CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW FOR REGULATORY ACTION

Date	December 18, 2013
From	Lydia Gilbert-McClain, MD, FCCP Deputy Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Subject	Summary Review
NDA#	204-640
Applicant Name	JHP Pharmaceuticals, LLC
Date of Submission	March 7, 2012
PDUFA Goal Date	June 2, 2014
Proprietary Name/Established (USAN) Name	Adrenalin (epinephrine injection, USP)
Dosage forms/Strength	Injection 1 mg/mL
Proposed Indication (s)	1. Emergency treatment of allergic reactions (Type I) including anaphylaxis, (b) (4)
Recommended Action	Approval

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
Pharmacology/Toxicology Review	Matthew Whittaker, PhD; Timothy Robison, PhD
CMC Review	Ying Wang, PhD, Prasad Peri, PhD
ONDQA-Biopharmaceutics Review	
Clinical Pharmacology review	Sheetal Agarwal, PhD; Satjit Brar, PhD
DPDP Review	Roberta Szydio
Product Quality - Microbiology	Erika Pfeiler, PhD
OSE/DMEPA	Teresa McMillan, PharmD; Lubna Merchang, PharmD, MS; Lissa Owens

OPDP = Office of Prescription Drug Promotion
DSI = Division of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
CDTL = Cross Discipline Team Leader

Reference ID: 3424331

1. Introduction

JHP Pharmaceuticals LLC (JHP) submitted a 505(b) (2) application for Adrenalin® (epinephrine injection, USP) 1 mg/mL (1:1000) 30 mL multi-use vial for marketing approval for epinephrine injection for the emergency treatment of allergic reactions and anaphylaxis on March 7, 2012. In that same submission JHP submitted a single-use vial presentation of epinephrine injection (1mg/mL). Both presentations are for the anaphylaxis indication but the 30 mL multi-use vial contains a preservative chlorobutanol, and is not suitable for intraocular use. The reference product for the 505(b) (2) application is EpiPen ®, an epinephrine auto-injector product marketed by Meridian Pharmaceuticals for the emergency treatment of allergic reactions including anaphylaxis. Because the two formulations were not qualitatively and quantitatively the same and because of the different routes of administration (the 1 mg/mL single use vial includes intraocular use for inducing and maintaining mydriasis during intraocular surgery, whereas the 30 mL multi-use vial does not), the submission was administratively split into 2 NDAs: NDA 204-200 (epinephrine 1 mg/mL single use vial) and NDA 204-640 (epinephrine 1 mg/mL 30 mL multi-use vial). JHP declined to pay the user fee for NDA 204-640 making the application unacceptable for filing (unacceptable for filing letter issued September 20, 2012). NDA 204-200 for the 1 mg/mL single use vial was approved on December 7, 2012. On August 2, 2013, JHP submitted a letter to the Agency indicating that they have submitted the full payment of the appropriate user fees for NDA 204-640 and the application was filed 60 days after August 2, 2013 and given a standard review clock with a PDUFA user fee goal date of June 2, 2014. JHP also indicated that they will stop manufacturing the 30 mL multi-use vial product [the product is a marketed unapproved product] while awaiting FDA approval. Therefore, in order to avoid a potential drug shortage of this medically necessary product, the Division has worked with an internally accelerated timeline so that an earlier action can be taken.

There is no new clinical information submitted to support the 30 mL multi-use vial. The clinical support for the efficacy and safety of the product for anaphylaxis is based on literature references and the clinical experience of the use of epinephrine for anaphylaxis that dates over 100 years. The pertinent information to support the 30 mL multi-use vial is primarily CMC. This review briefly summarizes the salient aspects of the application and the Agency decision on approvability.

