

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207534Orig1s000

CLINICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION: NDA 207-534	TRADE NAME: Symjepi
APPLICANT/SPONSOR: Adamis Pharmaceuticals Corp.	USAN NAME: Epinephrine injection, USP, 1mg/mL, 0.3 mg (prefilled syringe)
MEDICAL OFFICER: Peter Starke, MD	CATEGORY: Catecholamine: nonselective alpha and beta adrenergic agonist
DEPUTY DIRECTOR: Lydia Gilbert-McClain, MD	ROUTE: Intramuscular or subcutaneous
DATE: May 22, 2017	

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
December 14, 2016	December 15, 2016	SD-22	Complete Response to CR action of 6/3/2016
January 25, 2017	January 25, 2017	SD-23	Labeling, but not Prescribing Information (PI)
February 8, 2017	February 8, 2017	SD-24	Prescribing Information
March 14, 2017	March 14, 2017	SD-26	Updated labeling
April 28, 2017	April 28, 2017	SD-27	Response to IR of March 22, 2017; revised case and device labels; Patient Information
May 19, 2017			Labeling fax; CDRH Fault Tree Analysis IR

REVIEW SUMMARY:

This is a 3rd cycle summary review of a 505(b)(2) application from Adamis Pharmaceuticals Corp. (Adamis) for a drug/device combination of Epinephrine Injection, USP (b)(4) 0.3 mg in a pre-filled, single-dose, manually-injected syringe. The original NDA was dated May 23, 2014, and received on May 28, 2014, and a Complete Response (CR) action was taken in the first cycle on March 27, 2015, because the device was not capable of delivering the labeled claim amount of drug. Adamis was asked to redesign the pre-filled syringe so that it would deliver the labeled target volume, and they were asked to submit data to support the redesigned device. Other than tightening some of the specifications, there were no other issues or concerns remaining for the pre-filled syringe device or its sterile manufacture.

To address this issue, Adamis modified (b)(4) to deliver the labeled dose of 0.30 mL (0.3 mg). Additionally, they made changes to the device, (b)(4). This resulted in a device (b)(4) raising the new concern that it might result in confusion and critical use failures in the hands of patients. A human factors study that was submitted confirmed the Agency's concern because it demonstrated an unacceptably high failure rate in the performance of certain critical tasks that could lead to users not getting the intended dose. Therefore, a second Complete Response action was taken on June 3, 2016.

A teleconference was held between the Agency and Adamis on November 8, 2016, to further explain the issues. To resolve the deficiency, the Agency recommended modification of the device and repeating the human factors study. Adamis responded on December 15, 2016, with slight modifications to the device and the device labeling, and new human factors data. The modifications to the design and the labeling appear to resolve the Agency's concerns, and the product is now considered approvable.

OUTSTANDING ISSUES:

An IR was sent on May 19, 2017, on behalf of CDRH, requesting an updated fault tree analysis for the scenario of *less than full delivered dose*. If Adamis is unable to provide the updated analysis within the review period, this will be requested to be carried out as a post-marketing commitment.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: APPROVAL COMPLETE RESPONSE

Introduction

This is a 3rd cycle summary review of a 505(b)(2) application from Adamis Pharmaceuticals Corp. (Adamis) for a drug/device combination of Epinephrine Injection, USP (b) (4) 0.3 mg in a pre-filled, single-dose, manually-injected syringe. The original NDA was dated May 23, 2014, and received on May 28, 2014, and a Complete Response (CR) action was taken in the first cycle on March 27, 2015, the device was not capable of delivering the labeled claim amount of drug: the targeted dose of the pre-filled syringe was (b) (4) (b) (4) whereas the approved dosage in this setting is 0.3 ml (0.3 mg). Adamis was asked to redesign the pre-filled syringe to deliver the labeled target volume and provide data to support the redesigned device. A second concern was that the drug substance specifications needed to be tightened, specifically related to the acceptance criteria for (b) (4) and the residual solvent limits.

To address this issue, Adamis made modifications to (b) (4) (b) (4) be on target for the labeled dose of 0.30 mL (0.3 mg). In addition, Adamis made a number of other changes to the device, (b) (4)

This resulted in a device (b) (4) (b) (4) raising the new concern that it might result in confusion and critical use failures in the hands of patients. A human factors study that was submitted confirmed the Agency's concern because it demonstrated an unacceptably high failure rate in the performance of certain critical tasks that could lead to users not getting the intended dose. Therefore, a second Complete Response action was taken on June 3, 2016.

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The CR submission is all electronic in eCTD format, and was received on December 15, 2016. The PDUFA date is June 16, 2017.

Relevant Background

The proposed indication for this product is for the emergency treatment of severe allergic reactions (anaphylaxis). The product is intended for self or caregiver administration in the medically unsupervised, emergency setting. Only one dosage strength is proposed, 0.3 mg (0.3 mL) for patients who weigh ≥ 30 kg (66 pounds).

The application references EpiPen® (NDA 19-430), which is listed in the Orange Book as a reference drug. However, this product differs from EpiPen as well as all of the other approved epinephrine products that are intended for use in the medically unsupervised setting in that it is a prefilled syringe that is intended for manual injection (intramuscularly [IM] or subcutaneously [SC] into the lateral thigh), whereas all of the other approved products (EpiPen®, AdrenaClick®, Auvi-Q®) are auto-injectors.

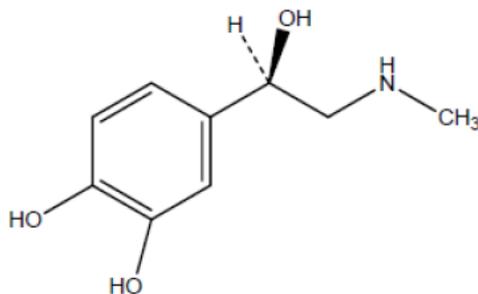
In December of 2014, the applicant proposed the proprietary name Symjepi (pronounced sim-JEP-ee), and the name was found acceptable (correspondence dated March 2, 2015). With this

Complete Response, Adamis has resubmitted the proposed proprietary name request, which DMEPA again found acceptable on February 8, 2017.

CMC/Device

Drug Substance

The drug substance (DS) or active pharmaceutical ingredient (API) in this drug product is epinephrine base, sourced from (b) (4) (DMF# (b) (4)). Epinephrine is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. Epinephrine is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation. The chemical formula of epinephrine is $C_9H_{13}NO_3$, and its chemical structure is shown below. The chemical structure consists of benzene ring and an



ethylamine side chain.

As shown in the structural diagram above, epinephrine has two optical isomers (enantiomers): substitution of an hydroxyl group at the beta carbon atom on the ethylamine side chain yields *l*- and *d*- isomers [also described as L- or (-) and as D- or (+)]. Levorotatory rotation (*l*- form or *l*-epinephrine) confers at least 10-15 times higher systemic potency than the *d*-isomer (Patil 1975; Westfall 2011), with *l*-epinephrine being the natural form produced by the adrenal medulla. The drug substance is manufactured (b) (4)

(b) (4)

Drug Product

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 (b) (4) to adjust the pH to 2.2-5, and water for injection.

(b) (4)

It should be noted that, (b) (4) this product has a (b) (4) % overage of active drug (b) (4)

(this is within the USP specifications (b) (4) for epinephrine products). The solution is packaged as 0.8 mL of solution in a 1 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 (b) (4) is the manufacturer of the drug product and the primary packaging. Secondary packaging is performed (b) (4)

Redesigned Device

The device and labeling have been modified. The prefilled syringe is packaged within a (b) (4) 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 for sharps protection (Figure 1). (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, and once extended, locks into place. The needle guard is the same color as the outer plastic case.

Each device is packaged in a holding case, (b) (4) as a two-pack so that two doses are available to a patient should a second dose be needed (Figure 1). An overview of the features of the device is shown in Figure 3. (b) (4)

Figure 1. Delivery device and storage cases

Source: Submission of 12/15/2016; Figure 5.3.5.4.1-3, summary-human-factors.pdf, p9



Figure 2. Revised case and device labels

Source: Submission of 4/28/2017; Figure 1-1



Figure 3. Features of the device

Source: Submission of 12/15/2016; Figure 3.2.P.1, p15; (b) (4)-epinephrine-inejction.pdf

Based on the stability data, Adamis is requesting a shelf-life (expiry dating) of 18 months, when stored at room temperature 77°F (25°C) in the plastic case provided, with the following additional storage and handling instructions: Do not refrigerate. Protect from light, extreme heat and freezing.

Conclusions from the CMC Review

The final CMC review is still pending as of the date of finalization of this review. However, my understanding is that CMC has concluded that the product is approvable from a CMC perspective, and that the proposed shelf life is acceptable.

CDRH Review

The CDRH review is still pending as of the date of finalization of this review. However, CDRH has raised the concern that the fault tree analysis previously provided to the Agency for *Less Than Full Dose Delivered* is incomplete because it does not include the probability data to support the reliability specification. On behalf of CDRH, an IR was sent on May 19, 2017, requesting an updated fault tree analysis. If Adamis is unable to provide the updated analysis within the review period, this will be requested to be carried out as a post-marketing commitment.

1. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology issues were noted during this review cycle.

2. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics issues were noted during this review cycle.

3. Clinical Microbiology

No new microbiology issues were noted during this review cycle.

4. Clinical/Statistical- Efficacy

No new clinical efficacy or safety issues were noted during this review cycle.

5. Safety

No new clinical efficacy or safety issues were noted during this review cycle. However, the Division of Medication Error Prevention and Analysis (DMEPA) provided a consult reviewing the Human Factors data, and found the data acceptable.

6. Advisory Committee Meeting

An AC meeting was not held for this application.

7. Pediatrics

There were no pediatric issues with this application. Adamis has only proposed a 0.3 mg dosage strength for patients 30 kg and above, and not a 0.15 mg dosage strength for patients 15 to 30 kg, as is available for other epinephrine products approved for this indication. However, the application did not trigger PREA because the product does not include a new active ingredient,

new indication, new dosage form, new dosing regimen, or new route of administration. Since the application did not trigger PREA, there is no regulatory requirement for Adamis to provide lower doses.

8. Other Relevant Regulatory Issues

There were no other relevant regulatory issues noted during this review cycle.

9. Labeling

Labeling Issues

No substantive labeling issues. The PI is in PLR format. With the exception of product-specific information, the PI is substantially similar to the other epinephrine products. While Adamis did not submit labeling in PLLR format, the Division decided to convert to PLLR format because conversion would be due by June 2019 anyway. To do so, the Division performed the necessary literature searches and provided the references that were used in labeling sent to Adamis on May 19, 2017. Updated labeling was sent to the company on May 19, 2017, and a reply is pending as of the time of completion of this review.

Proprietary name

In the first review cycle, Adamis requested review of the proposed proprietary name, Symjepi. That name was found acceptable. With the Complete Response submitted on December 15, 2016, Adamis requested re-review of their proposed proprietary name, Symjepi. Upon review DMEPA again found Symjepi to be an acceptable trade name (2/8/2017).

10. Recommendations/ Benefit-Risk Assessment

Recommended Regulatory Action

I recommend an Approval action for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER R STARKE
05/22/2017

LYDIA I GILBERT MCCLAIN
05/22/2017

SUMMARY REVIEW FOR REGULATORY ACTION

Date	June 3, 2016
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 04, 2015
PDUFA Goal Date	June 03, 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	Complete response

Materials Reviewed/Consulted OND Action Package, including:	Names of Discipline reviewers
Medical Officer Review	Peter Starke, MD
Cross Discipline Team Leader Review	Janet Maynard, MD
CMC Review	Craig Bertha, PhD; Julia Pinto, PhD; Venkateswara Pavuluri, PhD; Ying Wang, PhD
CDRH	Kathleen FitzGerald, Nurse consultant
OSE/Division of Medication Error Prevention and Analysis	Lisa Owens, PharmD; Mishale Mistry, PharmD, MPH; Lubna Merchant, PharmD, MS

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 and the submission was classified as a Class II response with a 6-month PDUFA clock. The PDUFA goal date is June 3, 2016

2. Background

The product is a pre-filled syringe and with the original design of the product the volume of epinephrine that could be delivered was (b) (4). In addition, there were other CMC quality reasons including unacceptability of the applicant's proposed specification criteria for the (b) (4) impurity (proposed (b) (4) by drug substance manufacturer), the residual solvent (b) (4) limit ((b) (4) proposed by the drug substance manufacturer), and deficiencies in the definition of the volume determination as described in USP <1>, that led a lack of assurance of the identity, strength, quality, purity, and potency of the drug product per CFR 314.50(ii)(a).

A type A meeting was held with the Division on August 5, 2015 to address the Applicant's questions regarding CMC issues and the Applicant's complete response was submitted on December 04, 2015.

To address the delivered volume, the applicant redesigned the device (b) (4). This has inherent problems (b) (4) because the product is for use in life-threatening circumstances when rapid administration of epinephrine is critical. During the review cycle, two information requests (IRs) were sent to the applicant seeking information regarding human factors data (if any) that may have been obtained with the new device. The Applicant submitted the results of human factors studies that they had performed. 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 by DMEPA and several deficiencies were noted which are summarized later in this memo.

3. Chemistry Manufacturing and Controls

No changes were made to the drug substance or formulation. The Applicant provided revised specifications for the drug substance which were found to be adequate to support the quality of the drug product. The CMC drug quality issues have been adequately addressed and there are no facilities or DMF issues with the application. In order to address the incorrect dose target problem, the applicant made modifications to (b) (4) be on target with the clinically acceptable dose ($0.30 \text{ mL} \pm \frac{(b)}{(4)}\%$ for self-administration in the non-medically supervised setting). In addition, the applicant introduced (b) (4) a pre-filled syringe. (b) (4) look more like an autoinjector (see below). That

said, there are positive aspects of the redesign

(b) (4)

(b) (4)

Figure 1: Symjepi redesigned device

The extra components add to the complexity of the device and CDRH was consulted during the review. From CDRH's review, there are several outstanding issues with the device that remain unresolved. First, the Applicant conducted reliability testing and proposes that the device would be capable of delivering 0.30 mL +/- (b) (4)% of drug over the 18-month expected use life with (b) (4)% reliability (CI (b) (4)%). This translates to a failure rate of (b) (4) devices which is unacceptable for a product that is to be used for life-threatening emergencies. Furthermore, given that the functionality of the device is that of pre-filled syringe, there really should be no mechanical failure to deliver an injection and the functional reliability of this product should essentially be 100%. If that cannot be achieved, the acceptability of the device for use for the emergency treatment of anaphylaxis will need to be re-considered. CDRH's consult review also notes that they applicant did not provide an adequate response regarding biocompatibility testing

The Applicant proposed to conduct biocompatibility testing

This approach is reasonable however the product is not going to be approved in this review cycle.

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.

Human Factors Testing

The Applicant submitted results of a human factors study they performed to support the device changes. Of note, the Applicant did not submit these study results with the complete response. These results were submitted in response to two information requests to the Applicant regarding any human factors studies that may have been performed (IRs dated March 3rd, and March 16th). The division raised concerns that the new device (while it addressed the initial problem of volume control) now looked substantially different from the original pre-filled syringe submitted with the original NDA. In fact, the device looks very much like an autoinjector which raises safety concerns because the functionality of the device for medication delivery is still that of a pre-filled syringe.

The Applicant confirmed that they had conducted human factors testing. During review of the resubmission, the human factors validation protocol and results were reviewed by DMEPA. Importantly, the Applicant did not seek advice from the Agency prior to the conduct of their human factors and usability engineering testing; neither did they seek advice from the Agency about the redesign of the device. The Agency has published guidance on human factors engineering “*Applying Human Factors and Usability Engineering to Human Devices*” available at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

It appears that the applicant did not follow through with all the necessary formative studies as outlined in the guidance prior to conducting their validation study. According to the guidance, the formative evaluation is the “process of assessing, at one *or more* [emphasis supplied] stages during the device development process, a user interface or user interactions with the user interface to identify the interface's strengths and weaknesses and to identify potential use errors that would or could result in harm to the patient or user”¹.

The Applicant conducted a small formative study in 14 subjects with the new product design and changes to the information for use (text and imaging) and to the case label were made based on that study, but there were no further changes to the device. The Applicant proceeded

¹Applying Human Factors and Usability Engineering to Human Devices: page 3

to test the new device in a human factors validation study. Upon review, this validation study has significant issues both in terms of protocol study design and methodology. The applicant enrolled a small number of participants (n = 36) 28 of whom were trained and 8 were naïve participants. The number of participants is smaller than the recommended number of 15/group and the variety of cohorts [in terms of age ranges and prior experiences or lack thereof with autoinjectors and pre-filled syringes] that should have been included in order to carry out a complete human factors assessment as per the guidance recommendations were not in the study. Study design issues notwithstanding, the results raised significant concerns because of failure to perform critical tasks on multiple occasions. The Agency's Human Factors guidance define critical task as "*A user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care.*" For this product, timely delivery of epinephrine to the appropriate biospace is a critical task. The product is for self-administration for hypersensitivity reactions including anaphylaxis which can be life-threatening and effective administration of epinephrine without delay is paramount to averting serious or fatal outcomes. While there were design methodology issues with the study [i.e. a limited number of participants; the testing environment not representative of an emergent situation; the training and instructions to participants not representative of a real-world scenario], of more significant concern was the finding of multiple instances of failure on the part of the user to use the device properly resulting in the inability to deliver the injection. The study was designed so that each participant had to deliver 2 injections (i.e. total of 72 injections in the completed study).

Failure to deliver the injection due to difficulty on the part of the participant to remove the needle cap and/or premature deployment of the needle guard (n = 3 injections) and failure to fully depress the plunger (n = 2 injections) were the critical failures noted in this study. These 5 errors resulted in the injection not being delivered which is not acceptable for a medication for use in a life-threatening emergency. The other failures noted (failure to call 911 [4 instances], injection in a non-muscular part of the body [6 instances], or failure to deploy the needle guard after administering the injection [54 instances]) while concerning, do not carry a potentially life-threatening risk, and while important, may be reasonably addressed with appropriate labeling. Once the needle guard is deployed, or the plunger is pushed, the device locks and no medication is delivered. Therefore, performing these functions incorrectly could have serious consequences as the patient would not receive the injection. Of note, the Division's concerns that the redesigned product looks more like an autoinjector than a PFS was borne out by some of these results. Of the 3 cases where the needle cap was an issue, two of the users attempted to use the device without removing the needle cap. In these scenarios, the participants showed a lack of understanding as to how to properly use the device (one participant prematurely deployed the needle guard in an attempt to use the device, while another user depressed the plunger in an attempt to remove the needle cap) resulting in the device being locked and no injection delivered. Another participant pulled the needle cap off at an angle which resulted in the needle cap rim catching the safety guard lip and prematurely deploying the needle guard resulting in the device locking and no medication being delivered. In summary, there were 5/72 (7%) of failed injections which is a significant percentage of failures in such a small study. In addition to these failures 6% of the 72 injections resulted in "close calls."

A teleconference was held with the Applicant on May 23rd to discuss these findings. The Applicant deems the product acceptable and believes that the failures noted in the human

factors testing are minimal. The Applicant also cited post-marketing experience with EpiPen Autoinjector citing that a published paper (subsequently submitted to the Division)² notes that many patients (or healthcare providers) use EpiPen incorrectly. The Applicant also cited a survey that they conducted (not submitted to FDA) showing that most patients prefer their device compared to EpiPen.

The paper describes a small study (n =48) in which patients used 2 prototype epinephrine autoinjectors that have a unidirectional perceived injection end, and a self-retracting needle, and, with one of the prototypes having voice instructions to assist in guiding users through administration. The study concluded that patients preferred the prototype with voice instructions. This paper provides nothing to support approving this product without further addressing the failures observed in the human factors testing.

The Agency has published draft guidance on incorporating patient preference information in regulatory decision making. While patient preference can provide helpful information, the guidance notes that *“in making such a determination, FDA would consider patient preference information along with the totality of evidence from clinical and nonclinical testing. If FDA determines the device would expose patients to an unreasonable or significant risk of illness or injury, or the benefits do not outweigh the risks for some definable target population, FDA would not approve such a device.”*³ The risks identified with the Applicant’s product are not acceptable as they carry the risk of serious harm if not corrected. While patients may prefer a pre-filled syringe device (compared to one of the currently marketed epinephrine autoinjectors) the risk to the potential user identified in this human factors study needs to be addressed prior to marketing. With these findings, the proposed “validation study” can be viewed as another formative study that should lead to corrective action and additional testing. The human factors guidance acknowledges that it is practically impossible to make any device error-proof or risk-free and that some residual risk will remain, even if best practices were followed in the design of the user interface. To that end, all risks that remain after human factors validation testing should be thoroughly analyzed to determine whether they can be reduced or eliminated. The Applicant has not done due diligence with fully evaluating the critical errors identified and the results of their human factors testing indicate that further corrective action and testing is required to ensure safe and effective use of the product.

8. Safety

No new safety data on epinephrine was submitted with the complete response.

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

² A comparison of 4 epinephrine autoinjector delivery systems: usability and patient preference. Stephanie Guerlain et.al *Ann Allergy Asthma and Immunol.* 2010 February; (104)2: 172-177

³<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandguidance/guidanceDocuments/UCM296379.pdf>

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. The acceptability of the proprietary name was conveyed to the applicant on both March 2, 2015, and May 6, 2016.

Physician labeling Carton and Immediate Container Labels/ Patient labeling

The labeling was not completed because the application is not going to be approved in this cycle

13. Action and Risk Benefit Assessment

Regulatory action

The recommended regulatory action for the application is a Complete Response. The product as designed has not been shown to be safe and effective for its intended use. Human factors study results show that the device as designed could fail in the hands of the intended users. Thus, delivery of epinephrine cannot be assured in an emergency situation. While the redesign addressed the initial concern regarding the volume of the product, the new design features introduced complexities in the actual use of the device which resulted in 5 injections (7%) not being delivered. These critical failures are all the more concerning given that this study was relatively small (n = 36 participants) without adequate representation of intended users and also had several design flaws (adequacy of simulated emergency environment and training).

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. The critical errors identified in the re-designed product raise significant safety concerns as these errors render the product ineffective (unable to deliver the medication) in an emergency situation where time is of the essence. For these reasons, while the Division is cognizant of the need for additional therapeutic options for epinephrine products for self-administration for anaphylaxis the risks

associated with this product are unacceptable and the product cannot be approved as currently designed.

Postmarketing Risk Management Activities

Not applicable given that the product is not going to be approved. However, given the extensive use of epinephrine for the proposed indication, postmarketing risk management activities are not anticipated.

Postmarketing Study Commitments/Requirements

Not applicable given that the product is not going to be approved. However, given the extensive use of epinephrine for the proposed indication, postmarketing studies are not anticipated.

