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RESEARCH**

APPLICATION NUMBER:

204200Orig1s000

204200Orig2s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

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| Date | November 29, 2012 |
| From | Theresa M. Michele, MD |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | NDA 204-200, Original #1 |
| Supplement# | |
| Applicant | JHP Pharmaceuticals, LLC |
| Date of Submission | March 7, 2012 |
| PDUFA Goal Date | January 7, 2013 |
| Proprietary Name / Established (USAN) names | Adrenalin (epinephrine injection, USP) |
| Dosage forms / Strength | Solution containing 1 mg/ml, 1 mL dose in 3 mL vial |
| Indication | Emergency treatment of severe acute anaphylactic reactions [REDACTED] (b) (4) |
| Recommended: | Approval |

1. Introduction

JHP Pharmaceuticals (JHP) submitted this original 505(b)(2) new drug application (NDA 204-200) for epinephrine injection 1 mg/ml [trade name Adrenalin] on March 7, 2012 for two indications: 1) emergency treatment of severe acute anaphylactic reactions [REDACTED] (b) (4) and 2) induction and maintenance of mydriasis during intraocular surgery. The NDA refers to the literature and 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. This review focuses on the anaphylaxis indication only. The mydriasis indication is reviewed separately by the Division of Transplantation and Ophthalmology Products (DTOP); for further details see CDTL review by Dr. William Boyd dated September 6, 2012.

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, is currently a marketed unapproved drug.

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 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 January 7, 2013, with a standard 10-month review clock. DTOP gave the mydriasis indication a priority review because this would be a new indication; however, the date was extended by 3 months due to a major chemistry amendment, giving a PDUFA date of December 7, 2012. In order to provide for a single, integrated product label, DPARP plans to take an early action by the same date.

2. Background

2.1. 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 reaction 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).

2.2. Related drugs

Epinephrine is the drug of choice for treatment of anaphylaxis¹, 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 0.3 mg or pediatric dose of 0.15 mg 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.

No single ingredient epinephrine products for injection are currently approved on the US market, although a number of marketed, unapproved products exist. Products listed in the National Drug Code (NDC) Directory include those marketed by American Regent, Amphastar Pharmaceuticals, General Injectables and Vaccines, and McKesson Packaging

¹ Sampson HA, Muñoz-Furlong A, Campbell RL, et al. J Allergy Clin Immunol 117:391-7, 2006.

Services, all at a concentration of 1 mg/mL (1:1000). Amphastar also markets a 0.1 mg/mL (1:10,000) solution.

Currently, JHP markets 3 different presentations of Adrenalin in the following presentations:

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

The first two presentations differ in formulation, with the 3 mL vial containing 1 mL of 1 mg/mL sodium metabisulfite as an antioxidant, and the 30 mL vial containing 1.5 mg/mL sodium metabisulfite as an antioxidant and (b) (4)

the current proposal from the sponsor is for only the 3 mL vial (1 mL dose). The sponsor is not proposing a marketing application for the non-sterile nasal solution at this time.

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 condition epinephrine is being used to treat, there are no contraindications. Adverse reactions include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties.

2.2. Regulatory history

Adrenalin® is currently marketed for the following indications:

1. Severe acute anaphylactic reactions, urticaria, angioedema
2. Prolongation of local anesthetic action
3. Hemostasis (including topical application), nosebleeds
4. Acute asthma exacerbations, severe bronchospasm in chronic bronchitis, emphysema and other obstructive pulmonary disease
5. Advanced cardiovascular life support (ACLS) during cardiopulmonary resuscitation (CPR)
6. Nasal decongestion and nasal preparation prior to flexible laryngoscopy or sinus surgery.

