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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 12, 2013
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204,640
Supplement#	
Applicant	JHP Pharmaceuticals, LLC
Date of Submission	August 2, 2013
PDUFA Goal Date	June 2, 2014
Proprietary Name / Established (USAN) names	Adrenalin/epinephrine injection
Dosage forms / Strength	1 mg/mL, 30mL multiple-dose vial
Proposed Indication(s)	Emergency treatment of allergic reactions (Type 1), including anaphylaxis
Recommended:	Approval

1. Introduction

JHP Pharmaceuticals (JHP) submitted this 505(b)(2) new drug application for epinephrine injection 1mg/ml (trade name Adrenalin) 30mL multiple-dose vial on March 7, 2012 but it was found unacceptable for filing because the applicant had not paid the user fee. The applicant paid the user fee on August 2, 2013 and the application was accepted for review. This application is for the indication of emergency treatment of allergic reactions (Type 1), including anaphylaxis. The NDA references the listed drug EpiPen[®], which is an injectable epinephrine administered via an autoinjector for home use for anaphylaxis marketed by Meridian Medical Technology under NDA 19,430.

Adrenalin has been available in the United States since 1901, originally marketed by Parke Davis & Co., and subsequently transferred to Parkedale Pharmaceuticals in 1998, then JHP in 2007. Because the product predates both the original Federal Food and Drugs Act of 1906, the Federal Food, Drug and Cosmetic Act of 1938, and the Kefauver-Harris amendment in 1962, it was not subject to FDA review or the Drug Efficacy Study Implementation (DESI) process review. As such, Adrenalin, as well as other epinephrine solution products, were marketed unapproved drugs. Adrenalin is currently marketed by JHP in both 1mL (single-use) and 30mL (multiple-dose) vials. The 1mL presentation was approved for IM and SC administration on December 7, 2012 for two indications: 1) emergency treatment of allergic reactions (Type 1), including anaphylaxis, and 2) induction and maintenance of mydriasis during intraocular surgery. The 30mL Adrenalin presentation remains a marketed unapproved drug. The current application cross-references data from NDA 204,200 to support the safety, efficacy, and manufacturing controls for the 30mL vial presentation.

The proposed anaphylaxis indication is supported by over one hundred years of clinical use and the literature. No clinical studies were performed for approval of the reference listed drug (RLD), EpiPen[®], which also relied on the literature for support of efficacy and safety for treatment of anaphylaxis. The difference between the two indications is that EpiPen[®] is intended for home (patient/caregiver) use, while Adrenalin is intended for use by a medical practitioner.

The PDUFA goal date for the anaphylaxis indication of this application is June 2, 2014, with a standard review clock. The Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) plans to take an early action.

2. Background

The following section is adapted from Dr. Theresa Michele's CDTL review dated November 29, 2012

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).

Related Drugs

Epinephrine is the drug of choice for treatment of anaphylaxis, with other treatments considered to be adjunctive or supportive. There are currently 4 approved auto-injectors 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 0.3mg or pediatric dose of 0.15mg except Twinject, which contains 2 doses. These products are intended for self or caregiver administration prior to the patient arriving in a medical facility. As such, the doses are lower than those proposed for use in a healthcare setting.

Adrenalin (epinephrine injection), 1mg/mL (1:1000) in a 1mL vial presentation was approved for myadriasis and anaphylaxis in December 2012. In addition, a number of marketed, unapproved single ingredient epinephrine products exist. Products listed in the National Drug Code (NDC) Directory include those marketed by American Regent, Amphastar

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

Pharmaceuticals, General Injectables and Vaccines, and McKesson Packaging Services, all at a concentration of 1mg/mL (1:1000). Amphastar also markets a 0.1mg/mL (1:10,000) solution.

Currently, JHP markets 2 different Adrenalin presentations for injection:

- Epinephrine 1mg/mL sterile solution in a single use, 1mL dose in 3mL vial
- Epinephrine 1mg/mL sterile solution in a multi-use 30mL vial

The two presentations differ in formulation, with the 1mL presentation containing 1mL of 1mg/mL sodium metabisulfite as an antioxidant, and the 30mL vial containing 1.5mg/mL sodium metabisulfite as an antioxidant and (b) (4).