Comments to the Applicant

Clinical Efficacy/Safety

You have not submitted adequate data to support the safe and effective use of Symjepi (epinephrine) prefilled syringe (PFS) for the emergency treatment of allergic reactions (Type I) including anaphylaxis. Specifically, the data from your human factors and usability assessment study raise concerns that the product as designed will not be safe and effective for the intended users, and use environments. We note the following deficiencies:

1. There were limitations in the conduct of the submitted study, such as inadequate representation of various user groups (such as adult subjects, adolescent subjects, trained subjects, trained subjects with adequate elapsed time between training and study to account for decay of memory, untrained subjects, subjects with prior experience with epinephrine autoinjector, subjects naïve to epinephrine autoinjector, etc.), and use environments (such as simulated emergent situation with distractions and loud noises). Furthermore, in your submitted study, approximately 75-85% of the participants were trained by video or written material or both, which is likely not reflective of the actual use scenario for your proposed product.
2. The limitations in the conduct of the submitted study notwithstanding, the results demonstrate an unacceptably high failure rate in performances of critical tasks that could result in serious harm because with these errors the users may not receive the intended dose of epinephrine. Failures in critical tasks elements that rendered the product incapable of delivering the injection included: failure to remove the needle cap and/or premature deployment of the needle guard (n = 3 [4%]) and premature depression of the plunger (n = 2 [3%]). One participant had difficulty with removing the needle cap and pulled the needle cap off at an angle which resulted in the needle cap rim catching the safety guard lip and prematurely deploying the needle guard resulting in the device locking and no injection being delivered.

INFORMATION NEEDED TO RESOLVE DEFICIENCY

To support approval of Symjepi Prefilled Syringe for the emergency treatment of allergic reactions (Type I) including anaphylaxis you will need to provide adequate data to support the safe and effective use of your product in this emergent life-threatening situation as follows:

Conduct a human factors and usability assessment program that includes formative evaluation, as necessary, and human factor validation testing with adequate representation of user groups and use environments as mentioned above. The extent of the training that participants receive should approximate the training that actual users would receive. Include clear brief step wise instruction of critical elements on the device, each of which is tested as part of the formative and validation studies. Depending on the findings of these studies, device changes may be necessary, because modifying the device design is usually more effective than revising the labeling or training. We acknowledge that even if best practices were followed in the design of the user interface, it may not be possible to make a device error-proof or risk-free. All risks that remain after human factor validation testing should be thoroughly analyzed to determine whether they can be reduced or eliminated. We recommend that you submit all protocols for human factors validation for our review and recommendations prior to conducting the validation study. Refer to the guidance for industry “*Applying Human Factors and Usability Engineering to Human Devices*” available at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocumentsucm259760.pdf>

for guidance on conducting the human factors assessment program.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYDIA I GILBERT MCCLAIN
06/03/2016

Cross-Discipline Team Leader Review

Date	May 20, 2016
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	207,534 (resubmission)
Applicant	Adamis Pharmaceuticals Corp.
Date of Submission	December 4, 2015
PDUFA Goal Date	June 3, 2016 (actual is Saturday, June 4, 2016)
Proprietary Name / Established (USAN) names	Symjepi/epinephrine injection
Dosage forms / Strength	Epinephrine prefilled syringe 0.3 mg (0.3 mL) for IM or SC injection (epinephrine injection USP (b) (4))
Proposed Indication(s)	Emergency treatment of allergic reactions (Type 1), including anaphylaxis
Recommended:	Complete Response

1. Introduction

This is a summary review of Adamis Pharmaceuticals Corp.'s response to the Complete Response Letter issued March 27, 2015 for NDA 207,534. The application was originally submitted on May 23, 2014 as a 505(b)(2) new drug application for epinephrine injection (epinephrine USP (b) (4)) 0.3 mg in a prefilled, single-dose syringe, hereinafter referred to as "Epinephrine Injection." The proposed indication is for the emergency treatment of allergic reactions (Type 1), including anaphylaxis. The product is intended for self or caregiver administration in the medically unsupervised, emergency setting. The original application received a complete response on March 27, 2015. The primary deficiency was that the drug product was not capable of delivering the labeled claim amount of drug. Specifically, the targeted dose of the prefilled syringe was (b) (4) whereas the approved dosage in this setting is 0.3 mg (0.3 mL). Thus, the Applicant was told to redesign the prefilled syringe to deliver the target volume at labeling claim. In addition, the Applicant needed to revise the specification to match the specification of the drug substance supplier. Please see the CDTL review memo dated March 6, 2015 for details.

In this resubmission, the Applicant has redesigned the device. The redesign utilizes (b) (4)

During the review cycle, the Applicant provided information from human factors studies to support the safe use of the product. A significant consideration during the review

cycle was whether the information provided adequate support for the safe and effective use of the product in an emergency setting.

The proposed dose is 0.3 mg for patients who weigh at least 30 kg. There are no proposed dosage forms for patients who weigh less than 30 kg. The NDA references EpiPen® (NDA 19,430) which is injectable epinephrine administered via an autoinjector intended for self and caregiver administration in the medically unsupervised setting. In contrast to the listed product and other approved epinephrine products for use in the medically unsupervised setting, the proposed epinephrine product is a prefilled syringe intended for manual injection and is not an autoinjector. However, like the currently approved epinephrine autoinjectors, the proposed drug product is intended for use in the medically unsupervised setting for treatment of life-threatening allergic reactions, including anaphylaxis.

2. Background

Indication

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis consensus network defined criteria for anaphylaxis in 2006 that include acute onset of various combinations of one or more of the following symptoms: skin or mucosal involvement, respiratory compromise, reduced blood pressure or end organ dysfunction, and persistent GI symptoms¹. Anaphylaxis presents as a biphasic hypersensitivity response, with rapid evolution of symptoms after exposure in minutes to several hours for the initial response, and a late phase occurring in up to 20% of patients 1-72 hours later, most frequently within the first 4-6 hours. The most frequent cause of death is respiratory compromise. Given the severity and rapid evolution of symptoms, immediate systemic therapy is required, and the potential benefits of treatment are significant (i.e. life-saving therapy with rapid improvement back to normal functioning).

Epinephrine

Epinephrine is a non-specific adrenergic agonist. Epinephrine is the drug of choice for treatment of anaphylaxis, with other treatments considered to be adjunctive or supportive. Currently, there are multiple autoinjectors approved to treat life-threatening allergic (hypersensitivity) reactions: EpiPen® and EpiPen Jr.® (NDA 19,430), Twinject® (NDA 20,800), Adrenaclick® and authorized generics (NDA 20,800), and Auvi-Q® (NDA 201,739). All contain a single dose of epinephrine at an adult dose of 0.3 mg or pediatric dose of 0.15 mg except Twinject®, which contains two doses. These products are intended for self or caregiver administration, prior to arrival in the healthcare setting and are available as twin packs that contain two devices in case a second dose is required.

Additionally, single-use (1 mL [Adrenalin®] and 2 mL [Epinephrine Injection]) and multiple-use (30 mL) vials of epinephrine (Adrenalin®) are approved and intended for use by medical personnel in the medically supervised setting.

¹ Sampson HA, et al. J Allergy Clin Immunol 117:391-7, 2006.

Regulatory history

A Type B, pre-IND meeting was held with the Agency on April 21, 2014, to discuss the feasibility of a 505(b)(2) new drug application for this product. At the meeting, the Agency requested that, as part of the application, Adamis submit a rationale for administration of epinephrine via a prefilled syringe in the unsupervised medical setting.

The 505(b)(2) new drug application was originally submitted on May 23, 2014, for epinephrine injection (epinephrine USP (b) (4)) 0.3 mg in a prefilled, single-dose syringe. The original application received a complete response on March 27, 2015.

A Type A meeting was held on August 5, 2015, (meeting minutes dated September 4, 2015) to discuss the complete response letter. It was noted that the summary of the information provided appeared reasonable to address the deficiencies related to product quality, but the adequacy of the data would be determined following review of the resubmission. There was discussion regarding the testing required for container content and deliverable volume.

The Applicant submitted a complete response on December 4, 2015.

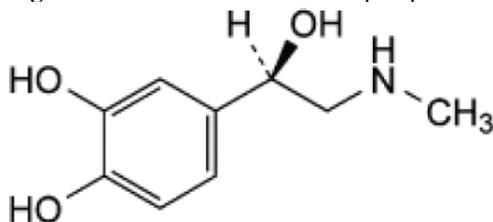
3. CMC/Device

Primary reviewer: Venkateswara R. Pavuluri, PhD, RPh; CMC Lead: Craig M. Bertha, PhD

- **General product quality considerations**

Epinephrine is a sympathomimetic catecholamine. The drug substance is a white to off-white crystalline powder, gradually darkening on exposure to light and air. The chemical structure of epinephrine is shown in Figure 1. The drug substance contains one chiral carbon and the active enantiomer is L-epinephrine (or (-)-(R)-Epinephrine). The inactive enantiomer is D-epinephrine.

Figure 1: Chemical structure of epinephrine



Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. The DMF was last reviewed on June 24, 2014 and was found to be adequate. In the original NDA submission, the specification proposed for drug substance was looser than the specification from the supplier and did not meet current ICH Q3A guideline. The drug

substance specification and test procedures were revised in this resubmission to i) update the limits for content (b) (4) meeting the limits as specified by the manufacturer (b) (4) and current ICH Q3A guideline ii) include the test for residual solvent (b) (4) and iii) update the appearance and solubility acceptance criteria. The revised specification for the drug substance is deemed adequate to support the quality of the drug product. Thus, the responses to the three issues in Agency's complete response letter and additional information request are deemed adequate from CMC perspective.

The drug product, Epinephrine injection, USP (b) (4) (0.3 mg prefilled single dose syringe) is a sterile, clear, colorless solution for injection in prefilled syringe. Each prefilled syringe contains approximately 0.8 mL epinephrine solution (b) (4) designed for single use to deliver a 0.3 mL dose by subcutaneous or intramuscular routes for self-administration by the patient or caregiver. The excipients include (b) (4) % sodium chloride, (b) (4) % sodium metabisulphite, hydrochloric acid (b) (4) to pH 2.2 to 5.0, and water for injection (b) (4). The levels of all the ingredients are considered safe for use because each has been previously approved for use in this type of or similar product, at or above the proposed concentration, as indicated in FDA's Inactive Ingredient Database (IID), where appropriate.

Epinephrine injection is proposed to be packaged in a syringe consisting of a Type I glass syringe barrel fitted with a (b) (4) needle (25G 5/8" cannula) and a rigid needle shield, which is sealed with a rubber stopper (b) (4). These primary packaging components are supplied sterile, clean, and ready to fill. The original Epinephrine injection prefilled syringe (Figure 2) was designed to deliver a dose (b) (4). The deliverable volume is a critical quality attribute of this drug/device combination product. During the first review cycle, it was determined that the deliverable volume specification should have a lower and upper limit with a target deliverable dose of 0.3 mg (0.3 mL) as per the label claim. The Applicant was told to modify the device so that it has a target deliverable volume of 0.3 mL with an associated specification acceptance criterion to a range of 0.30 mL \pm (b) (4) %.

The Applicant redesigned the device (Figure 3, Figure 4). The redesign utilizes (b) (4).

The components of the redesign and their function are outlined in Figure 5 and Figure 6. The Applicant states that the new design is more ergonomic and will also protect the solution from light, thus preventing degradation over the product's shelf-life. (b) (4)

(b) (4) The new device also 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)

(b) (4) The needle guard may be manually deployed after the injection. Importantly, once the needle guard is extended it locks into place and a dose cannot be delivered. The depth of needle penetration is not affected by the redesign, as no changes were made to the primary container closure system or the manufacturing of the prefilled syringe.

The General Hospital Devices Branch of CDRH completed a consultative review of the drug delivery device components. The consult reviewed the tests conducted to support the revised device, including dose volume accuracy testing, extractable volume testing, delivery rate and orientation testing, needle guard function, misuse and fault mode testing, accelerated life testing, drop and vibration testing, durability testing, and demonstration testing. The average delivered volume was 0.297 mL with a standard deviation of 0.010 mL. Thus, the modified device has a deliverable volume targeted at the labeling claim and the acceptance criterion for the deliverable volume is an appropriate range of the labeling claim (e.g., 0.3 ml \pm (b) (4) %). In addition, the Applicant provided data that the effect of delivery rate and needle orientation on deliverable volume was minimal. CDRH's final recommendations are pending at the time of this review.

Figure 2: Epinephrine Injection USP, (b) (4) Original Syringe Design



Source: Pharmaceutical Development, Figure 3.2.P.2-4, page 23

Figure 3: Epinephrine Injection, USP (b) (4) product: individual prefilled syringe is shown on left. Individual syringes will be supplied in a grey plastic case that assembles into a two-pack (right)



Source: Clinical Overview, Figure 2.5-1, page 6

Figure 4: Epinephrine Injection USP (b) (4) Redesign Overview



Source: Pharmaceutical Development, Figure 3.2.P.2-5, page 25

Figure 5: Components in Redesign



Source: Pharmaceutical Development, Figure 3.2.P.2-6, page 25

Figure 6: Mechanical function of redesign



Source: Pharmaceutical Development, Figure 3.2.P.2-8, page 26

All currently licensed epinephrine products (for self or caregiver administration) are autoinjectors that automatically inject epinephrine when pressed firmly against the thigh. In contrast, the container closure system of this product is a prefilled syringe for manual injection. The need for manual injection raises considerations regarding potential clinical issues with the different type of device. While use of a manual prefilled syringe in the emergency setting by the patient or caregiver is accepted medical practice, the redesigned product is different in appearance from the originally proposed product. Specifically, the proposed product includes (b) (4) the

prefilled syringe. The redesigned product does not appear like a typical prefilled syringe and patients and caregivers may think that the proposed product is an autoinjector. This could lead to difficulty administering the product during anaphylaxis because the injection steps for the proposed product are different than the injection steps for an autoinjector and there is a risk of negative transfer if this is used by previous epinephrine autoinjector users. The proposed design has not been marketed for any other products.

In consultation with the Division of Medication Error Prevention and Analysis (DMEPA) an information request was sent to the Applicant on March 3, 2016 that sought clarification of whether human factor studies were performed to support the use of the product in an emergency situation. Initially, the Applicant submitted a summary of the human factors data. After a subsequent information request, the Applicant submitted detailed information including a summary of formative studies, human factors study protocol, and human factors study results. This information was not included in the initial resubmission. DMEPA did not review the human factors protocol prior to the Applicant conducting the study as it was not submitted to the Agency for review and feedback. The human factors study included a total of 36 participants, who each completed two injection simulations. DMEPA identified several notable flaws in the study methodology. First, the number of test participants was too low. The Applicant included 8 injection naive lay users and 28 injection-experienced patients/lay users, while DMEPA recommends a minimum of 15 participants for each distinct user group. Second, the majority (77.8% [n=28]) of the participants were trained without adequate justification that this is reflective of the U.S. population. Third, the training was a 3-minute online video that may not reflect the training that is expected to occur in the real world which actual users would receive. Fourth, the participants were asked to perform the first injection and then were asked to read through the IFU prior to the second injection, which may introduce bias. Fifth, the study report did not provide information regarding whether the testing environment simulated an emergent situation or stressful conditions, which would be recommended for this product.

DMEPA did not feel that the human factors study results demonstrated that users can use the device safely and effectively as their review concluded that there were errors that occurred in the study which could result in delayed treatment. See DMEPA's reviews for additional details. Failures occurred in the following critical tasks:

1. Remove needle cap
2. Insert needle into muscular area of the body (ideal placement is the thigh)
3. Depress plunger fully until plunger clicks
4. Deploy needle guard
5. Call 911 or report to emergency room

Failure to remove needle cap (n=3)

Of the 36 participants, two naïve, trained lay users did not remove the needle cap in the first injection and one trained patient did not remove the needle cap in the second injection. During both injections, the participants prematurely deployed the safety guard to the complete locked position. In addition to these failures in the critical task, out of all 72 injection attempts, 6% resulted in close calls and 7% resulted in struggle with removing the needle cap. Failure

and/or delay in removing the needle cap represent a safety concern as anaphylaxis is an emergent condition that can progress in severity in a short time; thus, treatment with epinephrine in a timely fashion is critical. Furthermore, premature deployment of the safety guard occurring in attempts to remove the needle cap results in the inability to deliver a dose with the syringe. Based on DMEPA's analysis, it was felt that the failures occurred due to inherent issues with the product design. To potentially mitigate this risk, modifications need to be made to the device design to differentiate the safety guard from the needle cap.

Failure to insert needle into muscular area of body (n=6)

In the first injection, four participants (2 trained lay users, 1 trained patient, and 1 untrained patient) failed to insert the needle into a muscular area of the body. Failure to insert the needle into a muscular area could affect the absorption and onset of action of the medication. To potentially mitigate this risk, modifications could be made to the IFU to make this important information more prominent.

Failure to depress plunger fully (n=2)

One untrained patient participant did not depress the plunger fully in both trials and failed to successfully administer the injections. The participant was recently prescribed and trained on the EpiPen within the last 3 months. In both simulated injections, the participant swung the prefilled syringe like an EpiPen, immediately removed the syringe, and did not press the plunger, thinking that it was similar to EpiPen. DMEPA and the Applicant agreed that the error observed may be caused by negative transfer based on the user's expectations of how the proposed product should be administered based on their familiarity with the use of EpiPen. Additionally since this product does not look like a typical prefilled syringe, this may have further confused the participant.

In the real-world, many potential end users of the Epinephrine injection prefilled syringe may be previously trained on other epinephrine autoinjectors, including EpiPen. The observed error suggests that some users of Epinephrine injection prefilled syringe would be expected to fail to appropriately administer the product, thus not receiving a potentially life-saving drug in actual use. To potentially mitigate this risk, modifications may be made to the device design to align the appearance to that of a standard prefilled syringe, which may serve as a key visual indicator to end users that the product differs from currently approved products (i.e., autoinjectors).

Failure to deploy needle guard (n=54)

With regard to deploying the needle guard, 29 participants failed this task in the first injection and 25 participants failed this task in the second injection. Failure to deploy the needle guard may result in potential needle stick injuries. DMEPA's analysis indicates that the failure occurred due to inherent issues with the product design. To potentially mitigate this risk, modifications could be made to the device design to further differentiate the safety guard from the needle cap. Additionally, modifications to the IFU to increase the prominence of this important information should also be considered.

Failure to call 911 or report to emergency room (n=4)

Four patient participants (2 trained and 2 untrained) failed to call 911 or report to the emergency room in the first injection as they stated they would wait to see if the injection would alleviate the anaphylaxis symptoms before taking further action. After reading the IFU between injections, all participants corrected their error in the second injection.

Failure to call 911 or report to the emergency room may lead to a potential life threatening situation if the anaphylaxis symptoms persist. To potentially mitigate this risk, modifications could be made to the IFU to increase the prominence of this important information.

Table 1: Summary of Critical Task Failures

Critical Tasks	Number of Failures in Injection 1	Number of Failures in Injection 2	Clinical Implication
Open case	0	0	Delay in dosing medication
Remove syringe from case	0	0	Delay in dosing medication
Remove needle cap	2	1	Failure to dose medication and therefore potential life-threatening situations
Insert needle into muscular area of body	4	2	Failure to dose medication and therefore potential life-threatening situations
Depress plunger fully	1	1	Failure to dose medication and therefore potential life-threatening situations
Deploy needle guard	29	25	Potential needle stick injuries
Call 911 or report to emergency room	4	0	Delay in therapy

Source: DMEPA review

In summary, despite notable flaws in the human factors study methodology, the study did not demonstrate the intended population is able to use the proposed Epinephrine injection prefilled syringe safely and effectively. Anaphylaxis is an acute, life-threatening condition, and a proposed epinephrine product must deliver the drug quickly and reliably. In the human factors study, there were 40 errors related to critical tasks in the first injection and there were 29 errors related to critical tasks in the second injection. DMEPA’s analysis concludes that some of the errors observed in the study could be attributed to the product design. Of specific concern, are errors with the manual needle guard that prevented patients from administering the dose and the errors due to negative transfer from EpiPen in which participants did not depress the plunger fully as they were using the product as an autoinjector. These errors occurred in critical tasks in a product used in an emergency situation and any failure to perform these tasks correctly may lead to an inability to treat anaphylaxis in a timely fashion.

While the number of errors decreased from the first injection to the second injection, patients were instructed to read the IFU between the first and second injection, which is not representative of a real world scenario. Further, anaphylaxis is an emergent condition that can progress in severity in a short time; therefore, treatment with epinephrine in a timely fashion is

critical. In addition, use of epinephrine is intermittent, unpredictable, and occurs under conditions of stress. Thus, in actual use, the ability of users to self-correct an initial mistake associated with administering the Epinephrine prefilled syringe may be diminished due to the circumstances under which the product is used.

Thus, DMEPA recommends the Applicant either redesign the product or implement corrective and preventative measures to improve the device design and validate these changes in another human factors study prior to approval.

A teleconference will be held with the Applicant on May 23, 2016, to discuss these concerns with the Applicant.

- **Facilities review/inspection**

No issues. CDRH/OC notes that the application is approvable from the perspective of the applicable Quality System Requirements.

- **Product Quality Microbiology**

No issues

- **Other notable issues (resolved or outstanding)**

The CMC review team has recommended approval for this application from a CMC perspective. DMEPA notes that the human factors validation study was unable to show that the intended population is able to use the product safely and effectively.

4. Nonclinical Pharmacology/Toxicology

- **General nonclinical pharmacology/toxicology considerations**

No nonclinical studies were submitted to or required for this application. During review of the original application, the nonclinical review included review of the nonclinical portions of the label and epinephrine-related impurities through a CMC consultation. The levels of the epinephrine-related impurities [REDACTED] (b) (4) [REDACTED] did not warrant further nonclinical qualification studies. No new issues were identified, and there are no outstanding toxicology issues.

- **Other notable issues (resolved or outstanding)**

None

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology studies were conducted or required for this resubmission. During review of the original application, the biopharmaceutics team granted a biowaiver from conducting an in vivo bioequivalence study for the IM and SC routes.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary reviewer: Peter Starke, MD

- **Efficacy review**

No clinical studies were submitted or required for this application. The recommended dosing is based on the published literature and established clinical practice. Support for efficacy is based on the Agency's previous findings of efficacy for epinephrine in the treatment of allergic reactions and anaphylaxis. Other approved epinephrine products for the treatment of anaphylaxis have also relied on the literature. Based on the literature, all major guidelines for the treatment of anaphylaxis recommend epinephrine as first-line therapy for the treatment of anaphylaxis². It is noted in these guidelines that "the appropriate dose should be administered promptly at the onset of apparent anaphylaxis" (p. 478). Thus, any proposed epinephrine product must be able to administer epinephrine quickly and reliably. See Section 3 for review of the human factors study data for the proposed product. From a clinical perspective, these data do not support the safe and effective use of the product as there were critical use errors with the device that prevented administration of the product, such as failure to fully depress the plunger or errors with the manual needle guard that prevented patients from administering the dose of epinephrine. Many of these errors were attributed to the product design. Thus, the device must be modified taking into consideration the issues that render the product unusable in an emergent life-threatening situation or make it unclear that the device is a prefilled syringe.

Dr. Starke has concluded that the submitted data are inadequate to support the safe and effective use of the proposed epinephrine injection prefilled syringe and I concur.

8. Safety

There is adequate evidence to support the safety of epinephrine for anaphylaxis based on the Agency's previous findings of safety for epinephrine in the treatment of allergic reactions and

² Lieberman P, Nicklas RA, et al, 2010. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* 126(3):477-480 e471-442.

anaphylaxis. However, as noted in Section 7, the proposed device is unable to quickly and reliably deliver epinephrine to treat anaphylaxis in the medically unsupervised setting. Thus, the Applicant's proposed device will need to be redesigned to support its safe and effective use.