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 of an NDA for the Adrenalin products. Accordingly, a Pre-IND meeting was held with JHP on July 5, 2011. In the meeting with the Division of Pulmonary, Allergy, and Rheumatology Products, JHP proposed indications for anaphylaxis. (b) (4)

(b) (4) FDA agreed that it was reasonable to rely on the literature and reference EpiPen for an anaphylaxis indication. (b) (4)

(b) (4) It was also noted that the literature would be sufficient for a mydriasis claim. (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 are being reviewed by different review divisions (DPARP and DTOP). (b) (4)

DTOP gave the mydriasis indication a priority review because no approved agents are currently on the market and marketed, unapproved epinephrine products do not contain information pertinent to this indication in their labels. The initial PDUFA date for this indication was September 7, 2012; however, the goal date was extended 3 months to December 7, 2012 due to a major chemistry amendment received within 3 months of the goal date.

3. CMC

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 a nearly white microcrystalline powder or granules, which gradually darken on exposure to light and air. (b) (4)

The chemical structure of epinephrine is shown in Figure 1.

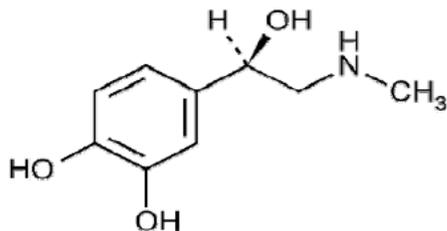


Figure 1: Chemical structure of epinephrine

The drug product (epinephrine injection, USP, 1:1000) is a sterile, injectable solution and is packaged as 1 mL of solution in 3 mL (b) (4) vials. The drug product contains sodium metabisulfite as an antioxidant at a level of 1.0 mg/mL (b) (4). The label contains a warning regarding allergic reactions including anaphylaxis in sulfite-sensitive individuals. This warning does not rise to the level of a contraindication due to the benefits of epinephrine and lack of suitable alternatives for the treatment of anaphylaxis.

The major drug product degradants (b) (4) (b) (4) The initial specifications proposed by the sponsor allowed up to (b) (4) of these impurities (b) (4)

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

The concern regarding high levels of degradants was communicated to the sponsor in a teleconference on June 21, 2012, in a written information request dated June 13, 2012, and in the 74-day filing letter dated May 4, 2012. CMC reviewers Ying Wang, PhD and Xiaobin Shen, PhD in their review dated August 14, 2012 recommended a complete response for this application due to high levels of impurities and inadequate analytical methods to measure these impurities. Subsequent to this review, the applicant submitted a major chemistry amendment dealing with these deficiencies and evaluating impurity levels across multiple batches, which were also independently tested by FDA laboratories. Based on this amendment, the clock for the mydriasis indication in DTOP was extended by 3 months.

After much discussion with the ONDQA team at FDA, the sponsor agreed to revised specifications for drug product impurities along with a PMC to further investigate and minimize the causes for high levels (b) (4). Based on this PMC, the acceptance criteria will be revised further in a post-marketing setting. The final agreed upon specifications are shown in Table 1.

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

| Test | Acceptance Criteria at Stability |
|---------|----------------------------------|
| (b) (4) | |

4. Nonclinical Pharmacology/Toxicology

Given the long history of clinical use of epinephrine, the sponsor relied on literature and the RLD EpiPen to support the non-clinical toxicology of epinephrine. To qualify the impurity (b) (4) the sponsor completed two 14 day IV toxicology studies in Sprague-Daly rats. In addition, an *in vitro* bacterial reverse mutation assay and an *in vitro* chromosome aberration test were performed.

Based on these data, the toxicology team determined that the proposed levels for the impurity (b) (4) are not supported by adequate safety margins (b) (4)

The label will reflect mutagenic potential, although this issue is of less clinical concern in a product not intended for chronic use.