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 was first obtained from extracts of the adrenal glands which was purified in 1901 by Jokichi Takamine and called "adrenalin". The name Adrenalin was trademarked by Parke, Davis & Co who marketed the product from 1901, until ownership was transferred to Parkedale Pharmaceuticals, Inc (a wholly owned subsidiary of King Pharmaceuticals, Inc,) in 1998. In 2007, ownership of Adrenalin was transferred to JHP.

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.

Due to its agonistic effects on non-selective alpha and beta-adrenergic receptors, epinephrine is the drug of choice for emergency treatment of allergic reactions (Type I) including anaphylaxis. Anaphylaxis affects the respiratory and cardiovascular systems and mucous membranes leading to a variety of signs and symptoms including bronchospasm, laryngospasm, hypotension, urticaria, pruritus, angioedema, vomiting, diarrhea, and abdominal cramps. Anaphylaxis is a serious and life threatening condition which can lead to death in minutes if not recognized and adequately treated.

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.

Until the approval of epinephrine 1 mg/mL solution in vials for injection (JHP pharmaceuticals) all epinephrine solution in vial products were marketed unapproved. The Agency's Office of Compliance has been working to bring marketed unapproved drugs in compliance with the Agency's regulations for approved products, and issued a Compliance Policy Guide for Marketed Unapproved Drugs in 2006. JHP pharmaceuticals' NDA submission for epinephrine 30 mL multi-use vial is in compliance with this process.

3. Chemistry Manufacturing and Controls

The drug substance epinephrine is a white, odorless, microcrystalline powder or granules that are sparingly soluble in water. Epinephrine is soluble in mineral acids and alkali hydroxide solutions. It is a sympathomimetic catecholamine with a molecular weight of 183.2. The drug product Adrenalin® (epinephrine injection USP) is a sterile aqueous solution for injection containing 1 mg/mL (1:1000) of epinephrine in a 30 mL multi-use glass vial with a rubber stopper. Each 1 mL solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, 5.4 mg of chlorobutanol (preservative), hydrochloric acid to adjust pH (pH range (b) (4)), and water for injection. There are no outstanding drug substance or drug product issues. However, there are no leachable data for the rubber stopper – information that was also missing for the single use vial product. The absence of this information is not an approvability issue and JHP will be asked to provide this information as a post-marketing commitment (see section 13 "Postmarketing Commitments").

There are no outstanding DMF issues. The drug substance is manufactured at (b) (4). The Office of Compliance issued an overall recommendation of Acceptable for the application on (b) (4). Of note, this site received a warning

letter in [redacted] however the issues noted were not directly related to epinephrine and the site has responded to the warning and is scheduled for a follow up inspection in [redacted]. Though the site will remain under an OAI status until the follow up inspection, the establishment was given acceptable recommendation on [redacted] under discretion for this NDA by the Division of International Drug Quality due to 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 microbiology attributes of the product are adequate. The product is manufactured according to a standard manufacturing process (i.e. [redacted]). The submitted data support an expiry of 14 months when stored at storage conditions of 25^0C/60% RH.

During the review cycle, for the 1 mg/1 mL single use vial presentation, there were several interactions with the sponsor to address specification limits for impurities in the drug product. Epinephrine is degraded by exposure to light or air. Metabisulfite in the formulation reduces the rate of oxidation of epinephrine. [redacted]

The agreed upon specifications for impurities for the 1 mg/1 mL single use vial product are shown in this table which was taken from the CMC reviewer Dr Ying Wang's CMC review amendment to NDA 204-200 dated November 15, 2012:

Table 1. Recommended Acceptance Criteria for the Drug Product (1 mL)

Test	Acceptance Criteria at Stability
[redacted]	

For the 30 mL multi-use vial product, the proposed specifications are similar with the exception of a slight increase in the limit for [redacted] which is acceptable.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies were not necessary to support approval of this application. The levels of chlorobutanol preservative in the formulation is supported by the known safety of chlorobutanol as a preservative and its listing in the FDA list of inactive ingredients located at http://www.accessdata.fda.gov/scripts/cder/IIG/index.cfm.