Dr. Starke has concluded that the submitted data are inadequate to support the safe and effective use of the proposed epinephrine injection prefilled syringe and I concur.

9. Advisory Committee Meeting

Epinephrine is not a new molecular entity, and no new issues were identified during the review that would require discussion at an Advisory Committee meeting. Therefore, an Advisory Committee meeting was not held for this application.

10. Pediatrics

This application does not contain a pediatric assessment as the proposed epinephrine prefilled syringe does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. The application was not discussed at the Pediatric Review Committee (PeRC) meeting and Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) does not apply.

11. Other Relevant Regulatory Issues

- **Financial disclosures**

No clinical trials were submitted as part of this resubmission. As such, financial disclosure does not apply.

- **Office of Scientific Investigation (OSI) audits**

No clinical safety or efficacy trials were submitted in this application. Thus, clinical study site inspections were not requested or performed.

- **Other outstanding regulatory issues**

None

12. Labeling

- **Proprietary name**

The proposed trade name is “Symjepi,” was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable on May 6, 2016.

- **Physician labeling**

The Applicant submitted a label in Physician’s Labeling Rule (PLR) format that is similar to the approved labeling for other epinephrine autoinjector products approved for treatment of anaphylaxis. The primary differences for this product are in sections that are product-specific, including the instructions for use, which is appropriate.

As the recommended regulatory action is complete response, labeling discussions were not conducted with the Applicant.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

Not applicable.

- **Carton and immediate container labels (if problems are noted)**

Not applicable as the recommended regulatory action is complete response.

- **Patient labeling/Medication guide (if considered or required)**

Not applicable.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action for this application is complete response for the indication of “emergency treatment of allergic reactions (Type I), including anaphylaxis.” The human factors validation study was unable to show that the intended population is able to use the product safely and effectively. The errors that occurred in the human factors study were in critical tasks in a product used in an emergency situation. Failure to perform an injection correctly may lead to an inability to treat anaphylaxis in a timely fashion. Thus, the recommended regulatory action is complete response.

- **Risk Benefit Assessment**

The risk/benefit of epinephrine for anaphylaxis is favorable. Epinephrine is the treatment of choice for anaphylaxis and has been demonstrated to be immediately life-saving, with over 100 years of continuous use. However, rapid and reliable administration of epinephrine is critical. Thus, the Applicant’s proposed Epinephrine injection prefilled syringe, which was

associated with critical use errors in human factors testing, does not have an appropriate risk/benefit for the treatment of anaphylaxis in the medically unsupervised setting.

- **Recommendations for Postmarketing Risk Evaluation and Management Strategies**

Not applicable as the recommended regulatory action is complete response.

- **Recommendation for other Postmarketing Requirements and Commitments**

Not applicable as the recommended regulatory action is complete response.

- **Recommended comments to applicant**

Recommended comments to the Sponsor are as follows:

1. There are multiple flaws in your human factors study design methodology and the study results did not demonstrate that your proposed product can be used safely and effectively. Of specific concern are errors that led to failure to administer a dose of the medication, such as errors with the manual needle guard that prevented patients from administering the dose of epinephrine and the errors due to negative transfer from other epinephrine autoinjectors in which participants did not depress the plunger fully because they used the product as an autoinjector. Our analysis concludes that some of the errors observed in the study could be attributed to the product design. Therefore, we recommend you redesign the device or modify the proposed product taking into consideration the issues that render the product unusable in an emergent life-threatening situation or make it unclear that the device is a prefilled syringe. Once completed, conduct a new human factors protocol following our guidance found at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>.

In addition, we recommend you submit your protocol for our review and for comments and/or recommendations prior to conducting the validation study. If you choose to reconfigure the device to a standard prefilled syringe without the housing components, additional human factors studies may not be needed.

2. If redesigning is not feasible, we recommend you outline in detail how you intend to mitigate the risk of errors involving the needle guard, premature deployment of the needle guard resulting in failure to administer the medication in a life-threatening situation, potential needle sticks, and failure to depress the plunger with the knowledge that patients may not be trained on the prefilled syringe and need to successfully inject in an emergent situation. The revised Instructions for Use (IFU) would need to be validated to confirm that patients were successful in performing the critical tasks and observed use-errors were successfully mitigated. We strongly

encourage you to submit the validation study protocol prior to implementation and to utilize our guidance listed under number 1 in the preparation of the protocol.

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/s/

JANET W MAYNARD
05/20/2016

MEDICAL OFFICER REVIEW

Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION: NDA 207-534	TRADE NAME: Symjepi
APPLICANT/SPONSOR: Adamis Pharmaceuticals Corp.	USAN NAME: Epinephrine injection, USP, 1mg/mL, 0.3 mg (prefilled syringe)
MEDICAL OFFICER: Peter Starke, MD	CATEGORY: Catecholamine: nonselective alpha and beta adrenergic agonist
TEAM LEADER: Janet Maynard, MD	ROUTE: Intramuscular or subcutaneous
DATE: May 9, 2016	

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
December 4, 2015	December 4, 2015	SD-12	Complete Response to CR action of 3/27/2015
January 27, 2016	January 27, 2016	SD-13	Word versions of labeling
February 11, 2016	February 11, 2016	SD-14	Proprietary name review request
March 3, 2016			Information Request #1 (Clinical and CMC)
March 15, 2016	March 15, 2016	SD-15	Response to Information Request #1
March 16, 2016			Information Request #2 (DMEPA)
March 24, 2016			Information Request #3 (DMEPA)
April 8, 2016	April 8, 2016	SD-17	Response to Information Requests #2 and #3

REVIEW SUMMARY:

This is a 2nd cycle summary review of a 505(b)(2) application from Adamis for a drug/device combination of Epinephrine Injection, USP (b) (4), 0.3 mg in a pre-filled, single-dose, manually-injected syringe. The original NDA was dated May 23, 2014, and received on May 28, 2014, and a Complete Response (CR) action was taken on March 27, 2015, because the device was not capable of delivering the labeled claim amount of drug. Adamis was asked to redesign the pre-filled syringe to deliver the labeled target volume and provide data to support the redesigned device. There were no other issues or concerns for the device or its sterile manufacture. As such, the Agency anticipated that the changes needed to address the dose issue would be relatively straightforward.

To address this issue, Adamis made modifications to (b) (4) be on target for the labeled dose of 0.30 mL (0.3 mg). However, a number of additional changes were made (b) (4)

This has resulted in a device (b) (4) raising the new concern (b) (4) and/or result in confusion and critical use failures in the hands of patients. The extra components also add to the complexity (b) (4) resulting in the need to have CDRH review the device design to ensure that it would not be prone to mechanical failure. As such, consults were sent to both CDRH and DMEPA to review the mechanical aspects of the device and the human factors studies / Instructions for Use, respectively. The CDRH and CMC reviews are still pending as of the date of finalization of this review. However, when DMEPA reviewed the human factors data, which was only submitted after the Agency requested the information, they found that the study did not demonstrate that users could use the device safely and effectively. There were several critical use failures, even after subjects were provided what appeared to be adequate instructions under close to ideal conditions. Therefore, the decision was made that, from a clinical perspective, this drug-device combination could not be approved as currently redesigned.

OUTSTANDING ISSUES:

The device will need to be redesigned to assure that it can be used safely and reliably.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: APPROVAL COMPLETE RESPONSE

1. Summary

This is a 2nd cycle summary review of a 505(b)(2) application from Adamis Pharmaceuticals Corp. (Adamis) for a drug/device combination of Epinephrine Injection, USP (b)(4), 0.3 mg in a pre-filled, single-dose, manually-injected syringe. The original NDA was dated May 23, 2014, and received on May 28, 2014, and a Complete Response (CR) action was taken in the first cycle on March 27, 2015, because of product quality issues. The main concern was that the device was not capable of delivering the labeled claim amount of drug: the targeted dose of the pre-filled syringe was (b)(4) whereas the approved dosage in this setting is 0.3 ml (0.3 mg). Adamis was asked to redesign the pre-filled syringe so that it would deliver the labeled target volume, and they were asked to submit data to support the redesigned device. Other than tightening some of the specifications, there were no other issues or concerns remaining for the pre-filled syringe device or its sterile manufacture. As such, the Agency anticipated that the changes needed to address the dose issue would be relatively straightforward.

To address this issue, Adamis made modifications to (b)(4) (b)(4) be on target for the labeled dose of 0.30 mL (0.3 mg). However, a number of additional changes were made to the device. (b)(4)

(see Figure 2). This has resulted in a device (b)(4), raising the new concern (b)(4) and/or result in confusion and critical use failures in the hands of patients. The (b)(4) also add to the complexity (b)(4) resulting in the need to have CDRH review the device design to ensure that it would not be prone to mechanical failure. As such, consults were sent to both CDRH and Division of Medication Error Prevention and Analysis (DMEPA) to review the mechanical aspects of the device and the human factors studies / Instructions for Use, respectively.

The final CMC and CDRH reviews are still pending as of the date of finalization of this review. DMEPA reviewed the human factors data, which surprisingly was only submitted by Adamis after the Agency requested the information. While there were flaws in the study design, the key finding was that the study did not demonstrate that users could use the device safely and effectively. Despite what would appear to have been adequate instruction for use with evaluations performed under near ideal conditions, there were a number of critical use failures, including confusion that it was an auto-injector, difficulty removing the needle guard, and premature deployment of the needle guard. As a result, the Division made the decision that this drug-device combination could not be approved as currently redesigned.

2. Introduction

This is a 2nd cycle summary review of a 505(b)(2) application from Adamis Pharmaceuticals Corp. (Adamis) for a drug/device combination of Epinephrine Injection, USP (b)(4), 0.3 mg in a pre-filled, single-dose, manually-injected syringe. The original NDA was dated May 23, 2014, and received on May 28, 2014, and a Complete Response (CR) action was taken in the first cycle on March 27, 2015, because of product quality issues. The main concern was that the device was not capable of delivering the labeled claim amount of drug: the targeted dose of the pre-filled syringe was (b)(4) whereas the approved dosage

in this setting is 0.3 ml (0.3 mg). Adamis was asked to redesign the pre-filled syringe to deliver the labeled target volume and provide data to support the redesigned device. A second concern was that the drug substance specifications needed to be tightened, specifically related to the acceptance criteria for [REDACTED] (b) (4) and the residual solvent limits.

The CR submission is all electronic in eCTD format, and was received on December 4, 2015. The PDUFA date is June 4, 2016.

3. Relevant Background

The proposed indication for this product is for the emergency treatment of severe allergic reactions (anaphylaxis). The product is intended for self or caregiver administration in the medically unsupervised, emergency setting. Only one dosage strength is proposed, 0.3 mg (0.3 mL) for patients who weigh ≥ 30 kg (66 pounds).

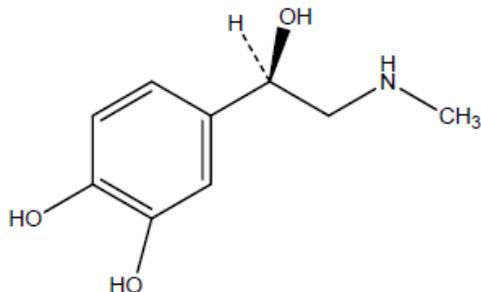
The application references EpiPen® (NDA 19-430), which is listed in the Orange Book as a reference drug. However, this product differs from EpiPen as well as all of the other approved epinephrine products that are intended for use in the medically unsupervised setting in that it is a prefilled syringe that is intended for manual injection (intramuscularly [IM] or subcutaneously [SC] into the lateral thigh), whereas all of the other approved products (EpiPen®, Adrenaclick®, Auvi-Q®) are auto-injectors.

In December of 2014, the applicant proposed the proprietary name Symjepi (pronounced sim-JEP-ee). The name was found acceptable (correspondence dated March 2, 2015); however, with the CR action Adamis was asked to resubmit the proposed proprietary name request with the Complete Response.

4. CMC/Device

Drug Substance

The drug substance (DS) or active pharmaceutical ingredient (API) in this drug product is epinephrine base, sourced from [REDACTED] (b) (4) (DMF# [REDACTED] (b) (4)). Epinephrine is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. Epinephrine is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation. The chemical formula of epinephrine is $C_9H_{13}NO_3$, and its chemical structure is shown below. The chemical structure consists of benzene ring and an



ethylamine side chain.

As shown in the structural diagram above, epinephrine has two optical isomers (enantiomers): substitution of an hydroxyl group at the beta carbon atom on the ethylamine side chain yields *l*-

and *d*- isomers [also described as L- or (-) and as D- or (+)]. Levorotatory rotation (*l*- form or *l*-epinephrine) confers at least 10-15 times higher systemic potency than the *d*-isomer (Patil 1975; Westfall 2011), with *l*-epinephrine being the natural form produced by the adrenal medulla. The drug substance is manufactured (b) (4)

Drug Product

The proposed drug product contains epinephrine injection, USP in a sterile solution at a labeled concentration of 1 mg/mL (b) (4). The formulation includes epinephrine, USP, sodium metabisulfite, sodium chloride, HCl (b) (4) to adjust the pH to 2.2-5, and water (b) (4) for injection.

It should be noted that, (b) (4)
this product has a (b) (4) % overage of active drug (b) (4)

The solution is packaged as 0.8 mL of solution in a 1 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 (b) (4). (b) (4) is the manufacturer of the drug product and the primary packaging. Secondary packaging is performed (b) (4).

Redesigned Device

Since the original submission, the device has now been fully redesigned with the stated intention to more accurately deliver the labeled dose of 0.3 mL (0.3 mg) as well as provide additional features. To be more specific, the prefilled syringe (b) (4) packaged within a (b) (4) 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, and an extendable needle guard intended to be manually deployed after the injection for sharps protection. Adamis states that the new design is more ergonomic and will also protect the solution from light and help prevent degradation over the product's shelf-life (Figure 2). (b) (4)

The new device now also 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, and once extended, locks into place. Contrary to some of the figures presented in the resubmission, the needle guard is the same color as the outer plastic case. The device is assembled into a two-pack so that two doses are available to a patient should a second dose be needed.

Each device is then packaged in a holding case, (b) (4) as a two-pack so that two doses are available to a patient should a second dose be needed (Figure 2). The old device is shown in Figure 1, the new device is shown in Figure 2, new features of the device are shown in Figure 3, new device components are shown in Figure 4, and functional design of the new plunger is shown in Figure 5.



Figure 1. Original syringe design

Source: Figure 3.2.P.2-4, p24; 3.2P.2, pharmaceutical-development.pdf; Submission of 3/15/2016



Figure 2. Redesigned  (b) (4)

Source: Figure 2.5-1, 2.5, clinical-overview.pdf, p6



Figure 3. New features of the device (color rendition does not reflect the actual product)

Source: Figure 3.2.P.2-5, p26; 3.2P.2, pharmaceutical-development.pdf; Submission of 3/15/2016



Figure 4. Revised (b) (4) (color rendition does not reflect the actual product)

Source: Figure 3.2.P.2-6, p26; 3.2P.2, pharmaceutical-development.pdf; Submission of 3/15/2016



Figure 5. Functional design (b) (4)

Source: Figure 3.2.P.2-8, p27; 3.2P.2, pharmaceutical-development.pdf; Submission of 3/15/2016

Based on the stability data, Adamis is requesting a shelf-life (expiry dating) of 18 months, when stored at room temperature 77°F (25°C) in the plastic case provided, with the following additional storage and handling instructions: Do not refrigerate. Protect from light, extreme heat and freezing.

Conclusions from the CMC Review

The final CMC review is still pending as of the date of finalization of this review. However, my understanding is that CMC has concluded that the product is approvable from a CMC perspective, and that the proposed shelf life is acceptable.

CDRH Review

The CDRH review is still pending as of the date of finalization of this review.

5. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology issues were noted during this review cycle.

6. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics issues were noted during this review cycle.

7. Clinical Microbiology

No new microbiology issues were noted during this review cycle.

8. Clinical/Statistical- Efficacy

No new clinical efficacy or safety issues were noted during this review cycle.

9. Safety

No new clinical efficacy or safety issues were noted during this review cycle. However, the Division of Medication Error Prevention and Analysis (DMEPA) provided a consult reviewing the Human Factors data.

Human Factors Study – DMEPA Review

The applicant performed a Human Factors (HF) study to support this new product. However, the resubmission did not state that the study had been conducted, nor was it included with the resubmission. Rather, the study protocol and results were only submitted after DMEPA sent IRs asking whether an HF study had been conducted and to submit the results.

Once the results were submitted, DMEPA reviewed the protocol and report and concluded that the study did not demonstrate that Symjepi prefilled syringe can be used safely and effectively. The study demonstrated critical failures in use of the product, despite the fact that it was conducted under near-ideal conditions and most subjects had been trained within the previous 3 weeks. Furthermore, even if the study results demonstrated no use errors/failures, DMEPA identified methodological flaws with regard to the number of participants, training, and testing environment were inadequate.

With regard to the study methodology, the study included 36 participants (8 injection naïve, 28 injection experienced), whereas DMEPA usually recommends inclusion of at least 15 participants for each distinct user group. Eighty percent of the participants were trained, whereas DMEPA typically expects that only half of the participants are trained. Further, the training consisted of a video and a follow-up survey. This approach does not represent a real-world scenario in the United States. Additionally, in between injection 1 and injection 2 the moderator instructed all participants to read the IFU, which does not represent a real-world scenario and is considered biased as participants have already performed a simulated injection. Finally, the report was not clear if the testing environment simulated an emergent situation (distractions, loud noises, etc.) or stressful conditions as there would be during an actual injection. Since this is a drug product that will be used in an emergency situation, it is expected that an HF study will be conducted using real-world conditions.

With regard to the study results, there were multiple errors that could result in delayed treatment, no treatment, or needle stick injuries (Table 1). They noted several critical task failures, including inaccurately trying to use the device as an auto-injector, difficulties with removal the needle cap, early pressure on the plunger releasing medicine prior to insertion of the needle, as well as early deployment of the needle guard that could result in inability to use the device or a needle stick injury. Overall, critical task failures occurred for over 10% of study participants, indicating that the device cannot be used successfully in an emergency situation.

Table 1. HF Study: Critical tasks and failures

Critical Tasks	Number of Failures in Injection 1	Number of Failures in Injection 2
Open case	0	0
Remove syringe from case	0	0
Remove needle cap	2	1
Insert needle into muscular area of body	4	2
Depress plunger fully	1	1
Deploy needle guard	29	25
Call 911 or report to emergency room	4	0

10. Advisory Committee Meeting

An AC meeting was not held for this application.

11. Pediatrics

There were no pediatric issues with this application. Adamis has only proposed a 0.3 mg dosage strength for patients 30 kg and above, and not a 0.15 mg dosage strength for patients 15 to 30 kg, as is available for other epinephrine products approved for this indication. However, the application did not trigger PREA because the product does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Since the application did not trigger PREA, there is no regulatory requirement for Adamis to provide lower doses.

12. Other Relevant Regulatory Issues

There were no other relevant regulatory issues noted during this review cycle.

13. Labeling

Labeling Issues

Since it was determined that the product would need to be redesigned before consideration of approval, labeling negotiations were not carried out for this product during this review cycle.

(b) (4)

(b) (4)

Proprietary name

In the first review cycle, Adamis requested review of the proposed proprietary name, Symjepi. That name was found acceptable, but with the CR action, the Agency noted that the trade name is conditional pending approval and must be resubmitted with the response to the CR action. On February 11, 2016, Adamis requested re-review of their proposed proprietary name, Symjepi. Upon review DMEPA again found Symjepi to be an acceptable trade name.

14. Recommendations/ Benefit-Risk Assessment**Recommended Regulatory Action**

I recommend a Complete Response action for this application.

Risk Benefit Assessment

The risk-benefit does not approval of this drug product for the treatment of anaphylaxis in patients who weigh 30 kg (66 pounds) or more. The product will need to be redesigned to be more obvious that it is a prefilled syringe, while at the same time delivering the labeled amount of medication.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

Recommended Comments to Applicant

The human factors study did not demonstrate that users could use your proposed device safely and effectively. Several subjects demonstrated critical use failures, despite the study having been conducted under ideal use conditions. The main problem appears to be the opaque plastic that now encases the prefilled syringe, no longer making it obvious that the device is a manually injected prefilled syringe and not an autoinjector. Additionally, subjects were confused as to the order of the steps involved in use of the product, and mistakenly did not remove the needle cap or prematurely deployed the needle guard. To address this issue, redesign the device to make it more obvious that it is a prefilled syringe, and perform human factors study that demonstrates that subjects can adequately follow the directions for use.

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/s/

PETER R STARKE
05/09/2016

JANET W MAYNARD
05/09/2016

SUMMARY REVIEW FOR REGULATORY ACTION

Date	March 27, 2015
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	May 23, 2014/May 28, 2015
PDUFA Goal Date	March 27, 2015 (actual is Saturday March 28, 2015)
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	Complete response

Materials Reviewed/Consulted OND Action Package, including:	Names of Discipline reviewers
Medical Officer Review	Peter Starke, MD
Cross Discipline Team Leader Review	Janet Maynard
Pharmacology/Toxicology Review	Jane Sohn, PhD, Timothy Robison, PhD
CMC Review	Ying Wang, PhD; Craig Bertha, PhD, Julia Pinto, PhD
ONDQA-Biopharmaceutics Review	Assadollah Noory, PhD, Tapash Ghosh, PhD
Clinical Pharmacology review	Sheetal Agarwal, PhD; Ping Ji, PhD
Product Quality - Microbiology	Vinayak B. Pawar, PhD
OSE/DMEPA	Matthew Barlow, RN, BSN, Kendra Worthy, PharmD

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 Meridian Pharmaceuticals for the emergency treatment of allergic reactions including anaphylaxis in the unsupervised medical setting. The application was submitted on May 23, 2014 and received on May 28th, 2014. The application was filed on July 27, 2014 and given a standard 10-month review clock and the PDUFA date

for this application is May 28, 2015 (effectively Friday May 27, 2015)¹. This review provides a brief summary of the salient issues for this application and the basis for the regulatory decision.

2. Background

Epinephrine, also known as adrenaline is a hormone and a neurotransmitter. It is a sympathomimetic catecholamine produced in some neurons of the central nervous system and in the chromaffin cells of the adrenal medulla. Epinephrine has many functions in the body including regulating heart rate, respiratory rate, and metabolic shifts. Epinephrine release is a crucial component of the “fight-or flight” response of the sympathetic nervous system.

Epinephrine has been in clinical use for over 100 years for the treatment of allergic reactions and anaphylaxis. The use of epinephrine for the treatment of allergic reactions and anaphylaxis has been defined over these decades of clinical use and is accepted as the standard of care in the treatment of patients with allergic reactions including anaphylaxis. The dose and route of administration has been defined by long-standing clinical practice and is accepted and cited in clinical practice guidelines for health care providers.

The currently approved epinephrine products for use in the unsupervised medical setting (self/care-giver administration) for the treatment of anaphylaxis are auto-injector products. These products were approved on the basis of the historical clinical use and the published literature that support the use of epinephrine for the treatment of allergic reactions and anaphylaxis. These products (EpiPen®, Twinject®, Adrenaclick®, and AUVI-Q®) are to be used by patients or caregivers as a temporizing measure at the immediate onset of signs and symptoms of anaphylaxis until patients receive additional care under medical supervision.