However, during the filing review period for NDA 204,200, the 30mL vial presentation was transferred to a separate NDA (NDA 204,640) because the two presentations are quantitatively and qualitatively different and the applicant was notified of the need to pay the appropriate user fee.

A number of other epinephrine products, both approved and unapproved, are also currently or previously on the market. These include combination products with injectable anesthetics for local or regional anesthesia, nebulized solutions for various breathing conditions such as asthma, and over the counter metered dose inhalers for asthma.

Epinephrine products for self-injection for anaphylaxis all contain similar safety information. There are warnings and precautions for injection into buttocks, digits, hands and feet, as well as a warning regarding angina and ventricular arrhythmias. There is also the required warning regarding allergic reactions in patients with sulfite sensitivity; however, the label notes that the presence of bisulfite should not preclude use of epinephrine for the treatment of serious allergic reactions as there are no satisfactory alternatives. Given the severity of the conditions epinephrine is being used to treat, there are no contraindications. Adverse reactions include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea, vomiting, headache, and respiratory difficulties.

Regulatory history

Adrenalin 30mL is a marketed unapproved product. In 2009, the FDA Office of Compliance questioned the grandfather status of the Adrenalin products and urged JHP to contact the Office of New Drugs to discuss filing an NDA for the Adrenalin products. Accordingly, a pre-IND meeting was held with JHP on July 5, 2011. In the meeting with DPARP, JHP proposed indications for anaphylaxis, (b) (4). FDA agreed that it was reasonable to rely on the literature and reference EpiPen for an anaphylaxis indication. (b) (4)

Based on the PIND interaction, JHP submitted NDA 204,200 for two indications: anaphylaxis and mydriasis. (b) (4)

(b) (4). The application was administratively split into the two different indications, which were reviewed by different review divisions (DPARP and DTOP). In addition, because the two presentations are quantitatively and qualitatively different, the application was further split into two different NDAs: 204,200 for the 1mL presentation and NDA 204,640 for the 30mL presentation, which requires a separate user fee. Because the sponsor chose not to submit a user fee for the 30mL presentation at that time, the applicant was issued an Unacceptable for filing letter. The 1mL presentation was approved for the indications of anaphylaxis and myadriasis in December 2012.

In the current application, for the 30mL presentation, the applicant is seeking one indication: anaphylaxis. The PDUFA date for this indication is June 2, 2014. However, the Division plans to take an early action on the application and has set February 2, 2014 (6 month clock) as the goal date for the application but may take an even earlier action to avoid a potential drug shortage.

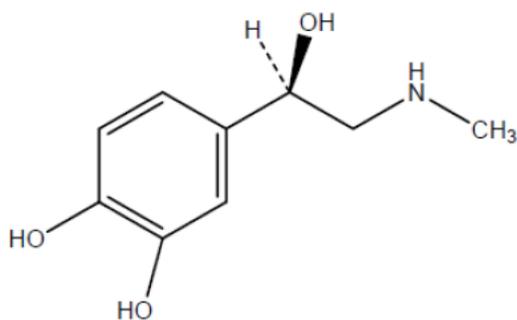
3. CMC/Device

- **General product quality considerations**

Epinephrine is a sympathomimetic catecholamine having the chemical name 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy- α -[2-(methylamino)ethyl]benzyl alcohol. The drug substance is white to nearly white, odorless, microcrystalline powder or granules, gradually darkening on exposure to light and air. The chemical structure of epinephrine is shown in Figure 1.

Figure 1: Chemical structure of epinephrine

Structural Formula:



Molecular Formula:

$C_9H_{13}NO_3$

Molecular Weight:

183.20 (free base); 333.30 (bitartrate 1:1 salt)

The drug product, Adrenalin (epinephrine injection, USP, 1:1000), is a sterile injectable solution and is packaged in 30 mL multi-dose vials (30 mg/30mL). The formulation of Adrenalin 30 mL is similar to Adrenalin 1mL presentation (approved in December 2012, NDA 204,200) with the addition of chlorobutanol preservative. The drug product is manufactured by JHP Pharmaceuticals, LLC according to a standard manufacturing process (b) (4)

(b) (4) that meets current GMP requirements for parenteral products. This 30mL presentation of Adrenalin has been marketed for over 100 years before submitting this NDA for approval. There is no pharmaceutical development information in the submission for the manufacturing process of the drug product. The quality is controlled by the end product testing according to the specification. The approved Adrenalin 1mL presentation has the same approach and was felt to be acceptable by the CMC review team.

