

The product is for single use and is designed to deliver 0.3 mg (0.3 ml). As with other epinephrine products, this product has a [redacted]% overage of active drug [redacted] (this is within the USP specifications [redacted] for epinephrine products). The solution is package as 0.8mL in an l mL prefilled glass syringe fitted with a 25 gauge 5/8 inch needle and a rigid needle shield, which is sealed with a rubber stopper [redacted]

The prefilled syringe is housed within a dark blue opaque plastic housing that incorporates flanges to support the fingers, a viewing window to allow viewing of the epinephrine solution, a semi-transparent removable needle cover that includes a flange with directions and an extendable needle guard that is manually deployed and locks in place after the injection is delivered. (b) (4) The device provides tactile and audible feedback (a "click") when the plunger reaches the end of the injection stroke, which is intended to inform the user that a dose has been delivered. (b) (4) The needle guard may be manually deployed after the injection. Once the needle guard is extended it locks into place.

The product is packaged in a holding case and is suppled as a single unit or 2 units. (b) (4) is the manufacturer of the drug product and the primary packaging. Secondary packaging is performed (b) (4)

There are no facilities issues with the application. One remaining issue regarding device reliability remains outstanding and will be handled as a post-marketing commitment. Based on stability data, Adamis is requesting a shelf-life (expiry date) of 18 months when stored at room temperature 77^0F in the plastic case provided. The Stability data support an 18-month expiry.

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 physico-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

None

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 treatment of the signs and symptoms of anaphylaxis 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 anaphylaxis is life saving and the benefits of using it outweigh the potential safety risks.

Postmarketing Risk Management Activities

None

Postmarketing Study Commitments/Requirements

PMC #1 Description:	Provide an updated Fault Tree Analysis, specifically for Less Than Full Dose Delivered that includes the probability data for each identified basic failure mode and show that the quantification of the fault tree analysis supports the device reliability specification, 99.99%. The data could include manufacturing controls (i.e. in process controls and release testing) or probability data from design verification tests.

PMC Schedule Milestones: Final Report Submission: August 15, 2017

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/s/

LYDIA I GILBERT MCCLAIN
06/15/2017