Epinephrine predates both the original Federal Food and Drugs Act of 1906 (prohibited the sale of adulterated or misbranded drugs), the Food Drug & Cosmetic Act (FD&C Act) of 1938 (required that marketed drugs demonstrate safety) and the Kefauver-Harris amendment in 1962 to the FD&C Act (required that drugs demonstrate both safety and efficacy for approval). Since epinephrine predates 1938, it was not subject to the DESI review that was put in place following the 1962 amendments to the FD& C Act to evaluate drugs approved by the agency as safe between 1938 and 1962.

Epinephrine solution in a pre-filled syringe for injection used to be a marketed unapproved product. The Agency’s Office of Compliance has been working to bring marketed unapproved products in compliance with the Agency’s regulations for approved products, and issued a Compliance Policy Guide for Marketed Unapproved Drugs in 2006. For epinephrine, the Agency has exercised its discretion regarding removal of epinephrine solution for injection from the market because these products are used for life-saving indications (e.g. Advance Cardiac Life Support (ACLS) or cardiogenic shock). At a Type B meeting held with the Division on April 21, 2014, the Applicant informed the Division that they discontinued marketing the product after receiving a Warning Letter from the FDA Office of Compliance in June 2010.

¹ The PDUFA date of March 23, 2015 stated on the cover page of the Primary Medical officer and CDTL reviews is incorrect.

The Agency approved the first epinephrine solution in vials for injection for the treatment of allergic reactions and anaphylaxis by healthcare providers in the medically supervised setting. Two presentations have been approved: 1) A single use vial without a preservative (approved December 7, 2012), and 2) A 30 mL multi-use vial that contains chlorobutanol as a preservative (approved December 18, 2013). Both presentations of Adrenalin® provide 1mg/mL of epinephrine.

To date, no epinephrine solution for injection in a pre-filled syringe (PFS) presentation has been approved for self/care-giver administration. At the Type B meeting held on April 21, 2014, the Division questioned the rationale for an epinephrine pre-filled syringe product for self/care-giver administration for anaphylaxis. The applicant suggested (among other things) that this product would fill a much-needed void for products that would be less costly than the auto-injector products. The division asked the applicant to include their rationale for such a product in their NDA submission.

3. Chemistry Manufacturing and Controls

The drug substance epinephrine is a white to off-white, odorless, crystalline powder that is slightly soluble in water and ethanol. Epinephrine is readily soluble in mineral acids. It is a sympathomimetic catecholamine with a molecular weight of 183.2. The drug substance supplier (b) (4) is responsible for the manufacturing and testing of the drug substance. Information about the drug substance manufacturing and testing is provided in DMF (b) (4) and the applicant provided a letter of authorization in their NDA submission to reference this DMF (b) (4) and the limit applied by the drug substance manufacturer for this solvent meets the requirements of USP <467> Residual Solvents.

The drug product epinephrine injection, USP, (b) (4) (0.3 mg Pre-filled Single dose Syringe) is a solution for injection. Each pre-filled syringe contains approximately 0.8 mL epinephrine solution for injection. The product is designed to be self-administered by the patient or caregiver, to deliver a volume (b) (4). This proposed delivered volume is unacceptable for an epinephrine product that is intended for self-administration or administration by caregivers in the non-medically supervised setting (b) (4).

This issue was communicated to the applicant on multiple occasions during the review cycle. The device (syringe) will need to be redesigned so that the delivered volume is $0.3 \text{ mL} \pm (b) (4) \%$ to be consistent with the dose of other approved epinephrine products for injection in the non-medically supervised setting. In the latest amendment to the application (received on February 6, 2015), the applicant was unable to provide any information regarding the re-designed device. The applicant did not submit a development or validation report, or batch data to support a new device. The applicant only submitted a revised acceptance criterion for the mean deliverable volume but without any supporting data. Therefore, the CMC team has recommended that the application not be approved in this cycle because of a lack of CMC information to evaluate the drug product and I concur with the recommendation.

In addition to this deficiency, the applicant's proposed drug substance specification of (b) (4) % for the (b) (4) impurity is (b) (4) the specification criterion for this impurity from the drug substance supplier which is set at (b) (4) %. Additionally, the applicant has not proposed a residual solvent (b) (4) limit in their drug substance specification. A specification for the residual solvent (b) (4) is contained in the (b) (4) specification ((b) (4) ppm). The applicant will be asked to address these specification issues in the action letter.

All facilities inspections and DMFs are acceptable and there are no outstanding DMF or facilities issues. The method of sterilization for the product (b) (4) and the microbiology attributes of the product are adequate and there are no outstanding product quality microbiology issues.

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. 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. Historically, clinical trials were not required to support the approval of the reference product EpiPen® autoinjector which relied on the literature and the extensive clinical experience with epinephrine for the treatment of anaphylaxis. All other epinephrine auto-injectors that were approved subsequent to EpiPen®, (Twinject®, Adrenaclick®, and AUVI-Q®) also relied on the published literature and the past clinical use experience with epinephrine. The epinephrine solution for injection product that is approved for the treatment of allergic reactions including anaphylaxis by healthcare providers was also approved without conducting clinical trials.

8. Safety

Based on the literature, the most common adverse reactions associated with epinephrine are pallor, tremor, anxiety, palpitations, dizziness, and headache. Serious events have also been reported and include lethal arrhythmias (i.e. ventricular fibrillation), cerebral hemorrhage related to rapid elevations in blood pressure, angina, and myocardial infarction. These adverse reactions do not preclude the use of epinephrine to treat anaphylaxis.

9. Advisory Committee Meeting

An advisory committee (AC) meeting was not convened for this application. There were no issues that required input from an AC.

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. The acceptability of the proprietary name was conveyed to the applicant on March 2, 2015. Since the application is not going to be approved, the applicant will need to resubmit the proposed proprietary name when they submit a complete response to the deficiencies in the action letter.

Physician labeling Carton and Immediate Container Labels/ Patient labeling

The labeling was not completed because the application is not going to be approved in this cycle

13. Action and Risk Benefit Assessment

Regulatory action

The recommended regulatory action for the application is a Complete Response because of product quality deficiencies. Because the product (as submitted in the application) is not capable of delivering the dose of the drug that has been shown to be safe and effective for the intended use, and the applicant has not provided any data to show that a redesigned syringe will deliver the target volume at labeling claim, the identity, strength, quality, purity, and potency of the drug product as required per CFR 3145.50 (ii) (a) cannot be assured.

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

Not applicable given that the product is not going to be approved. However, given the extensive use of epinephrine for the proposed indication, postmarketing risk management activities are not anticipated.

Postmarketing Study Commitments/Requirements

Not applicable given that the product is not going to be approved. However, given the extensive use of epinephrine for the proposed indication, postmarketing studies are not anticipated.

Comments to the Applicant

The following comments regarding product quality should be conveyed to the applicant in the action letter:

1. The deliverable volume of the drug product is a critical quality attribute for this drug for its intended use and use environment. The drug/device combination product as submitted in the application is not capable of delivering the labeling claim amount of the drug. This will not ensure the identity, strength, quality, purity, and potency of the drug product per CFR 314.50(ii) (a).

You need to redesign the pre-filled syringe to deliver the target volume at labeling claim. In your future submission you need to provide the following:

- i) Detailed device information with the original design and redesign comparison
- ii) Detailed validation report with the redesigned device performance data. It should include but not limited to; sample size, average deliverable volume, standard deviation, minimum and maximum volume delivered, etc.
- iii) Detailed validation batch (with the intended drug product solution) data with the redesigned device

You need to propose an acceptance criterion for the “deliverable volume” with reasonable lower and upper limits that is comparable to the limits of other approved drug products in this class. Please note the proposed acceptance criterion for “mean deliverable volume” with limit in the footnote (as in your amendment dated Feb 6, 2015) is not appropriate or adequate.

2. The volume determination as described in USP <1> is not specifically defined for which type of the volume. The (b) (4) is irrelevant regarding the analytical methods for the extractable volume for this pre-filled syringe to be used by the patients. You need to provide detailed analytical methods and adequate validation report for the extractable volume of the drug product.

3. Your proposed drug substance specification (Table 3.2.S.4.1-1) in the NDA is looser than that used by the drug substance supplier (b)(4) referenced in DMF (b)(4). Specifically,

- i) The proposed acceptance criterion for impurity (b)(4) is (b)(4)% in your NDA submission. The (b)(4) acceptance criterion for this impurity is (b)(4)%.
- ii) There is residual solvent (b)(4) limit of (b)(4) ppm in the (b)(4) specification. However, this limit is not in the drug substance specification proposed in the NDA.

Revise your specification to match the specification of the drug substance supplier (b)(4). Accordingly you also need to provide an appropriate analytical method and adequate validation report for the impurity (b)(4). Please note a limit test for any impurity is not acceptable. Alternately, provide justification to support your proposed specification (or lack of such specification). Please note that merely following the USP monograph is not sufficient justification for any impurity limit. ICH Q3A guideline also needs to be followed. Any potential residual solvent in the drug substance needs to be specifically listed and limit be set in the specification. Statement of (b)(4) is not sufficient.

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LYDIA I GILBERT MCCLAIN
03/27/2015

Cross-Discipline Team Leader Review

Date	March 6, 2015
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	207,534
Supplement#	
Applicant	Adamis Pharmaceuticals Corp.
Date of Submission	May 23, 2014
PDUFA Goal Date	March 23, 2015
Proprietary Name / Established (USAN) names	Symjepi/epinephrine injection
Dosage forms / Strength	Epinephrine prefilled syringe 0.3 mg (0.3 mL) for IM or SC injection (epinephrine injection USP (b)(4))
Proposed Indication(s)	Emergency treatment of allergic reactions (Type 1), including anaphylaxis
Recommended:	Complete Response

1. Introduction

Adamis Pharmaceuticals Corp. submitted this 505(b)(2) new drug application for epinephrine injection (epinephrine USP (b)(4) 0.3 mg in a prefilled, single-dose syringe, hereinafter referred to as “Epinephrine Injection,” on May 23, 2014. The proposed indication is for the emergency treatment of allergic reactions (Type 1), including anaphylaxis. The product is intended for self or caregiver administration in the medically unsupervised, emergency setting.

The proposed dose is 0.3 mg for patients who weigh at least 30 kg. There are no proposed dosage forms for patients who weigh less than 30 kg. The NDA references EpiPen® (NDA 19,430) which is injectable epinephrine administered via an autoinjector for self and caregiver administration in the medically unsupervised setting. In contrast to the listed product and other approved epinephrine products for use in the medically unsupervised setting, the proposed epinephrine product is a prefilled syringe intended for manual injection and is not an autoinjector. However, like the currently approved epinephrine autoinjectors, the proposed drug product is intended for use in the medically unsupervised setting for treatment of life-threatening allergic reactions, including anaphylaxis. A different product, Adrenalin®, is approved for use by medical professionals for the treatment of anaphylaxis in the medically supervised setting.

No efficacy and safety trials were conducted for this application. The basis of this submission is information on the drug constituent and device components, in conjunction with the Agency’s previous findings of efficacy and safety for epinephrine for the proposed indication. Supplementary information from a literature review was provided by the Applicant. The

proposed anaphylaxis indication is supported by over 100 years of clinical use and the literature. No clinical studies were performed for approval of the listed drug, EpiPen[®], which relied on the literature for support of efficacy and safety for treatment of anaphylaxis.

The PDUFA goal date for the anaphylaxis indication of this application is March 23, 2015, with a standard review clock.

2. Background

Indication

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis consensus network defined criteria for anaphylaxis in 2006 that include acute onset of various combinations of one or more of the following symptoms: skin or mucosal involvement, respiratory compromise, reduced blood pressure or end organ dysfunction, and persistent GI symptoms¹. Anaphylaxis presents as a biphasic hypersensitivity response, with rapid evolution of symptoms after exposure in minutes to several hours for the initial response, and a late phase occurring in up to 20% of patients 1-72 hours later, most frequently within the first 4-6 hours. The most frequent cause of death is respiratory compromise. Given the severity and rapid evolution of symptoms, immediate systemic therapy is required, and the potential benefits of treatment are significant (i.e. life-saving therapy with rapid improvement back to normal functioning).

Epinephrine

Epinephrine is a non-specific adrenergic agonist. Epinephrine is the drug of choice for treatment of anaphylaxis, with other treatments considered to be adjunctive or supportive. Currently, there are multiple autoinjectors approved for self-use to treat life-threatening allergic (hypersensitivity) reactions: EpiPen[®] and EpiPen Jr.[®] (NDA 19,430), Twinject[®] (NDA 20,800), Adrenaclick[®] and authorized generics (NDA 20,800), and Auvi-Q[®] (NDA 201,739). All contain a single dose of epinephrine at an adult dose of 0.3 mg or pediatric dose of 0.15 mg except Twinject[®], which contains two doses. These products are intended for self or caregiver administration, prior to arrival in the healthcare setting.

Additionally, single-use (1 mL) and multiple-use (30 mL) vials of epinephrine (Adrenalin[®]) are approved for use by medical personnel in the medically supervised setting.

Regulatory history

A Type B, pre-IND meeting was held with the Agency on April 21, 2014, to discuss the feasibility of a 505(b)(2) new drug application for this product. At the meeting, the Agency requested that, as part of the application, Adamis submit a rationale for administration of epinephrine via a prefilled syringe in the unsupervised medical setting.

¹ Sampson HA, et al. J Allergy Clin Immunol 117:391-7, 2006.

There were no additional regulatory interactions with the Applicant prior to submission of this new drug application.

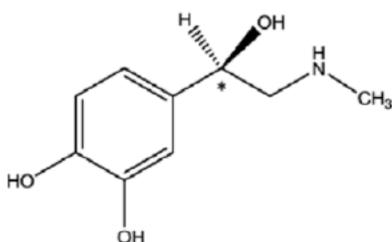
3. CMC/Device

Primary reviewer: Ying Wang, PhD; Acting CMC Lead: Craig M. Bertha, PhD; Supervisory Chemist: Julia Pinto, PhD

- **General product quality considerations**

Epinephrine is a sympathomimetic catecholamine. The drug substance is a white to off-white crystalline powder, gradually darkening on exposure to light and air. The chemical structure of epinephrine is shown in Figure 1. The drug substance contains one chiral carbon and the active enantiomer is L-epinephrine (or (-)-(R)-Epinephrine). The inactive enantiomer is D-epinephrine.

Figure 1: Chemical structure of epinephrine



Molecular Formula

C₉H₁₃NO₃

Relative Molecular Mass

183.20

Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. DMF (b) (4) was last reviewed in June 2014 and found to be Adequate. The specification proposed in this NDA for drug substance is looser than the specification from the supplier and does not meet current ICH Q3A guideline. Specifically:

1. The proposed acceptance criterion for impurity (b) (4) is (b) (4)% in the NDA submission. (b) (4) acceptance criterion for this impurity is (b) (4)%.
2. There is residual solvent (b) (4) limit of (b) (4) ppm in the (b) (4) specification. This limit is not in the drug substance specification proposed in the NDA.

The proposed specifications do not meet current regulatory requirements. Per ICH Q3A any impurity with level more than 0.15% needs to be qualified. Thus, the specifications need to match the specification of the drug substance supplier (b) (4)

The drug product, Epinephrine Injection, USP, (b) (4) (0.3 mg prefilled single dose syringe) is a solution for injection in prefilled syringe. The sterile solution is a clear, colorless solution. The excipients include (b) (4) % sodium chloride, (b) (4) % sodium metabisulphite, hydrochloric acid (b) (4) to pH 2.2 to 5.0, and water for injection (b) (4). The levels of all the ingredients are considered safe for use because each has been previously approved for use in this type of or similar product, at or above the proposed concentration, as indicated in FDA's Inactive Ingredient Database (IID), where appropriate.

Epinephrine injection is proposed to be packaged in a syringe consisting of a Type I glass syringe barrel fitted with a (b) (4) needle (25G 5/8" cannula) and a rigid needle shield, which is sealed with a rubber stopper (b) (4). The container closure system was felt to be suitable, without any compatibility concerns. Epinephrine injection is designed for ease of patient use. (b) (4)

The General Hospital Devices Branch of CDRH completed a consultative review of the drug delivery device components. The consult provided a list of recommendations that were carefully evaluated and addressed by the CMC and microbiology reviewers.

Figure 2: Diagram showing (b) (4)



Each prefilled syringe contains approximately 0.8 mL epinephrine solution for injection. Epinephrine injection is designed to be self-administered by a patient or caregiver. Each prefilled syringe is intended for single-use, and delivers a single dose of 0.3 mL (0.3 mg of epinephrine) by subcutaneous or intramuscular injection. The delivered (deliverable) volume is the amount of drug that the patient will receive. The target value should be around the labeling claim value (0.3 mL).

The deliverable volume is a critical quality attribute of this drug/device combination product. The originally proposed acceptance criterion was (b) (4) mL for the "deliverable volume." During manufacture, (b) (4) ultimately result in the required deliverable volume (b) (4). On the basis of the results of the validation batch runs the drug product manufacture proposed (b) (4)

Assessment of the actual delivered volume was conducted during capability testing with Water for Injection and during manufacture of 3 validation batches. In summary, the average delivered volume was (b) (4). This deliverable volume is unacceptable (b) (4)

[REDACTED] (b) (4)

The Applicant was told to modify the device to ensure that the deliverable volume is targeted at the labeling claim. In addition, the Applicant was told to revise the acceptance criterion for the deliverable volume to an appropriate range of the labeling claim (e.g., 0.3 ml \pm (b) (4) %). A teleconference was held with the Applicant on December 21, 2014, to discuss this request. The Applicant proposed a revised deliverable volume [REDACTED] (b) (4) but this was inadequate. The Applicant submitted an amendment on February 6, 2015, to further revise the acceptance criterion for the “mean deliverable volume” without any additional information about the redesigned device, or any validation report or new batch data with the redesigned the device. Thus, there are inadequate data to support the proposed modifications.

All currently licensed epinephrine products (for self or caregiver administration) are autoinjectors that automatically inject epinephrine when pressed firmly against the thigh. In contrast, the container closure system of this product is a prefilled syringe for manual injection. The need for manual injection raises considerations regarding potential clinical issues with the different type of device. However, use of a manual prefilled syringe in the emergency setting by the patient or caregiver is accepted medical practice and there are other products that are used in emergency settings by patients and caregivers that are not autoinjectors. In addition, the prefilled syringe presentation offers an additional choice for patients. As a result, a prefilled syringe packaging configuration is acceptable for this product.

After manufacturing, the Epinephrine injection prefilled syringe is packed into an opaque plastic case to protect the solution from light.

Due to deficiencies noted above, including a proposed specification for the drug substance that does not meet current ICH guidelines and a delivered volume that would cause the active drug to be delivered to patients outside (b) (4) % of the labeling claim value, the identify, strength, quality, purity, and potency of the drug product cannot be adequately assured per CFR 214.50(ii)(a). Therefore, the CMC team recommends a complete response action. See review by Dr. Ying Wang dated February 23, 2015, for complete details.

- **Facilities review/inspection**

The drug substance is manufactured [REDACTED] (b) (4)
[REDACTED] Manufacture of the drug product and primary packaging, quality control of drug substance, excipients, primary packaging materials, and finished product, stability testing of drug product, and batch release [REDACTED] (b) (4)
[REDACTED] are performed [REDACTED] (b) (4)
[REDACTED] Residual solvent testing for the drug substance is performed [REDACTED] (b) (4)
[REDACTED] Secondary packaging, quality control of secondary packaging materials, and batch release data to Adamis are

performed [REDACTED] (b) (4)

Batch release of drug product to market is performed at Adamis Pharmaceuticals Corporation, 11682 El Camino Real, Suite 300, San Diego, California 92130. The Office of Compliance issued an overall recommendation of Acceptable for the application on January 27, 2015.

- **Product Quality Microbiology**

[REDACTED] (b) (4)

The product quality microbiology measures were deemed to be adequate. For complete details, see review by Dr. Vinayak Pawar, dated January 16, 2015.

- **Other notable issues (resolved or outstanding)**

The CMC review team has recommended a complete response for this application from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

Primary reviewer: Jane Sohn, PhD; Team leader: Timothy Robison, PhD, DABT

- **General nonclinical pharmacology/toxicology considerations**

No nonclinical studies were submitted to or required for this application. The nonclinical review included review of the nonclinical portions of the label and epinephrine-related impurities through a CMC consultation. The levels of the epinephrine-related impurities [REDACTED] (b) (4) did not warrant further nonclinical qualification studies. No new issues were identified, and there are no outstanding toxicology issues.

See Labeling Review dated February 18, 2015, and CMC Consultation Review dated October 27, 2014, by Dr. Jane Sohn for complete details.

- **Other notable issues (resolved or outstanding)**

The pharmacology/toxicology review team has concluded that the application may be approved from a pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Primary clinical pharmacology reviewer: Sheetal Agarwal, PhD, RAC; Clinical pharmacology team leader: Satjit Brar, PharmD, PhD; Primary biopharmaceutics reviewer: Assadollah Noory, PhD; Acting biopharmaceutics supervisor: Paul Seo, PhD

No clinical pharmacology studies were conducted or required for this application. The Applicant requested a waiver of the requirement to provide evidence of in-vivo bioavailability for both routes of administration (IM, SC) of the proposed drug product. The biopharmaceutics team noted that 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 listed drug. Therefore, the biopharmaceutics team granted a biowaiver from conducting an in vivo bioequivalence study for the IM and SC routes.

See reviews by Dr. Agarwal dated February 26, 2015, and Dr. Assadollah Noory dated November 5, 2014, for complete details.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary reviewer: Peter Starke, MD

- **Efficacy review**

No clinical studies were submitted or required for this application. The recommended dosing is based on the published literature and established clinical practice. Support for efficacy is based on the Agency's previous findings of efficacy for epinephrine in the treatment of allergic reactions and anaphylaxis. Of note, clinical trials for safety and efficacy were also not performed for approval of EpiPen, which relied on literature and the extensive use of epinephrine for the treatment of anaphylaxis. Likewise, other approved epinephrine products for the treatment of anaphylaxis have also relied on the literature. Based on the literature, all major guidelines for the treatment of anaphylaxis recommend epinephrine as first-line therapy for the treatment of anaphylaxis².

- **Dose and dosing frequency**

The Applicant proposes weight-based dosing as follows:

One dose of 0.3 mg of epinephrine (USP, (b)(4) 0.3 mL) for patients who weigh 30 kg or more

² Lieberman P, Nicklas RA, et al, 2010. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 126(3):477-480 e471-442.

However, the proposed prefilled syringe device would deliver a volume of (b) (4)
epinephrine solution as discussed in Section 3. (b) (4)

Thus, from a clinical perspective, the proposed delivered dose is unacceptable for treatment of anaphylaxis in the unsupervised medical setting. To make changes to the delivered volume of the product, the device will need to be modified. The Applicant has agreed to modify the device and has provided specifications for the modified device. However, the Applicant has not provided any supporting data, including batch data or a validation report, for the revised device.

8. Safety

Support for safety is based primarily based on the Agency's previous findings of safety for epinephrine in the treatment of allergic reactions and anaphylaxis and review of the literature.