The main difference in the composition of the Adrenalin 30mL presentation and 1mL presentation is the addition of chlorobutanol preservative in the 30mL presentation for multi-dose use purpose. There are no safety concerns associated with this preservative, as discussed in Section 4.

High level of degradants in the drug product was a major concern in the review of the 1mL presentation. The proposed specification for the 30mL presentation is similar to that of the approved 1mL presentation and noted to be acceptable.

The container closure system utilizes Type I glass vials with a rubber stopper and flip off seal. The sponsor confirmed that the container closure used for the currently marketed Adrenalin 30mL injectable presentation (b) (4) commercial container closure system. During review of NDA 204,200 for the 1mL presentation of Adrenalin, the sponsor committed to conduct a leachable study for the stopper and submit the data to the NDA. During the current review cycle, the sponsor was asked to provide leachable study data. While this study has not yet been conducted, the sponsor provided sufficient evidence of safety and compatibility for the use of the proposed glass vial for the drug product container. Further, the sponsor provided a risk analysis from the stopper manufacture based on the extractable data. The risk analysis was felt to be reasonable. A post marketing commitment for a leachable study is recommended (Section 13).

See review by Dr. Ying Wang dated December 11, 2013 for complete details.

- **Facilities review/inspection**

The drug substance is manufactured at (b) (4). Of note, this site received a warning letter in (b) (4) due to failure to properly investigate and address contamination and dosage delivery variability in lots of (b) (4) however the issues noted were not directly related to epinephrine. This site has responded to the warning and is scheduled for a follow up inspection in (b) (4). The response was found adequate pending on-site confirmation of corrective actions to the quality system. Though the site will remain under an OAI status until the follow up inspection, the establishment was given acceptable recommendation on (b) (4) under discretion for this NDA by the Division of International Drug Quality due the medical need of the product and the reduced compliance risk subsequent to the promised corrective actions in the firm's warning letter response. The Office of Compliance issued an overall recommendation of Acceptable for the application on (b) (4).

- **Product Quality Microbiology**

The drug product is sterilized [REDACTED] (b) (4). The [REDACTED] (b) (4) manufacturing process was deemed to be adequate. Further, the sponsor's tests for sterility and endotoxin levels were likewise found to be adequate. For complete details, see review by Dr. Erika Pfeiler, dated November 25, 2013.

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

The CMC review team has concluded that the application may be approved from a CMC perspective. A postmarketing commitment for a leachable study is recommended (Section 13).

4. Nonclinical Pharmacology/Toxicology

- **General nonclinical pharmacology/toxicology considerations**

No nonclinical studies were submitted to or required for NDA 204,640. The current application cross-references data from NDA 204,200 to support the safety, efficacy, and manufacturing controls for the 30mL Adrenalin product. The sponsor also references nonclinical information in the approved label for EpiPen as well as publically available literature to provide nonclinical support for the proposed product.

The 30mL presentation of Adrenalin differs from the 1mL presentation in several respects, including: 1) excipients used, and 2) the acceptance criterion for the impurity [REDACTED] (b) (4). In terms of excipients use, the levels are within the range of currently approved injectable products and the safety of chlorobutanol at [REDACTED] (b) (4)% is based on its listing on FDA's inactive ingredient list: <http://www.accessdata.fda.gov/scripts/cder/IIG/index.cfm>. In terms of acceptance criterion for degradants, the proposed acceptance criteria allow for adequate safety margins and are considered safe from the nonclinical perspective.

See review by Dr. Mathew Whittaker dated December 9, 2013 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

The sponsor did not submit any clinical pharmacology trials. JHP 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 as per 21 CFR 320.22(b)(a), FDA shall waive the requirement for the submission of data demonstrating

bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. Of note, the proposed drug product contains chlorobutanol, but the reference listed drug does not. However, chlorobutanol has been, and still is, used as a preservative for many approved and unapproved drugs. There is no evidence that the addition of chlorobutanol to a drug changes its PK, efficacy, or safety profile. Further, chlorobutanol has no known or theoretical attributes that would result in the exacerbation of local or systemic adverse effects that may occur after IM or SC injections.