5. Clinical Pharmacology/Biopharmaceutics

The applicant did not conduct any clinical pharmacology studies to support the application. JHP requested a bioavailability/bioequivalence (BA/BE) waiver for the intramuscular and subcutaneous routes of administration and provided a quantitative and qualitative comparison

of their proposed product to the reference product EpiPen® auto-injector. The Biopharmaceutics team granted the applicant's request for a waiver from conducting an *in vivo* bioequivalence study for Adrenalin®, and I concur with granting the waiver. The proposed product Adrenalin® is a parenteral solution containing the same active ingredient epinephrine as the EpiPen® auto-injector. Although Adrenalin 30 mL multi-use vial contains the inactive ingredient chlorobutanol (not present in EpiPen), I concur with the biopharmaceutics team that a biowaiver is appropriate for a number of reasons. First, there are no concerns that the presence of chlorobutanol affects the pharmacokinetics or safety or efficacy of active ingredients as chlorobutanol is used widely as a preservative in many injectable products. Secondly, 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 of epinephrine. In addition, there is a lot of variation in the pharmacokinetic profiles for epinephrine when given by regular IM injection or auto-injection (SC/IM), as well as high individual to individual variation within the same product. Therefore any potential effect of chlorobutanol on systemic absorption will very likely be within the variability normally seen with SC and IM injections of epinephrine.

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.

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.

The drug product contains sodium bisulfite, which may cause mild to severe allergic reactions including anaphylaxis or asthmatic episodes in susceptible individuals. However, the presence of bisulfite in this product should not preclude its use for the treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive, as the alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

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 NDA for the 1 mg/mL single use vial (NDA 204-200) was discussed at the Pediatric Review Committee (PeRC) on June 12, 2012. The support for use of the proposed product in children comes from the clinical experience with the product and the published literature.

Based on the extensive use in all age groups including neonates the PeRC agreed that the pediatric assessment for this drug is considered fulfilled in all age groups and no clinical studies are required. This assessment is also applicable to the 30 mL multi-use vial.

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 Adrenalin® was reviewed by the DMEPA and found to be acceptable.

Physician labeling
The label has been worked out with the applicant and the label was reviewed by the standard review groups (SEALD, OSE, DRISK, and DMEPA) and by DTOP. Since the 2 presentations of epinephrine is presented in one label and only the 1 mL single use vial is approved for intraocular use, we involved DTOP in the labeling review to ensure the adequacy of the label to ensure that healthcare providers are aware that the 30 mL multi-use vial is not for intraocular use (because it contains the preservative chlorobutanol).

Carton and Immediate Container Labels
The carton and container labels have been reviewed and agreed upon with the applicant.

Patient Labeling and Medication Guide
There is no separate patient labeling and medication guide for this product. This product is intended for administration to patients by healthcare providers. The product is not for patient self-administration.

13. Action and Risk Benefit Assessment

Regulatory action
The recommended regulatory action for the application is approval for the indication of emergency treatment of allergic reactions (Type I) including anaphylaxis.

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
Given the extensive use of epinephrine for this indication and the well known adverse reactions, post-marketing risk evaluation and management strategies are not recommended for this product.

Postmarketing Study Commitments/Requirements

The applicant has agreed to the following postmarketing CMC commitment:

1. Leachable study for the container closure system. In their agreement the Applicant will do the following:
    - Develop and validate analytical method(s) if applicable for leachable testing
    - Update ongoing stability program and protocols to reflect leachable testing
    - Test retained samples at or near end of shelf life for leachables
    - Revise drug product specification to include leachable testing if necessary

The timetable JHP submitted on December 16, 2013, states that they will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Interim Report Submission: Develop and validate analytical methods	April 2014
Interim Report Submission: Update stability program and protocols to reflect Leachable testing:	June 2014
Final Report Submission:	December 2014

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
12/18/2013