Based on the literature, common adverse reactions associated with epinephrine are pallor, tremor, anxiety, palpitations, dizziness, and headache. More serious adverse effects include arrhythmias, cerebral hemorrhage related to rapid elevations in blood pressure, angina, and myocardial infarction. Accidental injection into the extremities may cause local ischemia and pain. However, these potential adverse effects need to be assessed in the context of a potentially life-threatening condition. Dr. Starke has concluded that there is adequate evidence to support the safety of epinephrine for anaphylaxis and I concur. However, as noted in Section 7, (b) (4)

(b) (4) the Applicant's proposed delivered dose, (b) (4) does not have an appropriate risk/benefit for the treatment of anaphylaxis in the medically unsupervised setting.

9. Advisory Committee Meeting

Epinephrine is not a new molecular entity, and no new clinical issues were identified during the review. Therefore, an Advisory Committee meeting was not held for this application.

10. Pediatrics

This application does not contain a pediatric assessment as the proposed epinephrine prefilled syringe does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. The application was not discussed at the Pediatric Review Committee (PeRC) meeting.

Although the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) does not apply, the Agency has previously encouraged the Applicant to explore dosing in lower weight patients given an existing public health need (Type B pre-IND meeting on April 21, 2014).

11. Other Relevant Regulatory Issues

- **Financial disclosures**

No clinical trials were submitted as part of this NDA. As such, financial disclosure does not apply.

- **Office of Scientific Investigation (OSI) audits**

No clinical safety or efficacy trials were submitted in this application. Thus, clinical study site inspections were not requested or performed.

- **Other outstanding regulatory issues**

None

12. Labeling

- **Proprietary name**

The proposed trade name is “Symjepi,” which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable on February 27, 2015.

- **Physician labeling**

The Applicant submitted a label in Physician’s Labeling Rule (PLR) format that is similar to the approved labeling for other epinephrine autoinjector products approved for self or caregiver treatment of anaphylaxis. The primary differences for this product are in sections that are product-specific, including the instructions for use, which is appropriate.

As the recommended regulatory action is complete response, labeling discussions were not conducted with the Applicant.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

Not applicable.

- **Carton and immediate container labels (if problems are noted)**

Not applicable as the recommended regulatory action is complete response.

- **Patient labeling/Medication guide (if considered or required)**

Not applicable.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action for this application is complete response for the indication of “emergency treatment of allergic reactions (Type I), including anaphylaxis.” The proposed prefilled syringe device would deliver a volume of (b) (4)

epinephrine solution. (b) (4)

Thus, from a clinical perspective, the proposed dose is unacceptable for treatment of anaphylaxis in the unsupervised medical setting. To make changes to the delivered volume of the product, the device will need to be modified. The Applicant has agreed to modify the device and has provided specifications for the modified device. However, the Applicant has not provided any supporting data, including batch data or a validation report, for the revised device. Further, the drug product specifications must be revised. Thus, the recommended regulatory action is complete response.

- **Risk Benefit Assessment**

The risk/benefit of epinephrine for anaphylaxis is favorable. Epinephrine is the treatment of choice for anaphylaxis and has been demonstrated to be immediately life-saving, with over 100 years of continuous use. However, the therapeutic window is narrow and significant toxicities exist (arrhythmias, cerebral hemorrhage, cardiac ischemia, and myocardial infarction). (b) (4)

Thus, the Applicant’s proposed delivered dose, (b) (4) does not have an appropriate risk/benefit for the treatment of anaphylaxis in the medically unsupervised setting.

- **Recommendations for Postmarketing Risk Evaluation and Management Strategies**

Not applicable as the recommended regulatory action is complete response.

- **Recommendation for other Postmarketing Requirements and Commitments**

Not applicable as the recommended regulatory action is complete response.

- **Recommended comments to applicant**

Recommended comments to the Sponsor are as follows:

1. *The deliverable volume of the drug product is a critical quality attribute for this drug for its intended use and use environment. The drug/device combination product as submitted in the application is not capable of delivering the labeling claim amount of the drug. This will not ensure the identity, strength, quality, purity, and potency of the drug product per CFR 314.50(ii)(a).*

You need to redesign the prefilled syringe to deliver the target volume at labeling claim. In your future submission you need to provide the following:

- i) *Detailed device information with the original design and redesign comparison*
- ii) *Detailed validation report with the redesigned device performance data. It should include but not limited to; sample size, average deliverable volume, standard deviation, minimum and maximum volume delivered, etc.*
- iii) *Detailed validation batch (with the intended drug product solution) data with the redesigned device*

You need to propose an acceptance criterion for the “deliverable volume” with reasonable lower and upper limits that is comparable to the limits of other approved drug products in this class. Please note the proposed acceptance criterion for “mean deliverable volume” with limit in the footnote (as in your amendment dated Feb 6, 2015) is not appropriate or adequate.

2. *The volume determination as described in USP <1> is not specifically defined for which type of the volume. The (b) (4) is irrelevant regarding the analytical methods for the extractable volume. For this prefilled syringe to be used by the patients. You need to provide detailed analytical methods and adequate validation report for the extractable volume of the drug product.*

3. *Your proposed drug substance specification (Table 3.2.S.4.1-1) in the NDA is looser than that used by the drug substance supplier ((b) (4) referenced in DMF (b) (4)). Specifically,*

- i) *The proposed acceptance criterion for impurity (b) (4) is (b) (4) % in your NDA submission. The (b) (4) acceptance criterion for this impurity is (b) (4) %.*
- ii) *There is residual solvent (b) (4) limit of (b) (4) ppm in the (b) (4) specification. However, this limit is not in the drug substance specification proposed in the NDA.*

Revise your specification to match the specification of the drug substance supplier (b) (4). Accordingly you also need to provide an appropriate analytical method and adequate validation report for impurity (b) (4). Please note a limit test for any impurity is not acceptable. Alternately, provide justification to support your proposed specification (or lack of such specification). Please note merely following USP monograph is not sufficient justification for any impurity limit. ICH Q3A guideline also needs to be followed. Any potential residual solvent in the drug substance needs to be

*specifically listed and limit be set in the specification. Statement of [REDACTED] (b) (4)
[REDACTED] is not sufficient.*

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/s/

JANET W MAYNARD
03/06/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207-534
Priority or Standard	Standard
Submit Date(s)	May 23, 2014
Received Date(s)	May 28, 2014
PDUFA Goal Date	March 23, 2015
Division / Office	DPARP/OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	February 18, 2015
Established Name	Epinephrine injection, USP, 1mg/mL, 0.3 mg
(Proposed) Trade Name	Symjepi (sim-JEP-ee) – under review
Therapeutic Class	Catecholamine: alpha and beta adrenergic agonist
Applicant	Adamis Pharmaceuticals Corp.
Formulation(s)	Prefilled syringe (PFS) with solution for injection
Dosing Regimen	0.3 mL (0.3 mg) manually injected IM or SC
Proposed Indication(s)	Emergency [self or caregiver] treatment of severe allergic reactions (Type I) including anaphylaxis
Intended Population(s)	Weight \geq 30 kg (66 pounds)

MEDICAL OFFICER REVIEW			
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)			
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
May 23, 2014	May 28, 2014	SD-1, eCTD-0000	New NDA submission
June 18, 2014	June 18, 2014	SD-2	ISE and ISS
August 25, 2014	August 26, 2014	SD-3	Draft labeling
Oct 8, 2014	Oct 8, 2014	SD-4	Response to CMC requests in 74-day letter
<i>Nov 21, 2014</i>			<i>CMC IR</i>
			<i>Clinical/CMC IR</i>
Nov 28, 2014	Nov 28, 2014	SD-5	Response to CMC/Clinical IRs
Dec 12, 2014	Dec 12, 2014	SD-6	Request for proprietary name review
Jan 20, 2015	Jan 20, 2015	SD-7	Quality response to IR
Feb 6, 2015	Feb 6, 2015	SD-8	Quality response to IR
Feb 13, 2014	Feb 13, 2014	SD-9	Revised labeling with proposed proprietary name

RECOMMENDED REGULATORY ACTION	
NDA/SUPPLEMENTS:	<input type="checkbox"/> APPROVAL
	<input checked="" type="checkbox"/> COMPLETE RESPONSE
OTHER ACTION:	<input type="checkbox"/>

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend a Complete Response action for this application.

Adamis Pharmaceuticals has submitted this NDA for a pre-filled, single-dose syringe containing 0.3 mg of epinephrine (0.3 mL (b) (4) solution) for the emergency treatment of severe allergic reactions (Type I) including anaphylaxis in patients who weigh ≥ 30 kg. However, the proposed device would deliver a volume of (b) (4)

(b) (4) epinephrine solution. From a clinical perspective, this dose is unacceptable for treatment of anaphylaxis in the unsupervised medical setting. The risk/benefit of epinephrine does not justify use of this dose in the medically unsupervised setting for patients who weigh ≥ 30 kg. (b) (4)

To make changes to the delivered volume of the product, the device will need to be modified. Adamis has agreed to modify the device, and submitted specifications for the modified device on February 6, 2015. However, while they revised the acceptance criterion of “mean deliverable volume” to $0.30 \text{ mL} \pm (b) (4) \%$, they did not provide any supporting data, including batch data or a validation report, to demonstrate that the revised device can deliver the volume stated in the acceptance criteria (i.e., there is no evidence that they actually have produced and tested the revised device). Therefore, ONDQA recommends that the Agency take a Complete Response (CR) action in this cycle, and I concur.

1.2 Risk Benefit Assessment

This is a 505(b)(2) application submitted by Adamis Pharmaceuticals for a drug/device combination of Epinephrine Injection, USP (b) (4) 0.3 mg in a pre-filled, single-dose syringe. The proposed indication is for the emergency treatment of severe allergic reactions (Type I) including anaphylaxis. The product is intended for self or caregiver administration in the medically unsupervised, emergency setting in patients who weigh ≥ 30 kg.

The risk/benefit of epinephrine for the treatment of anaphylaxis is overwhelmingly in favor of its use for treatment of anaphylaxis. Anaphylaxis affects both the respiratory and the cardiovascular systems leading to bronchospasm, mucous membrane congestion, angioedema, and severe hypotension. While the use of epinephrine

precedes the era of controlled clinical trials, extensive experimental and clinical experience has demonstrated that epinephrine is a life-saving drug in this setting. Even for those patients who are at increased risk for adverse reactions with epinephrine use, there is no contraindication for the use of epinephrine in the treatment of anaphylaxis. Nor, in this setting, is there a contraindication for the sulfite found in this product, even in patients with sulfite allergies. All patients who have anaphylaxis should receive epinephrine as early as possible after the start of symptoms and by whichever route is most appropriate for that patient, along with other supportive medical treatments and observation, to ensure that life-threatening signs or symptoms are treated immediately and appropriately.

The application references the Agency's prior findings of efficacy and safety of EpiPen (NDA 19-430), which is listed in the Orange Book as a reference drug, for this same indication. The applicant has also provided a brief literature review and references to support the application. The literature review provided and the Agency's previous findings of safety and efficacy for a similar product support approval of this application, but only if the device is modified to provide a mean delivered dose of 0.3 mg (0.3 mL of (b) (4) epinephrine solution).

It is important to note that this product differs from the currently approved epinephrine auto-injector products (EpiPen, Twinject, Adrenaclick, and Auvi-Q) in that it is a prefilled syringe (PFS) intended for manual injection (i.e., it is not an auto-injector). However, like EpiPen, Twinject, Adrenaclick, and Auvi-Q, the proposed drug product is intended for use by the medically untrained patient or caregiver for the treatment of anaphylaxis in the medically unsupervised setting for treatment of life-threatening allergic reactions, including anaphylaxis. A different epinephrine product, Adrenalin, is approved for use by medical personnel for the treatment of anaphylaxis in the medically supervised setting.

As noted above, all currently licensed epinephrine products that are designed for self or caregiver administration are auto-injectors that, when prepared and pressed firmly against the thigh, automatically inject the dose into the patient. However, the packaging configuration of this product is a PFS for manual injection. The need for manual administration raises considerations regarding patients who have needle phobia or who have not adequately been taught how to administer a manual injection. Nevertheless, use of a manual pre-filled syringe for use in the emergency setting by the patient or caregiver is accepted in medical practice. Additionally, there are other emergency-use products that are intended for manual injection, such as sumatriptan (approved as vials), approved for emergency use by patients or caregivers in the medically unsupervised setting. Finally, some patients may prefer a PFS packaging configuration for various reasons, including a potential price differential between an auto-injector and a PFS. As a result, a pre-filled syringe packaging configuration is acceptable for this product, as it provides an additional option for patients and caregivers.

All of the currently licensed epinephrine auto-injector products contain a single dose of epinephrine (except for Twinject, which has two doses), and all are intended to be administered by either the intramuscular (IM) or the subcutaneous (SC) route. Patients/caregivers are instructed to use the product by injecting into the outer thigh at

the first sign of an allergic emergency. The instructions also call for repeat a dose if needed, but patients are instructed to seek emergency medical care immediately after the first dose because they may need additional medical care. For this product, Adamis has only proposed to market a single dose, whereas to deal with the issue of a second dose both EpiPen and Adrenaclick are marketed only as twin-packs, thereby providing a second dose for patients who may need one. Although they choose to market their products as twin-packs, because the other products are licensed for use as single doses, this is an acceptable, although not ideal, marketing configuration.

Because the marketed epinephrine auto-injectors are intended for immediate patient self (or caregiver) administration, these products contain fixed doses of epinephrine standardized for several weight ranges: 0.3 mg of epinephrine for patients who weigh 30 kg (66 lbs) or more, and 0.15 mg of epinephrine for patients who weigh 15-30 kg (33-66 lbs). No products are currently available for patients below 15 kg (33 lbs). Adamis has only proposed a 0.3 mg (0.3 mL) dose for patients \geq 30 kg (66 pounds), and no lower doses. Since the application will not trigger PREA, there is no regulatory requirement for the applicant to provide lower doses. Restriction to the 0.3 mg dose is therefore the applicant's prerogative, and it also limits use to older children, adolescents, and adults who may be taught how to administer a manual injection. Therefore, restriction of this marketing application to the one 0.3 mg dose is acceptable.

In summary, this 505(b)(2) application is for a Epinephrine Injection, USP (b) (4), 0.3 mg in a pre-filled, single-dose, manually-injected syringe, for the emergency treatment of severe allergic reactions (anaphylaxis) in patients who are at risk for or have a history of serious allergic reactions. The product is intended for self or caregiver administration in the medically unsupervised, emergency setting. Adamis has only proposed a single 0.3 mg dose configuration for manual injection in patients who weigh 30 kg (66 lbs) or more. For the reasons discussed above, this marketing configuration is not ideal but is acceptable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

1.5 Pediatric Issues

This application will not trigger PREA because the product does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

That stated, the applicant has only proposed a 0.3 mg dosage strength for patients 30 kg and above, and not a 0.15 mg dosage strength for patients 15 to 30 kg, as is available for other epinephrine products approved for this indication. Since the application will not trigger PREA, there is no regulatory requirement for the applicant to provide lower doses. Restriction to the 0.3 mg dose is therefore the applicant's prerogative, and it also limits use to older children, adolescents, and adults who may be taught how to administer a manual injection. Therefore, restriction of this marketing application to the one 0.3 mg dose is acceptable.

Of note, the Agency has recognized that a lower dosage strength of 0.1 mg for patients who weigh approximately 10-15 kg would be a public health benefit, as this is a weight range in which anaphylaxis does occur and there are currently no products available for home/caregiver use in this dosage strength.

2 Introduction and Regulatory Background

This is a 505(b)(2) application submitted by Adamis Pharmaceuticals for a drug/device combination of Epinephrine Injection, USP (b)(4), 0.3 mg in a pre-filled, single-dose, manually-injected syringe. The proposed indication is for the emergency treatment of severe allergic reactions (anaphylaxis). The product is intended for self or caregiver administration in the medically unsupervised, emergency setting.

The application references EpiPen (NDA 19-430), which is listed in the Orange Book as a reference drug. It is important to note that this product differs from the currently approved epinephrine auto-injector products (EpiPen, Twinject, Auvi-Q) in that it is a prefilled syringe intended for manual injection via the intramuscular (IM) / subcutaneous (SC) route into the lateral thigh area. Additionally, Adamis has only proposed a 0.3 mg (0.3 mL) dose for patients ≥ 30 kg (66 pounds), and no lower doses.

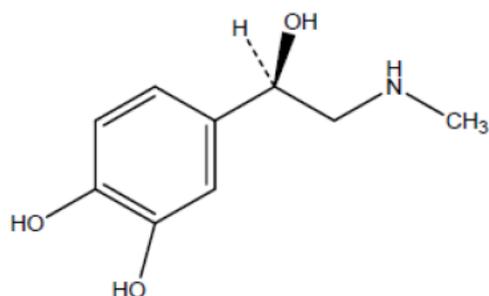
At the time of submission, the applicant did not propose a Proprietary (Trade) Name for the product. In December of 2014, the applicant proposed the name Symjepi (pronounced sim-JEP-ee), which is still under review at the time of completion of this review.

The submission is all electronic in eCTD format, and was received on May 23, 2014. The PDUFA date is March 23, 2015.

2.1 Product Information

The active ingredient in this drug product is epinephrine, a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. Epinephrine is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation. The

chemical formula of epinephrine is $C_9H_{13}NO_3$, and its chemical structure is shown below. The chemical structure consists of benzene ring and an ethylamine side chain.



As shown in the structural diagram above, epinephrine has two optical isomers (enantiomers): substitution of an hydroxyl group at the beta carbon atom on the ethylamine side chain yields *l*- and *d*- isomers [also described as L- or (-) and as D- or (+)]. Levorotatory rotation (*l*- form or *l*-epinephrine) confers at least 10-15 times higher systemic potency than the *d*-isomer (Patil 1975; Westfall 2011), with *l*-epinephrine being the natural form produced by the adrenal medulla. The drug substance is manufactured

(b) (4)

In the United States, the term epinephrine is the preferred name for this chemical, and the United States Approved Name (USAN) and International Nonproprietary Name (INN) is epinephrine. However, the British Approved Name (BAN) and European Pharmacopoeia (EP) term is adrenaline [with an e]. Pharmaceuticals that mimic the effects of epinephrine are termed 'adrenergics', and their receptors are called 'adrenergic receptors'. As a result, both epinephrine and adrenaline are terms used in the literature, although Adrenalin[®] [without an e] is the registered trade name for an approved epinephrine drug product in the United States (see Section 2.6 for details on the history of epinephrine).

The proposed drug product contains epinephrine injection, USP in a sterile solution at a concentration of 1 mg/mL (b) (4). The formulation includes epinephrine, USP, sodium metabisulfite, sodium chloride, HCl (b) (4) to pH 2.2-5, and water for injection. It is packaged as 0.8 mL of solution in a 1 mL prefilled glass syringe fitted with a 25 gauge 5/8 inch needle. The syringe plunger has a flange (b) (4)



Figure 1. Proposed Adamis Epinephrine for Injection, 0.3 mg

Adamis has only proposed to market a single dose of 0.3 mg of epinephrine for patients who weigh 30 kg (66 pounds) or more. The product is intended for use by the medically untrained patient or caregiver in the medically unsupervised setting for treatment of life-threatening allergic reactions, including anaphylaxis. A different epinephrine product, Adrenalin, is approved for use by medical personnel in the medically supervised setting. This product differs from the currently approved epinephrine products intended for self or caregiver use (EpiPen, Twinject, Adrenaclick, and Auvi-Q) in that they are all automatic injection devices (auto-injectors), whereas this product a prefilled syringe intended for manual administration.

2.2 Tables of Currently Available Treatments for Proposed Indications

Epinephrine is **the** primary treatment for anaphylaxis, with other treatments for this condition being adjunctive or supportive. Whereas there are a number of approved epinephrine-containing drug-device combination products available for the treatment of anaphylaxis, they differ from the proposed drug product in that they are disposable, prefilled automatic injection devices intended for immediate patient self (or caregiver) administration to treat life-threatening allergic reactions, including anaphylaxis, in people who are at risk for or have a history of serious allergic reactions. They contain one (EpiPen, Adrenaclick, and Auvi-Q) or two (Twinject) doses of epinephrine, depending upon the product. Although the term “epinephrine” is used in the description of these products, all of the products contain *l*-epinephrine as the active pharmaceutical ingredient (API) rather than a mixture of optical isomers.

Additionally, single-use (1 mL) and multiple-use (30 mL) vials of epinephrine (Adrenalin) are approved for use by medical personnel in the medically supervised setting. The approved epinephrine products for anaphylaxis are shown in Table 1.

All of the epinephrine products are currently in Physician Labeling Rule (PLR) format.

Table 1. Approved Epinephrine Products for Treatment of Anaphylaxis

Product	NDA	Packaging and Dose	Strength* and Dispensed Volume
Adrenalin [®]	204-200 204-640	Single use 1 mL vials Multiple-use 30 mL vials	1:1000 1:1000 Dosing is weight-based up to 0.5 mL (0.5 mg) per dose for treatment of anaphylaxis
EpiPen [®] EpiPen [®] Jr	19-430	Single dose of 0.3mg Single dose of 0.15 mg	(b) (4) 0.3 mL (b) (4) 0.3 mL
Twinject [®]	20-800	0.3 mg 0.15 mg 2 doses per injector	1:1000 0.3 mL 1:1000 0.15 mL <i>Note:</i> This product is no longer being marketed
Adrenaclick [™] and authorized generic	20-800	Single dose of 0.3mg Single dose of 0.15 mg	(b) (4) 0.3 mL (b) (4) 0.15 mL
Auvi-Q [™]	201-739	Single dose of 0.3mg Single dose of 0.15 mg	(b) (4) 0.3 mL (b) (4) 0.15 mL

*Strength of Epinephrine Injection, USP: 1:1000 = 1 mg/mL

2.3 Availability of Proposed Active Ingredient in the United States

2.3.1 Single-ingredient epinephrine products for injection

Epinephrine is a pre-1938 [and pre-1906] drug that has been marketed under the trade name Adrenalin[®] since the turn of the 20th Century. The first epinephrine drug product marketed, Adrenalin[®], was originally marketed by Parke-Davis. It was later sold to Parkedale Pharmaceuticals, Inc. (a wholly owned subsidiary of King Pharmaceuticals, Inc.) on February 27, 1998, and sold to JHP on July 14, 2007. These products were marketed as unapproved drug products until recently. NDA 204200 for Adrenalin 1 mg/mL (1:1000) in 1 mL single-use vials, and NDA 204640 for Adrenalin 1 mg/mL (1:1000) in 30 mL multiple-use vials, were approved on December 7, 2012 and December 18, 2013, respectively. Additionally, there are a number of unapproved single-ingredient epinephrine injection products listed in the NDC directory. Table 2 shows a listing of unapproved epinephrine injectable products that have National Drug Code (NDC) numbers listed in the NDC directory as of September 25, 2014. The Agency is aware that a number of manufacturers market unapproved epinephrine products without NDC numbers. However, products without an NDC number are not shown in the table below because it is difficult to track a product without an NDC number.