The biopharmaceutics team recommended granting a waiver from conducting an in vivo bioequivalence study for the Adrenalin IM and SC routes. The safety of chlorobutanol at (b) (4) % in the proposed product is based on its listing on FDA's inactive ingredient list: <http://www.accessdata.fda.gov/scripts/cder/IIG/index.cfm>.

See reviews by Dr. Agarwal dated December 7, 2013 and Dr. Assadollah Noory dated December 5, 2013 for complete details.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

- **Efficacy review**

No clinical studies were submitted or required for this application. The sponsor is relying on reference to the RLD, EpiPen and cross-reference to NDA 204,200, which relied on literature. 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 sponsor proposes weight-based dosing as follows:

Adults and Children 30kg (66lbs) or more: 0.3 to 0.5mg (0.3 to 0.5mL) IM or SC into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.

Children 30kg (66lbs) or less: 0.01mg/kg (0.01mL/kg), up to 0.3mg (0.3mL), IM (or SC) into anterolateral thigh every 5 to 10 minutes as necessary.

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.

The proposed dose, dosing frequency, and route of administration are consistent with the currently approved 1ml presentation of Adrenalin and are reasonable.

8. Safety

The 30mL presentation of Adrenalin is a marketed unapproved product. This application relies on the Agency's previous findings of safety for EpiPen for the treatment of anaphylaxis, and also cross references the 1mL Adrenalin presentation that was approved in December 2012. 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. 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 Adrenalin for anaphylaxis and I concur.

Of note, the presence of chlorobutanol in the 30mL vial presentation makes the risk/benefit for this presentation unacceptable for the mydriasis indication. However, the presence of chlorobutanol does not impact the risk/benefit of the presentation for the anaphylaxis indication. The safety of chlorobutanol at (b) (4)% in the proposed product is based on its listing on FDA's inactive ingredient list: <http://www.accessdata.fda.gov/scripts/cder/IIG/index.cfm>

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

10. Pediatrics

The application was not discussed at the Pediatric Review Committee (PeRC) meeting. The application for the 1mL Adrenalin presentation was discussed at PeRC on June 12, 2012 and it was determined that the pediatric assessment for the drug was considered to have been fulfilled in all age groups based on the extensive clinical use in all age groups including neonates for treatment of anaphylaxis, as well as for the treatment of asthma [in all age groups] for which the IM/SC dose is the same. This assessment is also applicable to the 30 mL multi-use vial presentation.

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 Division of Medication Error Prevention and Analysis (DMEPA) conducted a review of the proposed proprietary name, Adrenalin, under which this product has been marketed for over 100 years. Per the review dated December 9, 2013, there are no objections to the proposed trade name.

- **Physician labeling**

The sponsor submitted a label in the Physician's Labeling Rule (PLR) format that added the 30mL presentation to the currently approved Adrenalin label for the 1mL presentation label. The 30mL presentation will be limited to the indication of anaphylaxis, in contrast to the 1mL presentation which will include the anaphylaxis and induction and maintenance of mydriasis during intraocular surgery indications. The other proposed differences relate to the CMC sections to describe the new presentation. It was felt that the proposal to have one label is reasonable because there is no difference in the concentration of the active ingredient. The labeling will include statements to indicate that the 30mL presentation is not for intraocular use.

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

Labeling negotiations are ongoing with the sponsor at the time of this review.

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

Revisions to the carton were recommended and the sponsor has agreed to these proposed changes.

- **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 approval for the indication of “emergency treatment of allergic reactions (Type I), including anaphylaxis.”

- **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. While the therapeutic window is narrow and significant toxicities exist (arrhythmias, cerebral hemorrhage, cardiac ischemia, and myocardial infarction), the significant benefit of this product outweighs even these potentially serious events. ,

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

A Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

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

There are recommendations for one post-marketing commitment (PC) related to CMC issues as described in Section 3. The final language and dates for completion of this PMC are still being finalized as of the date of this review.

- 1. Develop and validate analytical method(s) if applicable for leachable testing – April 2014*
- 2. Update ongoing stability program and protocols to reflect leachable testing – June 2014*
- 3. Test retained samples at or near end of shelf life for leachables. Report results in NDA – Dec. 2014.*
- 4. Revise drug product specification to include leachable testing if necessary – Dec. 2014*

- **Recommended comments to applicant**

There are no additional comments to the applicant.

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/s/

JANET W MAYNARD
12/17/2013