Products previously marketed in the United States for the treatment of anaphylaxis include: Epi EZ Pen [and Epi EZ Pen Jr] and Ana-Kit[®]. Meridian Medical Technologies,

the maker of EpiPen, marketed Epi EZ Pen and Epi EZ Pen Jr (single doses of 0.3 and 0.15 mg) for a short period of time in the mid to late 1990s (NDA 19-430). The product differed from EpiPen in that it was a manually-triggered, pen-like epinephrine injection device; otherwise it was similar to the EpiPen devices. Ana-Kit (epinephrine injection, USP (b) (4) manufactured by Hollister-Stier Laboratories) was a marketed unapproved product that contained multiple doses of epinephrine in an Ana-Guard® syringe, co-packaged with an oral antihistamine (chlorpheniramine), tourniquet, and alcohol swab. The product was discontinued in 2001 after the supplier of epinephrine, Wyeth Pharmaceuticals, stopped production (<http://www.wildmed.com/blog/discussion-on-epi-pen-prescription-increase/>, accessed 4/30/2012). In 2004, Hollister-Stier received FDA approval for a successor product, Twinject (NDA 20-400), and in 2006, Verus Pharmaceuticals bought the rights to Twinject [now owned by Amedra Pharmaceuticals] and Ana-Kit. However, Ana-Kit and/or Ana-Guard are still marketed in Europe by various companies, including Bayer Schering Pharma, Hollister Stier, and Milex Products (<http://www.telefonica.net/web2/insect/POSI.html#MM5>, accessed 4/30/2012).

Table 2. Unapproved Epinephrine Injectable Products with NDC Numbers

Labeler's Name	Strength	Listed Route of Administration	Marketing Date	NDC #
American Regent, Inc.	(b) (4)	INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	9/30/1990	0517-1071
		INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	3/1/1994	0517-1130
(b) (4)				
Cardinal Health	(b) (4)	ENDOTRACHEAL; INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	5/8/2013	55154-2381
		ENDOTRACHEAL; INTRACARDIAC; INTRAVENOUS	4/5/1985	55154-3186
			5/1/1985	(b) (4)
General Injectables and Vaccines, Inc.	(b) (4)	INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	7/1/2010	(b) (4)
		INTRAVENOUS	8/1/2010	(b) (4)
			8/1/2010	52584-004

Labeler's Name	Strength	Listed Route of Administration	Marketing Date	NDC #
	(b) (4)		Stated to be under NDA 20800	
		INTRAMUSCULAR; SUBCUTANEOUS	3/1/2010 Stated to be under NDA 20800	52584-241
Hospira, Inc.		ENDOTRACHEAL; INTRACARDIAC; INTRAVENOUS	5/1/1985 4/5/1985	0409-4901 0409-4921
		INTRAMUSCULAR; SUBCUTANEOUS	9/8/2005 and 8/12/2013	0409-7241
		INTRACARDIAC; INTRAVENOUS	12/1/1976	76329-3316
International Medication Systems, Limited		PARENTERAL	7/1/2000	76329-9061
		INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	5/3/2010	(b) (4)
McKesson Packaging Services Business Unit of McKesson Corporation		INTRACARDIAC; INTRAVENOUS	5/3/2010 Stated to be under NDA 20800	63739-456
		INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	3/1/1994	44827-301

Source: Table created from search of NDC Directory, downloaded 7/28/2014 from <http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm>.

2.3.2 Other epinephrine-containing products

NDA 205029 (Belcher Pharmaceuticals, LLC) was approved on July 29, 2014, for epinephrine injection to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

Over-the-counter (OTC) use of epinephrine and racemic epinephrine (racemic mixture of *l*- and *d*-epinephrine) for the treatment of asthma is approved under the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) monograph (21 CFR 341.16). The OTC monograph process was similar to the DESI process for Rx drugs with the exception that once monographed, a drug product may be marketed OTC without a new drug application as long as the manufacturer adheres to good manufacturing practices

(GMP). However, the CCABA monograph is specific in referring to the formulation as a 1% solution of epinephrine to be administered with a hand-held bulb syringe, a device which is no longer available. Racemic epinephrine products claiming to be marketed under the CCABA monograph include several nebulization solutions (2.25%, e.g., Asthmanephrin [Nephron, NDC 0487-2784], Vaponephrine, S2 [Nephron, NDC 0487-2784], Prime Asthma Relief [DrNaturalHealing, NDC 15343-104 and 15343-105), which are/were marketed for the treatment of symptoms of asthma, emphysema, and other breathing conditions such as bronchiolitis and croup.

Additionally, several manufacturers sold epinephrine bitartrate metered dose inhalers for the treatment of asthma (MediHaler-Epi [NDA 10-374, 3M]; Bronitin Mist and Primatene Mist [NDA 16-126, Wyeth Cons; ANDA 87907, Armstrong]; Bronkaid Mist, NDA 16-803, Sterling). However, all of the inhalers used chlorofluorocarbons (CFCs) as the solvent/propellant, and with the discontinuation of production of CFCs all of the CFC-containing products have been discontinued.

Multiple companies and generic manufacturers sell combinations of epinephrine with lidocaine, articaine, bupivacaine, and/or etidocaine as FDA-approved injectable anesthetic combinations to prolong local or regional anesthesia (RLDs for lidocaine with epinephrine: Xylocaine with Epinephrine, NDA 06-488, originally marketed November 19, 1948 by Astra, now manufactured by App Pharm; Xylocaine with Epinephrine, NDA 10-418, AstraZeneca, approved November 28, 1972). This use was approved under the DESI process. Lidocaine HCl and Epinephrine was/is also approved for topical use in iontophoresis systems (NDA 20-530, lomed; NDA 21-486, Empi) and as a patch to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions (NDA 21-504, Vyteris).

Finally, multiple companies sell homeopathic combinations of various ingredients with small amounts of epinephrine listed in the ingredient listing.

2.4 Important Safety Issues With Consideration to Related Drugs

Epinephrine is the primary treatment for anaphylaxis. Safety issues with epinephrine products intended for administration by the SC or IM routes are well known and characterized, and are reflected in the labeling of the auto-injector products.

The auto-injector products intended for self-administration in an anaphylactic emergency include the following safety information:

CONTRAINDICATIONS:

None

WARNINGS AND PRECAUTIONS:

Do not inject into the buttock, digits, hands, or feet. The presence of sulfite in the product should not deter use. Administer with caution in patients with heart disease. May aggravate angina pectoris or produce ventricular arrhythmias.

ADVERSE REACTIONS:

Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

DRUG INTERACTIONS:

- Cardiac glycosides or diuretics: observe for development of cardiac arrhythmias.
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine.
- Beta-adrenergic blocking drugs: antagonize cardiostimulating and bronchodilating effects of epinephrine.
- Alpha-adrenergic blocking drugs: antagonize vasoconstricting and hypertensive effects of epinephrine.
- Ergot alkaloids: may reverse the pressor effects of epinephrine.

USE IN SPECIFIC POPULATIONS:

- Elderly patients may be at greater risk of developing adverse reactions

Pregnancy Category C: Teratogenic in rats, mice and hamsters.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Type B meeting was held with the Agency in April 2014, to discuss the feasibility of a 505(b)(2) new drug application for this product, which was previously marketed as an unapproved drug product. Adamis states that they discontinued marketing of the product after receiving a warning letter from the FDA Office of Compliance in June 2010. Adamis does not state the reason for the warning letter. However, it is likely that the letter was sent to comply with the Compliance Policy Guide (CPG) for Marketed Unapproved Drugs

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>). The two main thrusts of the CPG are to ensure adequate compliance with good manufacturing procedures and adequate labeling to ensure safe use. At the meeting, the Agency requested that, as part of the application, Adamis submit a rationale for administration of epinephrine via a pre-filled syringe in the unsupervised medical setting.

Various forms of epinephrine have been marketed since 1901, predating the original Federal Food and Drugs Act of June 30, 1906, which prohibited the sale of adulterated or misbranded drugs, and the Federal Food, Drug, and Cosmetic Act (the FD&C Act) of 1938, which required that new drugs be approved for safety. In 1962, Congress amended the Act (Kefauver-Harris amendment) to require that a new drug must be shown to effective as well as safe in order to obtain approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug

products that had been approved by the Agency as safe between 1938 and 1962. The Agency's administrative implementation of the effectiveness evaluations was called the Drug Efficacy Study Implementation (DESI) process. To make the determinations, the Agency contracted with the National Academy of Science/National Research Council to review the available efficacy data and provide recommendations to the Agency, which were then reviewed by the Agency. The Agency's final determinations were then published in the Federal Register. Because it was a pre-1938 drug, the originally marketed epinephrine product, Adrenalin, was not subject to DESI review¹.

2.6 Other Relevant Background Information

This section contains some historical background on the isolation of the hormone, epinephrine, and the terminology of 'epinephrine' and 'adrenaline,' with side notes about various related topics of interest.

Depending upon the author, the discovery of epinephrine may be attributed to one of several individuals who were working in the field of endocrine physiology in the late 1800s. William Bates reported the discovery of a substance produced by the adrenal gland in the New York Medical Journal in May 1886. In 1894, George Oliver found that the adrenal glands contained a substance with dramatic pharmacological effects. (Oliver and Schafer 1895) In 1895, Polish physiologist Napoleon Cybulski found that adrenal extracts contain biologically active substances that elevate blood pressure. (Pawlik, Konturek et al. 2006)

John Jacob Abel, the first Professor of Pharmacology at Johns Hopkins, coined the term 'epinephrin' in 1897 when he prepared crude extracts of the adrenal glands. (Abel and Crawford 1897) However, his extracts did not behave physiologically like epinephrine (Aronson 2000) and were later found to be the benzoylated derivative. (Davenport 1982) By Abel's calculations, the substance he isolated had the chemical formula of $C_{17}H_{15}NO_4$. At around the same time Otto von Furth in Strasbourg prepared a small amount of an isolate (0.4 g) from the adrenal glands of pigs, which had the chemical formula of $C_5H_9NO_2$ or $C_5H_7NO_2$. He called his isolate 'suprarenin'. Neither of these, however, had the chemical formula of epinephrine ($C_9H_{13}NO_3$) and neither produced the same pharmacologic effect as the crude extracts themselves. (Jowett 1904; Dakin 1905; Davenport 1982; Yamashima 2003) Of course, it took almost a decade before it was discovered that the adrenal medulla produces a combination of epinephrine and norepinephrine so the pharmacologic effects of the crude extracts would never match that of epinephrine alone, and another decade before the concept of neurotransmitters was more fully understood. And it was not until the mid-20th century and beyond that alpha and beta sympathetic receptors were described, allowing a more complete

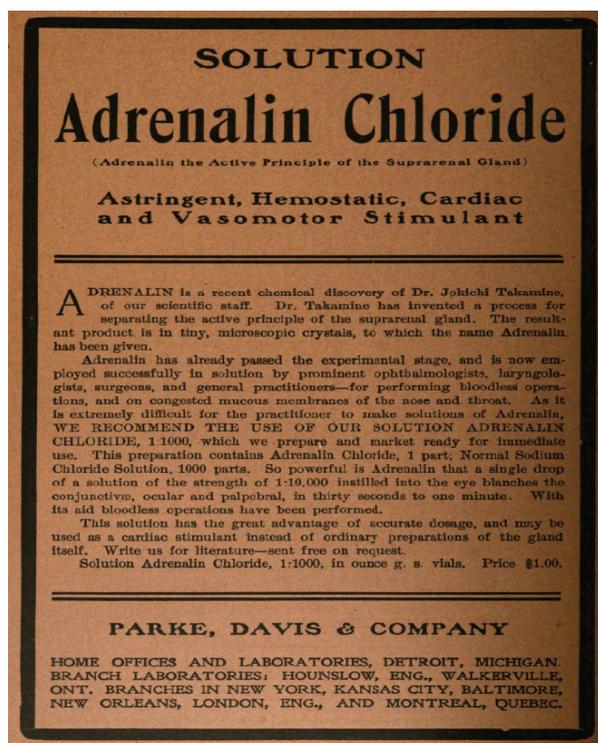
¹ Note: Although Adrenalin predates the DESI authority, a post-1938 drug, Sus-Phrine Suspension, which was an aqueous suspension of epinephrine manufactured by Cooper Laboratories, Wayne, N.J (NDA 7-942), was found under DESI 366 to be 'effective' for bronchial asthma, on the basis of clinical studies that provided substantial evidence of effectiveness. [42FR38647, July 29, 1977]

understanding of how these hormonal neurotransmitters actually exert their effects. (Pearce 2009)

In the summer of 1900, Keizo Uenaka, working in the laboratory of the Japanese chemist Jokichi Takamine in New York, developed the methodology to prepare a purified extract of the “active principle” from the adrenal glands of sheep and oxen. (Takamine 1901; Takamine 1901; Yamashima 2003) As it turns out, Takamine had visited Abel’s laboratory and observed Abel’s process, but whether he had visited Abel’s laboratory prior to his lab completing the isolation steps is uncertain and the subject of some debate. Takamine called his isolate, a diluted drop of which had the physiological property of blanching the white of the eye, ‘adrenalin’. T.B. Aldrich, working in the Parke, Davis & Co laboratory, calculated the chemical formula of Takamine’s extract to be $C_9H_{13}NO_3$, which was later confirmed to be the actual formula for epinephrine. Aldrich himself had already isolated a small amount of an extract from the adrenal gland, but never completed his work because Takamine presented his findings at a professional meeting in January of 1901. (Jowett 1904; Davenport 1982)

Dr. Takamine already had a previous business relationship with Parke, Davis & Co to market Taka-Diastase, a form of amylase derived from *Aspergillus oryzae* and used in the distillation process and as a digestive aid, and it was Parke Davis that funded his independent laboratory in New York. Takamine had also studied patent law in Washington, DC. (Yamashima 2003; Bennett and Yamamoto 2004) Takamine applied for a patent on November 5, 1900, trademarked the name Adrenalin® in the United States in 1901², and shortly thereafter Parke, Davis & Co began marketing of the product under the trade name Adrenalin, after which ‘epinephrine’ gradually became the generic name used in the United States, although the term ‘adrenaline’ continued to be used in Britain and elsewhere. (Bennett and Yamamoto 2004)

² Davenport (1982) reports that Takamine received a United States Trade Mark (86,269) on April 16, 1901. However, my search revealed that Adrenalin has active U.S. Trademark 53,934, dating from June 12, 1906. <http://www.uspto.gov/trademarks/index.jsp>, Searched May 7, 2012.



Of interest, it took three years for Dr. Takamine to receive his patents³. Although he submitted the patent application in 1900, the application was repeatedly denied by a senior patent examiner between 1900 and 1903, because the examiner believed that this product was merely an isolated hormonal product of nature, and therefore was unpatentable. This view was based on principles articulated in an 1889 case in which a patent on a pine-needle core used for making textiles was denied because the core was an isolated product of nature (Ex parte: Latimer). Takamine succeeded in obtaining patents by accepting the Latimer precedent but arguing that his product was different and not just a purified product of nature, because it was now “a stable, efficient, pure, concentrated, and reliable product, uniform and permanent in its action and free from injurious and decomposing ingredients.” (Takamine 1903; Harkness 2011)

The molecule was synthesized independently in two laboratories in 1904, by Friedrich Stolz and by Henry Drysdale Dakin. (Stolz 1904; Dakin 1905; Bennett 1999) Takamine developed several processes for the isolation of epinephrine, which he also patented.⁵ Which of these was used by Parke-Davis for the production of Adrenalin is unclear. Parke-Davis eventually changed the manufacturing process from one of isolation to chemical synthesis, but the exact date when this change took place is unknown.

3 The application (35,546) was divided (35,546, 37,729, 37,730, 42,550, 155,747, and 156,746) and re-filed on seven occasions. Dr Takamine eventually received at least six United States Patents, including four process patents (730,175; 730,196; 730,198; 753,198) and a product patent for the isolate (730,176) issued on June 2, 1903, and a second product patent for the solution (753,177) issued on February 23, 1904. He also applied for an English Patent (1467), which he received on June 22, 1901. (Davenport 1982; Harkness 2011; Opinion of Judge Learned Hand 1911)

Takamine's patents were the subject of a famous lawsuit that is considered crucial to modern patent law and now serves as the basis of most biotechnology patents. By 1904, multiple companies had begun to produce products similar to Adrenalin. In 1911, Parke, Davis brought a lawsuit against the most successful of these, H.K. Mulford, on the grounds that their product, 'Adrin' infringed in the patent for Adrenalin. After a protracted court battle, Judge Learned Hand ruled in favor of Parke-Davis and Mulford was ordered to cease infringing on the patent. By ruling in favor of Parke-Davis, Judge Hand cleared the path for subsequent biotechnology patents, including patents on genes. (Bennett and Yamomoto 2004; Harkness 2011) Although his opinion made no mention of the Pure Food and Drug Act of 1906⁴, which provided the first legal definition of a drug⁵, it was nevertheless the first instance in which a legal distinction was made between a natural product and a drug product:

“...even if it were an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it available for any use by removing it from the other gland tissue with which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.” (Opinion of Judge Learned Hand 1911)

As a side note, it was Takamine who funded several gifts of cherry trees from the Mayor of Tokyo to the City of Washington. The trees are planted at the tidal basin in downtown Washington, DC. (Bennett and Yamomoto 2004)

In Great Britain, where Adrenalin was not marketed, the term 'adrenaline' was adopted as the generic name after much debate, primarily because Henry Dale, a pharmacologist working at the Wellcome Physiological Research Laboratories, insisted upon using that term in his publications. [In part, Dale insisted on using the term adrenaline because editors insisted that he do so in order to publish his articles.] Other authors used yet additional names; however, these two names stuck. (Aronson 2000) The term epinephrine (derived from the Greek) became the preferred name in the United States, the United States Approved Name (USAN), and International Nonproprietary Name (INN). However, adrenaline [with an e] (derived from the Latin) became the British Approved Name (BAN) and European Pharmacopoeia (EP) term.

Although descriptions of anaphylaxis may be found dating to the early Greek and Chinese medical literature, an understanding of the phenomenon roughly paralleled the isolation of epinephrine, early work on neurohumoral transmission and on immunizations, pharmacologic evaluations of the effect of epinephrine in animals, and the testing of epinephrine for the treatment of various allergic conditions. Nobel prize

4 Judge Hand's opinion would not have referred to the Act because this was a patent dispute, whereas the Act was concerned with ensuring that foods and drugs were not adulterated, misbranded, or poisonous.

5 Section 6 of the Act states “That the term “drug,” as used in this Act, shall include all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances *intended to be used for the cure, mitigation, or prevention of disease of either man or other animals.*” [my emphasis added]

winner Charles Richet coined the term ‘anaphylaxis’ in 1902 in contra-distinction to the term ‘prophylaxis’, after trying to immunize dogs with a toxin purified from the tentacles of sea anemone and discovering an opposite effect, i.e., that far smaller doses would cause intense repeated reactions in dogs that had survived the first dose. (Editorial 1921; Ring 2004) Use of epinephrine for asthma is documented as early as 1904, with use of epinephrine for anaphylaxis as early as 1906. (Kaplin and Bullowe 1904; Doig 1905; 1906)

Several historical notes are relevant. First, the date that animal extraction of epinephrine was terminated in favor of chemical synthesis is unknown. Second, the dosage of epinephrine [/-epinephrine] for treatment of various conditions, including anaphylaxis, was established by clinical practice experience, but has never been evaluated in clinical trials. At this point, it would be impossible to do so.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Not applicable (NA). There were no clinical trials or studies conducted to support this application.

3.2 Compliance with Good Clinical Practices

NA. There were no clinical trials or studies conducted to support this application.

3.3 Financial Disclosures

NA. There were no clinical trials or studies conducted to support this application. As a result, there were no disclosures to report. Please see Appendix Section 9.4 of this review for my Clinical Investigator Financial Disclosure memo.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug substance [API] is manufactured (b) (4)
(DMF# (b) (4)), and the drug product is manufactured (b) (4)

The proposed drug product is a sterile, prefilled syringe a single 0.3 mg (0.3 mL) dose of epinephrine solution, USP, 1 mg/mL (b) (4). The formulation contains Epinephrine,

(b) (4) However, a less potent product is of particular concern for the anaphylaxis indication because administration of a dose that is perhaps 60% as potent systemically as expected could result in serious adverse outcomes, such as intubation and death, even in a closely monitored setting. Because the course of anaphylaxis is variable from patient to patient and patients may deteriorate rapidly, the medical practitioner would have no way of determining if the patient's clinical course and rapid deterioration was due to lack of expected potency of the product or due to worsening disease.

Adamis requested 18-months expiration dating for the drug product when stored at the recommended label storage conditions of 20° to 25° C (68° to 77° F). To support the proposed expiry dating, Adamis submitted stability data from 18 months storage under longer term (25° C / 60% RH) and 6 months of storage under accelerated conditions (40° C / 75% RH) in the container closure system proposed for marketing. As of completion of this review, a decision regarding the expiry dating of the product has not been made.

4.1.2 Proposed Delivered Volume

With the submission, Adamis proposed that the product would deliver a volume of (b) (4) epinephrine solution. The Agency sent an IR on November 21, 2014, and a teleconference was held on December 15, 2014, to discuss this issue. Adamis stated that the delivered volume of the product was (b) (4). Further, they contended that this would be acceptable, (b) (4). However, the Agency disagreed (b) (4). The Agency stated that (b) (4). Therefore, the acceptance specifications should include a specification for a dose delivery volume of 0.3 mL ± (b) (4) %.

To make changes to the delivered volume of the product, the device will need to be modified. Adamis has agreed to modify the device, and submitted specifications for the modified device on February 6, 2015. However, while they revised the acceptance criterion of "mean deliverable volume" to 0.30 mL ± (b) (4) %, they did not provide any supporting data, including batch data or a validation report, to demonstrate that the revised device can deliver the volume stated in the acceptance criteria (i.e., there is no evidence that they actually have produced and tested the revised device). Therefore, ONDQA recommends that the Agency take a Complete Response (CR) action in this cycle, and I concur.

4.2 Clinical Microbiology

There were no microbiological issues noted in this application, and the recommendation from Clinical Microbiology is approval.

4.3 Preclinical Pharmacology/Toxicology

To support the nonclinical pharmacology and toxicology, Adamis conducted a literature review.

4.4 Clinical Pharmacology

4.4.1 Requirement for *in vivo* bioequivalence

No clinical pharmacology studies were conducted for this application. Adamis has requested a waiver of *in vivo* bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is an injection solution and is proportionally similar in its active and inactive ingredients as the referenced drug (i.e., EpiPen). This is acceptable clinically, and Biopharmacology is recommending to waive this requirement.

4.4.2 Pharmacology of Epinephrine

Epinephrine belongs to a family of endogenous compounds called catecholamines, which include epinephrine, norepinephrine, and dopamine. The biosynthetic pathway for epinephrine is from the precursor tyrosine, through DOPA, dopamine, and norepinephrine, as shown in Figure 2.

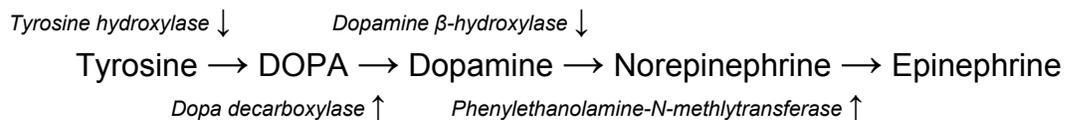


Figure 2. Biosynthetic Pathway for Epinephrine

As noted in Section 4.1, epinephrine has two optical isomers (enantiomers), the naturally occurring form being the *l*-form (*l*-epinephrine). When measured by its systemic effects (BP, etc), *l*-epinephrine has approximately 10-15 times more systemic activity than the *d*-form, *d*-epinephrine. (Patil 1975; Westfall 2011) This is important because *d*-epinephrine is generally found in epinephrine drug products as a degradant that increases over the shelf life, and therefore lowers the potency of a product. Please see the discussion under Section 4.1 for further details.

Epinephrine (i.e., *l*-epinephrine) is secreted by the adrenal medulla primarily in response to physical or mental stress. The adrenal medulla also makes secretes the precursor to

epinephrine, norepinephrine, although in far smaller quantities than epinephrine (estimates are about 4-20%).

The pharmacologic and physiologic effects of epinephrine are well characterized, including stimulation of the sympathetic nervous system to increase heart rate and the force of heart contractions, increase blood pressure, and increase the breakdown of glycogen into glucose resulting in increased blood glucose levels. In short, epinephrine prepares the body for action in perceived emergency situations, boosting the supply of oxygen and energy, while at the same time suppressing some non-vital bodily processes. Other effects that make it suitable for treatment of anaphylaxis are further discussed below.

Sympathomimetics are classified by their interaction, including their specificity, with the various receptor types. Epinephrine is a non-selective adrenergic agonist that interacts with α_1 , α_2 , β_1 , β_2 , [and perhaps β_3] receptors. Its effects on target organs are, therefore, complex, as shown in Table 3. For additional and more detailed explanations than need be presented herein, the reader is referred to basic texts, such as Goodman & Gilman's *The Pharmacological Basis of Therapeutics, Basic & Clinical Pharmacology*, or Greenspan's *Basic & Clinical Endocrinology*. (Westfall 2011; Biaggioni 2012; Fitzgerald 2011)

Epinephrine only has a brief duration of action because it is rapidly removed from the circulation and metabolized. Organic cation transporters, which are expressed in many tissues, including the liver, rapidly remove epinephrine from the circulation where it is oxidized by monoamine oxidase (MAO) and then methylated by catechol-*O*-methyl transferase (COMT), and eventually converted to vanillyl mandelic acid (VMA), which is excreted by the kidneys. In the adrenal medulla and in extraneuronal sites, epinephrine may be acted on first by COMT and then by MAO to VMA. MAO, which is located on the outer surface of mitochondria; it is widely distributed, although it is particularly abundant in adrenergic nerve endings. COMT is also widely distributed, and is found in the liver, kidneys, and smooth muscle. As a result of these processes, epinephrine exhibits high first-pass metabolism, especially when administered by the oral route. (AHFS 2011; Fitzgerald 2011; Westfall 2011)

The second of the two stress hormones released by the adrenal medulla is norepinephrine, which was discovered by Swedish Nobel-prize winning physiologist and pharmacologist Ulf von Euler⁶ in the mid-1940s. Norepinephrine differs from

6 Ulf von Euler (1905-1983) was born in Stockholm, the son of Dr. Hans von Euler-Chelpin, a Nobel Prize winner (1929) and Professor of Chemistry, and Dr. Astrid Cleve, a Professor of Botany and Geology. His maternal grandfather, Per Teodor Cleve, was a Professor of Chemistry at the Uppsala University and the discoverer of the chemical elements thulium and holmium. von Euler studied medicine at the Karolinska Institute, and worked in Sir Henry Dale's laboratory as a postdoctoral student, where he co-discovered substance P with John H. Gaddum in 1931. After returning to Stockholm, von Euler discovered four other important endogenous substances, prostaglandin, vesiglandin (1935), piperidine (1942), and norepinephrine (1946). From 1946 on, von Euler devoted most of his research work to the distribution and fate of norepinephrine, and made the key discovery that norepinephrine was produced and stored in intracellular vesicles at synaptic terminals. In 1970, he was awarded the Nobel Prize for his work jointly with Sir Bernard Katz and Julius Axelrod.

epinephrine in that norepinephrine has a hydrogen atom attached to its nitrogen, whereas epinephrine has a methyl group. Norepinephrine is also a non-selective adrenergic agonist. However, it interacts with α_1 , α_2 , and β_1 receptors, and not with β_2 receptors. (Westfall and Westfall 2011), and its actions are both as a hormone and as a neurotransmitter. As a hormone (and, when injected into the body), it acts to increase blood pressure by increasing peripheral vascular tone (α -adrenergic) and as an inotropic stimulator of the heart and dilator of coronary arteries (β -adrenergic). However, ~80% of norepinephrine release is via the sympathetic nervous system rather than via the adrenal medulla, whereas the reverse is true for epinephrine.

Norepinephrine release by sympathetic nerves in the heart acts to increase the heart rate and dilate the coronary arteries, and in the brain acts to stimulate the nucleus in the brainstem called the locus cereleus to trigger the sympathetic pathways [in the brain] that extend into the cerebral cortex, limbic system, and the spinal cord. Activation of this pathway increases attention and prepares the body for the fight-or-flight stress reaction. Norepinephrine also acts as a neurotransmitter within the central nervous system, acting on both alpha and beta adrenoreceptors to relay, amplify, and modulate the electrical signals in the brain. As such, it is implicated in a number of conditions including attention deficit / hyperactivity disorder, depression, and schizophrenia.

Whereas both epinephrine and norepinephrine have similar α and β_1 effects, norepinephrine differs from epinephrine in that it exhibits little effect on β_2 receptors, resulting predominantly in α receptor-mediated (peripheral vasoconstriction) and cardiac effects. The added β_2 effects of epinephrine, which include relaxation of bronchial smooth muscles resulting in an increase in bronchial airflow, dilation of blood vessels in skeletal muscles and the liver, release of glucose into the circulation, and inhibition of release of mediators from stimulated eosinophils, mast cells, and basophils (Winslow and Austen 1982), explain why epinephrine is ideally suited for the treatment of anaphylaxis, whereas the lack of β_2 receptor stimulation makes norepinephrine a good drug to support blood pressure in shock but less than ideal for the treatment of anaphylaxis.⁷

Table 3. Main pharmacologic effects of epinephrine

Receptor	Pharmacologic effect
α_1	Increased vasoconstriction and vascular resistance Increased blood pressure Decreased mucosal edema in the airways
α_2	Inhibition of insulin secretion

Abstracted from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1970/euler-bio.html and http://en.wikipedia.org/wiki/Ulf_von_Euler, April 20, 2012.

⁷ Because of its intravascular effects, the bitartrate salt of norepinephrine is approved (Levophed, NDA 7513, Hospira, approved July 13, 1950; and generics) for control of blood pressure in certain acute hypotensive states (e.g., pheochromocytectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions), and as an adjunct in the treatment of cardiac arrest and profound hypotension.

β_1	Increased myocardial contractility force (inotropic) Increased heart rate (chronotropic) Coronary vasodilation
β_2	Decreased mast cell mediator release Bronchial smooth muscle relaxation, increased bronchodilation Increased skeletal muscle vasodilation ¹ Increased glycogenolysis and release of glucose from liver
1 Skeletal muscles contain both α and β_2 receptors. Skeletal muscle β_2 receptors are more sensitive to epinephrine stimulation than α receptors, resulting in mixed responses and only small changes in blood pressure (BP) with lower administered doses, but significant increases in BP with higher doses.	

Sources: Kemp 2008; Simons 2011; Westfall 2011

5 Sources of Clinical Data

Adamis has not performed any clinical trials to support the application. Instead, Adamis submitted relevant literature references (in Module 5) and overview documents (in Module 2). This is in conformance with discussion held at a pre-NDA meeting on April 21, 2014, at which time the Agency expressed that submission of relevant literature reviews would be acceptable, along with a rationale for use of a prefilled, manually-administered syringe for use by patients and caregivers in the unsupervised emergency medical setting.

5.1 Tables of Studies/Clinical Trials

None

5.2 Review Strategy

The review strategy was to review 1) the submitted literature references, 2) the Agency's previous findings of efficacy and safety of epinephrine products.

5.3 Discussion of Individual Studies/Clinical Trials

NA

6 Review of Efficacy

Efficacy Summary

Anaphylaxis is “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.” (Sampson 2006) Although

no clinical trials have been performed, the efficacy and safety of epinephrine use is supported by a vast literature published over a span of over 110 years of clinical use, and such use is supported by the pharmacology of the drug and is accepted by all medical authorities.

This review finds support for the proposed dosing schema. Most patients respond to a dose of 0.01 mg/kg (b) (4) with the maximum dose being 0.5 mg for adults and 0.3 mg for children. The IM route is the preferred route in the medically supervised setting. Repeated dosing is based on continued [or recurrent, as in the case of biphasic reactions] clinical signs and symptoms, with repeated doses administered every 5-15 minutes as needed. Some patients do not respond to IM or SC dosing, and require additional treatment, including IV dosing and other care such as rapid IV fluid bolus.

(b) (4)

6.1 Indication: Treatment of Anaphylaxis

6.1.1 Introduction and Discussion

Anaphylaxis is “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.” (Sampson 2006) Although there is no universal agreement on the definition or the criteria for diagnosis, significant strides have been made in the last decade in this respect, with multiple publications from panels of scientific experts that help to standardize the criteria for diagnosis as well as treatment. (Sampson 2006; Lieberman 2010; Simons WAO 2011) Anaphylaxis has thereby been defined via one of three clinical scenarios, [often referred to as the Sampson criteria] as shown in Table 4.

Previously, the term “anaphylactoid reaction” was used for episodes that were clinically similar to anaphylaxis, but were not IgE-mediated. However, the World Allergy Organization (WAO) has suggested that this term be eliminated, and that all episodes clinically similar to IgE-mediated reactions be called anaphylaxis. Anaphylaxis may then be divided into immunologic and non-immunologic reactions. Likewise, immunologic reactions may be divided into those mediated by IgE mast cell/basophil mediator release and those occurring through other immunologic mechanisms (e.g., certain transfusion reactions). (Johansson WAO 2004) This is a reasonable approach from a clinical perspective, since the available evidence suggests that treatment is the same regardless of etiology.

During an anaphylactic reaction, vasoactive mediators are released from tissue mast cells and circulating basophils, including histamine, eosinophilic chemotactic factor of anaphylaxis (ECF-A), slow-reacting substance of anaphylaxis (SRS-A), platelet activating factor (PAF), kinins, and prostaglandins. Mediator release is independent of

the trigger, i.e., it is not dependent upon whether the trigger is IgE mediated (so-called ‘anaphylactic reaction’) or directly mediated (so-called ‘anaphylactoid reaction’); therefore anaphylaxis includes both types of reactions. Histamine, one of the mediators of the initial or acute manifestations, causes decreased systemic vascular resistance through effects on vascular smooth muscle, increased vascular permeability, and coronary vasoconstriction. These effects are mediated by both H₁ and H₂ receptors, although evidence suggests that H₁ and H₂ antihistamines are not effective in treating anaphylaxis once these mediators have been released.

Table 4. Clinical Criteria for Diagnosing Anaphylaxis

<p>Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:</p> <ol style="list-style-type: none"> 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING <ol style="list-style-type: none"> a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): <ol style="list-style-type: none"> a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): <ol style="list-style-type: none"> a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline <p>PEF, Peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 [2 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.</p>

Source: Sampson 2006, Table 1.

From a regulatory viewpoint, supports for accepting the use of epinephrine for the indication of anaphylaxis comes from the Agency’s previous findings of efficacy and safety of various epinephrine products for the same indication, and from the literature.

The Agency has made a number of prior regulatory decisions with regard to efficacy and safety of epinephrine for this indication, including several auto-injectable forms of epinephrine such as EpiPen, Twinject/Adrenaclick, and Auvi-Q, which are approved for emergency self-administration for the [initial] treatment of anaphylaxis, and epinephrine

vials (Adrenalin, NDA 204200 1 mL vials, and NDA 204640 30 mL vials) , which are approved for treatment of anaphylaxis (primarily by caregivers in the medical setting). By referencing EpiPen, the application gains support from the Agency's prior regulatory decision with regard to efficacy and safety of epinephrine for this indication. However, it should be noted that the approval of EpiPen in December 1987, was itself based entirely on literature support and no clinical trials, and the same is true for all subsequent NDA applications for epinephrine products that have been approved for an anaphylaxis indication.

The basis for approval of EpiPen was briefly summarized by Richard Nicklas, MD⁸, the Medical Officer who reviewed the original EpiPen application, after which he cited all of the references that served to support the indication [Medical Officer Review of NDA 19-430, dated February 18, 1985]:

“The onset of anaphylaxis is usually sudden and unexpected. Reactions are characterized by rapid progression with involvement of the cutaneous, respiratory, and/or circulatory systems. The most common manifestations of anaphylaxis are urticaria, flushing, or angioedema. Major life-threatening manifestations are those involving the circulatory and respiratory systems. Reactions occurring immediately tend to be more severe. Control of mild symptoms can prevent more severe reactions (Patterson and Valentine, 1982). The clinical course is extremely variable and can be fatal.

Epinephrine is the drug of choice in the initial treatment of anaphylaxis. The pharmacologic actions of epinephrine inhibit further release of mediators and reverse end-organ responses. Its use is indicated in all major or severe reactions and acutely in apparent minor reactions to abort a potential severe reaction (Fath and Cerra, 1984).

Due to the rapid clinical course and potentially life-threatening nature of anaphylaxis, prompt therapy is essential. Because prevention by avoidance is not always possible, emergency self-treatment is widely advocated. In fact, increasing the availability of emergency treatment for insect sting allergy was the subject of a NIH Consensus Development Conference in 1978.

The EpiPen Auto-Injector is designed for easy use by the lay person. It is a reliable means for injecting epinephrine in a predetermined therapeutic dose, quickly, safely, and conveniently. The EpiPen Auto-Injector is especially useful in emergency circumstances where rapid administration is critical. The simplicity of use of the auto-injector allows wider availability of earlier treatment, an important therapeutic objective in that the incidence of severe and fatal reactions may be reduced.”

Of note, this product differs from EpiPen and the other auto-injector epinephrine products is that this product is a manually-injectable prefilled syringe that will only be

⁸ Note: Dr. Nicklas is currently a Clinical Professor of Medicine at The George Washington University School of Medicine. He has served on multiple expert panels, including those for anaphylaxis. As such, he is listed a co-author of some of the expert opinion presented in the applicant's references.

available in a 0.3 mg dose for patients 30 kg and over, whereas all of the auto-injector epinephrine products are also available in a 0.15 mg dose for patients 15-30 kg. Therefore all weight and age groups are not included in the application for this product. Further, ease of use becomes an issue for a manually-injectable product intended for self or caregiver use. Therefore, some of Dr. Nicklas' statements that are specific to the auto-injector aspect of EpiPen do not necessarily apply to this product, whereas his statements regarding epinephrine and the anaphylaxis indication do apply.

Historically, epinephrine [and specifically Adrenalin®] predates the DESI process (see Section 2.1), which mandated an examination of efficacy for those drugs marketed between 1938 and 1962 that had only been required to be safe in order to receive marketing approval. However, the DESI process indirectly supports use of epinephrine for the treatment of anaphylaxis because a number of first generation antihistamines were examined and found by the DESI panels, and subsequently by the Agency, to be "effective" as adjunctive treatments to epinephrine for the treatment of anaphylaxis [DESI 6290, 42 FR 44275, 1977], thereby *de facto* implying that epinephrine is effective for this indication. Additionally, cortisone products were found to be "probably effective" for anaphylaxis, and "effective" for treatment of acute noninfectious laryngeal edema with a notation that epinephrine is the drug of first choice [DESI 7110, 37 FR 3775, 1972], again with the same implication.

Use of epinephrine for the treatment of anaphylaxis makes sense from a pharmacological and physiological perspective. Historically, the use of epinephrine for anaphylaxis is supported by pharmacologic and physiologic experiments in multiple animal models dating to the early to mid 20th century, thereby providing a substantial and reasoned body of evidence to support the pharmacologic basis for carrying this treatment into humans. Additional knowledge of specific α and β receptor subtypes and functions, which were not fully worked out until into the 1970s and 1980s, further supports this use. The efficacy of epinephrine for anaphylaxis is based on its mixed α and β adrenergic receptor effects, including α_1 , α_2 , β_1 , and β_2 effects. Alpha₁-receptor activation reduces mucosal edema and membrane leakage and increases vasoconstriction and vascular resistance, resulting in increased blood pressure to treat hypotension. Beta₁-receptor activation stimulates the myocardium to increase contraction force and heart rate, resulting in increased cardiac output. Beta₂-receptor activation produces bronchodilation, decreases mediator release, and relaxes coronary blood vessels. And mixed α and β effects stimulate glycogenolysis and redirect blood flow to vital end-organs. This combination is ideal from a pharmacologic and physiologic perspective, as it prevents and treats all of the signs and symptoms of anaphylaxis, including upper airway edema, urticaria, bronchospasm, hypotension, and shock. (Simons 2010; Westfall 2011; Simons WAO 2011)

Since its introduction over 110 years ago, there has been extensive anecdotal clinical experience with the use of epinephrine at the doses proposed and used for treatment of anaphylaxis. This experience comes from use to treat anaphylaxis, asthma, and shock, the doses being similar for all three indications except that the doses used during cardio-respiratory arrest (codes) can extend to much higher levels. Although no prospective, controlled clinical trials have been performed to substantiate the use of

epinephrine for treatment of anaphylaxis (Sheikh 2011), one prospective, uncontrolled trial (Brown 2004) does provide significant support and is further discussed below. The lack of prospective, controlled clinical trials for the treatment of anaphylaxis in humans is not surprising, and has its basis in the fact that anaphylaxis is a true life-threatening medical emergency and there is no other first-line therapy. Therefore, withholding of available treatment, even for short periods of time, would not allow for equipoise in a clinical trial. On the basis of this vast clinical experience, and as noted in Dr. Nicklas' review, epinephrine has been adopted as the standard-of-care, first-line treatment of anaphylaxis. This treatment is accepted by all medical authorities and all allergy and anaphylaxis experts in the United States and abroad. (Lieberman 2010; Samson 2006; Simons WAO 2011; Soar 2008)

All other treatments of anaphylaxis are often critical, but they are either supportive or second-line, and therefore adjunctive in nature. They include: discontinuation of any suspected allergen, recumbent positioning; establishment of an adequate airway and administration of oxygen; rapid administration of IV fluids to expand blood volume (crystalloids) for patients in shock; H₁ antihistamines such as diphenhydramine or chlorpheniramine; H₂ antagonists such as cimetidine or ranitidine; inhaled beta-agonists such as albuterol, glucocorticoids; and sedatives and vasodepressing agents. Additional treatment may include blood pressure support with intravenous norepinephrine or other pressors until adequate volume expansion has been achieved and glucagon for patients taking beta-blockers who have refractory hypotension. (Lieberman 2010; Simons WAO 2011)

One prospective, uncontrolled trial supports the use of epinephrine for the treatment of anaphylaxis. (Brown 2004) This study prospectively evaluated a protocol for the treatment of sting anaphylaxis using an infusion of IV epinephrine (1:100,000), oxygen, and volume resuscitation (if needed) in adults who had systemic allergic reactions to a diagnostic sting challenge following either venom or placebo immunotherapy. All 19 patients who experienced a reaction to insect venom received epinephrine treatment and recovered fully. Additionally, 5 patients required volume resuscitation and 2 patients also required atropine to treat bradycardia. Importantly, physical signs of anaphylaxis recurred in 9 of the cases after epinephrine was initially stopped, but resolved after restarting the infusion, suggesting that these patients fulfill Koch's postulates. The conclusion from this study was that carefully titrated intravenous epinephrine combined with volume resuscitation is an effective strategy for treating anaphylaxis due to stings.

Use of epinephrine is also indirectly supported by outcome studies that have looked, for example, at deaths due to anaphylaxis. These studies note the appalling lack of use, or late use, of epinephrine in these patients. However, many of these patients did not have immediate access to epinephrine, as would be expected in the case of first-time anaphylaxis episodes, in large part explaining why the numbers are not better. Additionally, in those unfortunate fatal cases in which the patient had been identified as needing a kit and had one available, only a few used it or used it correctly, suggesting that had it been available and used in a timely fashion many of these lives could have been saved. It is clear from these publications that much work remains in identifying

patients at risk, and ensuring that they are adequately trained and prepared to deal with an allergic emergency and carry their medication with them at all times. (Pumphrey 2000; Pumphrey 2007; Sampson 1992)

In sum, the efficacy [and safety] of epinephrine for the treatment of anaphylaxis by this vast array of data and is unquestionable.

6.1.2 Pediatric Use

Several pharmacokinetic and pharmacodynamic studies have been conducted evaluating dosing, PK, and PD effects of epinephrine in children. (Fischer 1993; Simons 1998; Simons 2002) The pharmacokinetic evaluations in children show linear clearance in all age ranges, and pharmacodynamic evaluations in children demonstrate similar pharmacologic response, including effects on BP, HR, etc. as seen in adults. Similarly, the underlying disease process is considered the same regardless of age, lending support for use in all pediatric age groups. That stated, the applicant's limitation of this application to patients 30 kg and over limits use of the product to the older pediatric age range and adults, who can be taught how to administer epinephrine using a prefilled needle/syringe.

6.1.3 Dosing and Administration

Because of the linear kinetics, dosing of epinephrine is appropriately and necessarily weight based. As a result, a dose of 0.01 mg/kg of (b) (4) dilution (which is what is contained in this product) is accepted, and appears to be adequate for most individuals to control anaphylaxis symptoms and maintain blood pressure. Because they are intended for use in the medically unsupervised setting, the epinephrine auto-injector products are available in dosage strengths that based on predefined weight ranges, which is also appropriate for this product (i.e., 30 mg for patients 30 kg and over).

Repeated dosing is based on the clinical response, i.e., the presence of continued or recurrent [as in the case of biphasic reactions] signs and symptoms. Therefore, most of the epinephrine auto-injectors are packaged in two-packs, with the instruction to both seek emergency medical help right away and to use a second dose in about 20 minutes should it be needed. This dosing schema appears to be effective for the majority of patients. Although some patients do not respond, for many the failure to respond may be due to a variety of other issues, such as a delay in recognition of the diagnosis, delay before administration or not administering the dose for any of a number of other reasons (including failure to recognize the severity of a reaction, and failure to have a dose immediately available). (Bock 2001; Bock 2007; Garvey 2011; Pumphrey 2000; Pumphrey 2007; Sampson 1992; Simons 2011) At this time, Amadis has only requested to market the product in individual single-dose packages. While not preferable, it is acceptable, given that the Agency has allowed this packaging schema for the other products.

Currently, the dosing recommendations include both intramuscular (IM) or subcutaneous (SC), administration, and there are reasons to that both routes are acceptable depending upon the clinical setting. The proposed IM/SC dosing regimen is supported by pharmacodynamic data in animals, PK data in adult and children, and a vast amount of clinical experience in all age groups. It is in keeping with the literature and is consistent the latest anaphylaxis dosing and treatment recommendations from the Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology). (Lieberman 2010) The IM route, which is associated with shorter time to maximum concentration, is definitely the preferred route in the medically supervised setting because it reaches the central circulation promptly, whereas the SC route leads to vasoconstriction and slower absorption. (Samson 2006; Lieberman 2010; Simons 2010) This recommendation is sensible in the medically supervised setting, where speed of onset is the overriding concern, repeated doses are available, and monitoring is also available. However, in the self-administered, medically unsupervised setting the dosing recommendation and rationale may reasonably differ. In this setting, either route is acceptable, and an argument may be made that the slightly slower absorption associated with SC injection may aid in prolonging the effects of initial self-therapy while awaiting additional emergency medical care, especially in situations where additional doses may not be available. (Pijak 2006) Further, the needle length of the approved self-administered auto-injectors cannot guarantee IM administration into the vastus lateralis muscle because of variability in the overlying fat layer of the thigh, and this is also acceptable for self-administered use. (Simons 2001; Chowdhury 2002; Simons 2010) The same applies to the proposed needle length for this product, which is 5/8 inch.

It is also of note that the anterolateral thigh (vastus lateralis muscle) is the most appropriate location/muscle for SC/IM administration because of its location, size, and available blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended because of differences in PK associated with this use. (Simons 2001) Injection into the buttock is not recommended because there have been reports of gas gangrene infections after dosing into this area. (Harvey 1968)

7 Review of Safety

Safety Summary

The safety assessment for this application is adequate and supports the safety of the proposed epinephrine PFS product for treatment of anaphylaxis. No clinical trials were conducted to support the indication of anaphylaxis. The safety information comes from the literature, including many pharmacological studies in animals, pharmacokinetic, pharmacodynamic, and epidemiologic studies in humans, one clinical trial in patients with anaphylaxis, adverse event reports, and over 110 years of clinical experience. This drug has been used in all age ranges to treat anaphylactic reactions. Given the serious nature of anaphylaxis, there are no absolute contraindications for such use.

Epinephrine has a narrow therapeutic window, with overlap between life-saving pharmacologic effects that are associated with therapeutic clinical efficacy and other pharmacologic effects that are seen as common adverse reactions. As a result, the higher the dose, the more likely that there will be side effects that potentially may be significant. Typical reactions include restlessness, pallor, tremor, anxiety, palpitations, dizziness, and headache; their presence indicates that the administered dose is having a pharmacologic effect. The most serious reactions include transient hypertension with attendant risks of cerebral bleeding, and cardiac toxicity including myocardial ischemia, infarction, and cardiac arrhythmias. Serious reactions are rare with IM and SC use at recommended doses. IV use carries significantly more risk, and should be restricted to the medical setting in which the patient can be adequately monitored and treated.

Injection into the buttock is not recommended because there have been reports of gas gangrene infections after dosing into this area, which are postulated as secondary to stool contamination. (Harvey 1968) It is also of note that alcohol does kill *Clostridium* spores; therefore, wiping with alcohol may not prevent this rare occurrence. (Harvey 1968; APIC *C diff Elimination Guide* 2008) Therefore, the recommendation/warning to avoid the buttock for epinephrine injections appears to be supported by a reasonable scientific rationale.

7.1 Methods

The literature was reviewed, including both the submitted literature and other literature found through PubMed searches, including searches regarding the history, pharmacology, toxicology, pharmacokinetic, safety, efficacy, clinical trials, reviews, and case reports of/for epinephrine.

7.2 Adequacy of Safety Assessments

The safety assessment is considered adequate. The applicant did not conduct clinical trials to support the indication of anaphylaxis, and no controlled clinical trials are published in the literature in patients with anaphylaxis. The safety information comes from the literature, including many pharmacological studies in animals as well as pharmacodynamic and epidemiologic studies in humans, PK data, safety reports and reviews, and over 110 years of clinical use. The data provide a sufficient understanding of safety to adequately label this drug for safe use.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

This drug has been used in all age ranges. The target population for this product is any individual who weighs 30 kg or over who has an anaphylactic reaction.

7.2.2 Explorations for Dose Response

The safety for use of epinephrine for treatment of anaphylaxis comes from over 100 years of clinical use, PK and PD studies, as well as clinical trials in the setting of asthma, which have demonstrated linear kinetics and clearly outlined the adverse reactions that may be expected with this drug.

Epinephrine is well known to have a narrow therapeutic window (Simons 2006; Kemp 2008), with overlap between life-saving pharmacologic effects that are associated with therapeutic clinical efficacy and other pharmacologic effects that are seen as common adverse reactions. In fact, restlessness, pallor, tremor, anxiety, palpitations, dizziness, headache are typical reactions to epinephrine treatment, and their presence indicates that the administered dose is having a pharmacologic effect. (Kemp 2008; Simons 2011; Westfall 2006). While texts usually recommend treatment with rest, recumbent positioning, and reassurance, adverse effects from epinephrine wear off quickly without additional treatment, and these treatments are just as likely to aid in treatment of the underlying condition, anaphylaxis.

Serious adverse reactions are rare. Most serious reactions are associated with medication errors and overdose, or IV use (McClean-Tooke 2003; Simons 2010; Simons 2011; Sheikh 2011) rather than being associated with the doses routinely administered IM or SC, although there are rare case reports at these dosage levels as well.

PK data in adults and children show a reasonably linear relationship between dose and weight, supporting weight based dosing as proposed for this product (Clutter 1980; Ensinger 1992; Fisher 1993; Simons 1998; Simons 2001; Simons 2002; Abboud 2009). These findings have also been demonstrated in animals (Gu 1999).

Higher doses are more frequently associated with cardiac toxicity, including transient hypertension, chest pain, palpitations, ST elevation, ventricular tachycardia, ventricular arrhythmias, cardiomyopathy, vasospasm-induced acute coronary syndromes (angina, myocardial infarction, arrhythmias), pulmonary edema, and cardiac arrest. Such toxicity is of more concern in patients with underlying organic heart disease, including patients with cardiac arrhythmias, coronary artery disease, or hypertension, in patients who are on drugs that may sensitize the heart to arrhythmias, in elderly patients with cardiovascular disease, and in patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women.

Since the heart is itself a potential target organ in anaphylaxis, it should be noted that acute coronary symptoms may be associated anaphylaxis itself rather than epinephrine treatment, regardless of whether the patient has known or coronary artery disease, i.e., these symptoms may occur in patients in whom subclinical coronary artery disease is unmasked as well as in patients who have no coronary artery disease, for whom the symptoms are the result of transient vasospasm. (Barach 1984; Brown 1998; Hema 2008; Kanwar 2010; Kounis 2006; Shaver 2006; Simons 2011; Sheikh 2011; Triggiani 2008)

For patients who require IV treatment, higher toxicity has been attributed to IV bolus treatment than IV drip infusion. This is postulated to be due to a concentration

dependent difference in α_1 receptor versus β_1 receptor activation, with higher (but transient) epinephrine concentrations associated with IV bolus treatment causing additional α_1 effects that temporarily reverse the coronary vasodilation induced by the β_1 effects, whereas these effects are less often reported with a constant IV drip infusion (Barach 1984; Brown 2005; Soar 2008). Higher IV doses are also associated with systemic hypertension (significantly increased systolic and diastolic blood pressures) with the attendant risks of cerebral bleeding and myocardial ischemia, infarction, and cardiac arrhythmias [due to increased myocardial consumption] (Brown 1998; Simons 2010; Sheikh 2011).

Additional discussion of dose response and toxicity with IV dosing may be found in Section 6.1.1.3.1.

7.2.3 Data from Animals

Epinephrine has physiologic and pharmacologic effects that are well known and well characterized. A large number of studies have been performed in animals and *in vitro* to evaluate the pharmacologic and physiologic effects of epinephrine. Many of these studies, dating to the 1890's, predate identification of the specific receptors that allow a detailed understanding of how the drug effects each organ system within the body, a process that took much of the 20th century and produced multiple Nobel Prize winners. That understanding is sufficiently understood that it is published in basic textbooks of pharmacology and medicine, a brief summary of which may be found in Section 4.4 of this review, and will not be discussed here.

Epinephrine is cardiotoxic in animals. These effects have also been demonstrated in humans, and this clinical information is reflected in the labeling.

Although epinephrine is an endogenous compound, *in vitro* data shows that epinephrine is genotoxic (see next paragraph). However, because there are no long-term clinical uses for epinephrine, long-term carcinogenicity studies have not been conducted in animals, and carcinogenicity has not been evaluated in humans.

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. However, this should not deter the use of epinephrine for any of the indications being considered in this application.

The potential for epinephrine to impair reproductive performance has not been evaluated, but epinephrine has been shown to decrease implantation in female rabbits.

7.2.4 Routine Clinical Testing

NA

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor did not conduct any metabolic, clearance, or drug interaction studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

NA.

7.3 Major Safety Results

7.3.1 Deaths

Anaphylaxis may result in death, and there are a number of publications in the literature that discuss that eventuality. Appropriate treatment with epinephrine (and other measures) can be life-saving. Epinephrine, however, can be cardiotoxic, especially in high doses and in patients with underlying heart disease. See other sections of this review for details.

7.3.2 Nonfatal Serious Adverse Events

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation, i.e., for the treatment of anaphylaxis. Patients for whom there is a greater risk for developing adverse reactions include:

- Patients with heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias including fatal ventricular fibrillation.
- Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease.
- Patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

The safety issue of injection into the digits has been reported with use of the epinephrine auto-injector products. This usually occurs when the user mistakes the live end for the top and mistakenly holds the thumb or another finger over the top (which is not part of the instructions). Because epinephrine causes vasoconstriction, lack of blood flow to the digit can potentially be associated with anoxic tissue loss. Epinephrine products used in conjunction with local anesthetics also carry a warning not to inject into a digit. That warning is carried into the proposed labeling for this product. While a

general warning is appropriate, detailed warnings are not necessary, as this safety issue is of more specific concern to the epinephrine auto-injector products that are intended for self-use rather than for epinephrine vials intended for use by the medical professional.

Gas gangrene has been associated with injections of epinephrine into the buttocks. Therefore, injection into the vastus lateralis muscle of the thigh is the most appropriate location for administration when injected IM or SC. See section 6.1.1.3.1 for further details.

7.3.3 Dropouts and/or Discontinuations

NA

7.3.4 Significant Adverse Events

NA

7.3.5 Submission Specific Primary Safety Concerns

NA

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events with epinephrine use are well described and include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

7.4.2 Laboratory Findings

Epinephrine causes transient decreases in potassium levels due to stimulation of potassium uptake into cells, particularly skeletal muscle (β_2) and decreased renal potassium excretion. (Westfall 2006)

7.4.3 Vital Signs

Epinephrine use can cause a rapid rise in blood pressure. See Section 7.3.2.

7.4.4 Electrocardiograms (ECGs)

Epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias including fatal ventricular fibrillation. See Section 7.3.2.

7.4.5 Special Safety Studies/Clinical Trials

NA

7.4.6 Immunogenicity

NA

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See other sections of this review that discuss dose dependency with regard to the pharmacodynamic as well as potentially toxic effects.

7.5.2 Time Dependency for Adverse Events

Epinephrine is short-acting, lasting only a few minutes before it is removed from the circulation and metabolized (see Section 4.4.2). Most side effects, including effects on blood pressure and the CNS resolve rapidly as the drug is metabolized.

7.5.3 Drug-Demographic Interactions

NA

7.5.4 Drug-Disease Interactions

Populations that are particularly vulnerable to the effects of epinephrine include individuals at the extremes of age, those with hypertension, peripheral vascular disease, coronary artery or ischemic heart disease, organic heart disease, patients with long-standing or significant emphysema who may also have degenerative heart disease, cerebrovascular disease, diabetes, untreated hyperthyroidism, and pheochromocytoma. In patients with diabetes, epinephrine may transiently increase blood glucose levels. Uncontrolled hyperthyroidism makes the myocardium more sensitive to the β -adrenergic effects of epinephrine due to an increased number of β -adrenergic receptors in the vasculature of these individuals. (Goldenberg 1950; Kemp 2008; Mclean-Tooke 2003)

Patients with Parkinson's disease may experience psychomotor agitation or notice a temporary worsening of symptoms.

7.5.5 Drug-Drug Interactions

Because the pharmacology of epinephrine is well characterized and there is vast clinical experience with this drug, drug-drug interactions are also well known. Some medications increase the risk of adverse reactions from epinephrine due to a drug-drug interaction. Others may decrease the effectiveness of epinephrine treatment. Nevertheless, the use of any of these drugs by a patient does not constitute an absolute contraindication the use of epinephrine to treat anaphylaxis. (Kemp 2008; Mclean-Tooke 2003)

Alpha-blockers, and Alpha- and Beta-adrenergics

Not surprisingly α -blocking agents can block the α -pharmacologic effects of epinephrine, and α - and β -adrenergic agents can potentiate the α - and β -pharmacologic effects of epinephrine, respectively.

Beta-blockers

The evidence suggests that anaphylaxis may be made worse by the presence of β -blockers such as propranolol. (Lang 1995) Furthermore, and perhaps not surprisingly, patients on β -blockers do not respond well to epinephrine treatment. (Barach 1984) While higher doses of epinephrine are required to overcome the lack of a β -adrenergic response, the unopposed α -adrenergic stimulation may increase the risk for use of even standard doses, leading to bradycardia, hypertension, coronary artery constriction, and bronchoconstriction. (Mclean-Tooke 2003) This finding has been noted even with use of eye drops containing a β -blocker. (Moneret Vautrin 1993) As a result, the general recommendation is to withdraw use of β -blockers in patients who are considered at risk of anaphylaxis, and substitute alternative treatments. (Mclean-Tooke 2003)

Treatment guidelines for patients on β -blockers who develop anaphylaxis have not been published. However, because of the sensitivity to unopposed α -adrenergic stimulation, use of drugs with pure β -adrenergic effects, such as glucagon, along with fluid resuscitation, is recommended. (Lieberman 2010)

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOI)

Tricyclic antidepressants and monoamine oxidase inhibitors are known to potentiate the effects of epinephrine and increase the risk of cardiac arrhythmias. Although at least one publication suggests halving the dose of epinephrine in these patients (Mclean-Tooke 2003), others suggest that the inter-individual variability in response is sufficiently large that the usual dose should be administered and the patient observed for a clinical response and side effects, with further dosing titrated accordingly (Soar 2008).

Other Drug Interactions

Ergot alkaloids may reverse the pressor effects of epinephrine. Coadministration with halogenated hydrocarbon anesthetics, such as halothane, or with cardiac glycosides,

digitalis, diuretics, quinidine, and other antiarrhythmics, may result in cardiac arrhythmias. Cocaine and amphetamines sensitize the myocardium to the effects of epinephrine, increasing the risk of toxicity. (Kemp 2008) Epinephrine should not be used systemically to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Although epinephrine is an endogenous compound, *in vitro* data shows that epinephrine is genotoxic. However, because there are no long-term clinical uses for epinephrine, long-term carcinogenicity studies have not been conducted in animals, and carcinogenicity has not been evaluated in humans.

7.6.2 Human Reproduction and Pregnancy Data

Epinephrine is Pregnancy Category C. There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women. Epinephrine has been shown to be teratogenic in rabbits, mice, and hamsters. As a result, the labels for the approved products carry the standard warning for this pregnancy category, i.e., that epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both). However, it should be noted that anaphylaxis is just such a use. The treatment of anaphylaxis with epinephrine involves short-term use, and the treatment is life-saving. Therefore, although the labels carry this concern, the benefits for use far outweigh the risks.

7.6.3 Pediatrics and Assessment of Effects on Growth

Epinephrine is an endogenous compound. As is the case in adults, the doses of epinephrine for use in children are empiric, having been used for much of the last 100 years in the clinical setting. The pharmacologic response to epinephrine, as well as the underlying disease process, are considered the same regardless of age, lending support for use in all pediatric age groups. There has been no assessment of the effects of epinephrine on growth, but given the way this drug is used there is no expectation that such an assessment would be beneficial.

Although no controlled clinical trials have been conducted to evaluate the safety and efficacy of epinephrine in children with anaphylaxis, adverse reactions are available from a range of controlled clinical trials conducted in pediatric patients with asthma [see Sections 9.1.1.7 and 9.1.2.2]. (Becker 1983; Ben-Zvi 1982; Lin 1996; Simons 1981; Turpeinen 1984) All of the pediatric asthma trials compared epinephrine with a beta

agonist. While asthma is a different disease and a different indication, the studies provide safety data with the use of epinephrine, since the dosing recommendations for asthma (0.01 mg/kg (b) (4) administered SC) and anaphylaxis are similar. [Note: Although similar, dosing for the two indications are not identical, as the dosing recommendations for asthma include repeated doses every 20-30 minutes, whereas the dosing recommendations for anaphylaxis are more frequent. Additionally, for asthma the SC route is preferred, whereas for anaphylaxis both routes are acceptable although the IM route is preferred in the medically supervised setting.] The asthma trials nevertheless demonstrate that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults. An additional study performed in wheezing children under 2 years of age demonstrated similar findings, supporting use of epinephrine in all pediatric age groups. (Lowell 1987)

In fact, with certain exceptions, adults, and in particular older adults, are more likely to be at risk from epinephrine use. Cardiac adverse effects from epinephrine are associated with higher doses and are more of a concern in patients with underlying heart disease. Children are less likely than adults to have underlying organic heart disease, coronary artery disease, be on a medication, or have some underlying disease such as hyperthyroidism or Parkinson's disease that would predispose them to arrhythmias or potentiate the adverse reactions associated with epinephrine administration. However, children are perhaps more likely to have an underlying acquired or congenital condition, such as congenital heart disease or other abnormality, that may place them at higher risk and predispose them to arrhythmias, perfusion problems, or other adverse effects secondary to epinephrine administration. For many children, their underlying condition is known and the risks identified. However, and unfortunately for some, these conditions have not been diagnosed prior to a significant event. For example, fatal arrhythmias are sporadically reported in children who are strenuously exercising, primarily in adolescents and older children for whom an underlying diagnosis was never made, and epinephrine can mimic those exercise effects. However, this risk cannot be generalized to all children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Because of the pharmacologic side effects, this drug is not likely to be abused.

7.7 Additional Submissions / Safety Issues

NA

8 Postmarket Experience

Since epinephrine products have been marketed since 1901, all of the experience with the epinephrine for the treatment of anaphylaxis is postmarket. However, that clinical experience is substantial. See other sections of this review for details.

9 Appendices

9.1 Literature Review/References

The applicant submitted a summary of the literature that supports use of epinephrine for the treatment of anaphylaxis. Because I have previously provided a substantive literature review for another epinephrine application (Adrenalin, NDA 204200), it is not necessary to repeat the review here, and the reader is referred to that review, which is available at the FDA website (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204200_adrenalin_toc.cfm). Various sections in this review include relevant efficacy, safety, and dosing information, with references provided that are captured below. What follows is a fairly substantive list of literature references. While not all were cited by the applicant, sufficient references were included with the application to conclude that epinephrine is safe and effective for the treatment of anaphylaxis. Therefore, the specific references provided by the applicant are not provided herein.

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9.2 Labeling Recommendations

Because the Division expects to take a CR action in this cycle, labeling revisions will not be sent to the Applicant in this cycle. Nevertheless, several general labeling comments may be made here.

The sponsor has submitted a label in Physician Labeling Rule (PLR) format that is similar to the approved labeling for other epinephrine [auto-injector] products approved for self or caregiver treatment of anaphylaxis. Labeling for the epinephrine auto-injector products was recently approved in PLR format. The dosing recommendations for this product are in keeping with the literature and are consistent with other epinephrine products approved for self or caregiver administration in the medically unsupervised setting. The only differences for this product are in sections that are product-specific, including the instructions for use, which is appropriate.

During the course of the review, labeling consults were sent to the Division of Medical Policy Programs (DMPP) for review of the PPI and IFU and the Office of Prescription Drug Promotion (OPDP) for review of the PI, PPI and IFU. DMEPA provided comments about the carton and container labeling to increase readability. These comments will be retained for future communication to the Applicant.

9.3 Advisory Committee Meeting

No advisory committee was convened to discuss this application.

9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 207534
Submission Date(s): May 23, 2014
Applicant: Adamis Pharmaceuticals Corp.
Product: Epinephrine injection, USP, (b) (4) 0.3 mg
Reviewer: Peter Starke, MD
Date of Review: August 28, 2014

Covered Clinical Study (Name and/or Number):

None. There were no clinical trials or studies performed to support this application. Therefore, financial disclosure information is not required for this application.

Clinical Investigator Financial Disclosure Checklist Form

Was a list of clinical investigators provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>None (NA)</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None (NA)</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None (NA)</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>None (NA)</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER R STARKE
02/18/2015

JANET W MAYNARD
02/18/2015

CLINICAL FILING REVIEW / CHECKLIST

NDA: 207-534
Drug Name: Epinephrine injection, USP (b) (4) 0.3 mg
Applicant: Adamis Pharmaceuticals Corp.
Type: 505(b)(2)
Stamp Date: May 23, 2014
PDUFA Date: March 23, 2015
Reviewer: Peter Starke, MD
Team Leader: Janet Maynard, MD
Review Date: July 14, 2014

Background

This is a 505(b)(2) new drug application submitted by Adamis Pharmaceuticals Corp (Adamis), for a drug/device combination of Epinephrine Injection, USP (b) (4) 0.3 mg in a pre-filled, single-dose syringe (Figure 1). The proposed indication for this product is the treatment of severe allergic reactions (anaphylaxis). The product is intended for self or caregiver administration in the medically unsupervised, emergency setting.

A Type B meeting was held with the Agency in April 2014, to discuss the feasibility of a 505(b)(2) new drug application for this product, which was previously marketed without FDA approval. The Agency requested that, as part of the application, Adamis submit a rationale for administration of epinephrine via a pre-filled syringe unsupervised medical setting.

The application references EpiPen (NDA 19-430), which is listed in the Orange Book as a reference drug. The application includes a literature review summarizing the efficacy and safety of epinephrine for treatment of anaphylaxis, and the rationale requested by the Agency. The submission is all electronic in eCTD format, and was received on May 23, 2014. The PDUFA date is March 23, 2015.

The applicant has not a proposed Trade Name for the product.

This new drug-device combination will not trigger PREA.

There are no filing issues and the application is complete and fileable from a clinical perspective.

Filing Recommendations

The application is fileable from a clinical perspective. I recommend a standard review timeline for this application.

Potential Review Issues and Clinical 74-Day Comments

None



Figure 1. Adamis’ proposed Epinephrine prefilled syringe product

Table 1. Clinical Filing Checklist

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic in eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?		X		Clinical section has references and a pro-forma ISE and ISS
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			References clinical overview in Module 2
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			References clinical overview in Module 2
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Risk-benefit submitted in the clinical overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) referencing EpiPen (NDA 19-430)

CLINICAL FILING CHECKLIST

NDA 207-534 • Adamis • Epinephrine Injection, USP (b) (4) 0.3 mg

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			PREA not triggered.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No clinical studies or trials.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST**NDA 207-534 • Adamis • Epinephrine Injection, USP** (b) (4) **0.3 mg**

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	No clinical studies or trials.

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/s/

PETER R STARKE
07/14/2014

JANET W MAYNARD
07/14/2014