See review by Dr. Jane Sohn dated June 1, 2012 for complete details.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor did not submit any clinical pharmacology trials. JHP requested a waiver of in vivo bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is administered as an injection solution (b) (4)

Therefore, the biopharmaceutics team initially recommended that a waiver not be granted. Subsequently, due to resolution of CMC issues regarding impurities (b) (4)

the biopharmaceutics team recommended granting a waiver from conducting an in vivo bioequivalence study for the Adrenalin IM and SC routes for the following reasons:

1. Adrenalin® is a parenteral solution intended solely for administration by injection.

2. Adrenalin® contains the same active and inactive ingredients in the same concentration as the RLD, EpiPen® Auto-Injector.
3. Data from a published study (Simons et al., 2001) indicate that mean plasma epinephrine concentrations versus time profiles following 0.3-mg (0.3-mL) dose of epinephrine administered intramuscularly by the EpiPen® Auto-Injector or by a needle injection are similar. Epinephrine solution also has a long documented history of use through the intramuscular and subcutaneous routes in emergency anaphylactic situations.
4. The proposed formulation of Adrenalin® is comparable to the epinephrine formulations investigated in the above mentioned published study.
5. Additionally, the clinical review team finds the safety and efficacy of the final labeled dosing of Adrenalin through the intramuscular and subcutaneous routes acceptable in a medical setting.

There is an extensive literature base to support the pharmacology of epinephrine and discussions may be found in many pharmacology textbooks. Epinephrine is a naturally-occurring hormone that is secreted by the adrenal medulla in response to stress. It acts on both alpha and beta-adrenergic receptors as a non-selective agonist. Due to its non-selective activity, the pharmacodynamic actions of epinephrine are complex. They include vasoconstriction leading to increased vascular resistance, increased blood pressure, and decreased airway mucosal edema mediated by α_1 receptors; inhibition of insulin secretion mediated by α_2 receptors; increased myocardial contractility, increased heart rate, and coronary vasodilation mediated by β_1 receptors; and decreased mast cell mediator release, bronchodilation, and release of glucose from the liver mediated by β_2 receptors. Many of these effects are beneficial in anaphylaxis (b) (4)

Epinephrine is rapidly metabolized and has a brief duration of action (3-5 minutes) when given SC or IM. It cannot be given orally, as it is rapidly metabolized by catechol-o-methyltransferase and monoamine oxidase in the wall of the gastrointestinal tract and by monoamine oxidase in the liver, with extensive first pass metabolism. Pharmacokinetics are linear.

See the reviews by Dr. Sheetal Agarwal dated August 17, 2012 and November 8, 2012 and the review by Dr. Kareen Riviere dated November 13, 2012 for complete details.

5.1. Drug-drug interactions

A number of drug-drug interactions are listed in the product labels of currently approved epinephrine products. These include:

- Concomitant use with cardiac glycosides, diuretics, or anti-arrhythmics may potentiate development of cardiac arrhythmias
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripeleminamine, and diphenhydramine, may have potential effects.

- Beta- adrenergic blocking drugs, such as propranolol, antagonize the cardiostimulating and bronchodilating effects.
- Alpha- adrenergic blocking drugs, such as phentolamine, antagonize the vasoconstricting and hypertensive effects.
- Ergot alkaloids may reverse the pressor effects of epinephrine.

The sponsor has also proposed inclusion of the following drug-drug interactions, which are supported by the literature:

- Other sympathomimetic agents may have additive effects.
- Coadministration with hydrocarbon general anesthetics, such as halothane, may cause arrhythmias.
- Epinephrine should not be used 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

5.3. Intrinsic factors and special populations

Dose adjustment in patients with renal impairment is not necessary. Reported clinical experience suggests that geriatric patients may be more sensitive to the systemic effects of epinephrine. The clinical reviewer found no evidence of increased sensitivity to epinephrine for the pediatric population.

5.5. QT assessment

Given the long clinical history of use, a QT assessment was not performed for this NDA.

6. Clinical Microbiology

The drug product is sterilized (b) (4)
(b) (4) Controls for monitoring (b) (4)
were deemed to be adequate. 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 August 7, 2012.

7. Clinical/Statistical–Efficacy

Clinical trials were not performed for this application. The sponsor is relying on the literature and reference to the RLD, EpiPen. Of note, clinical trials for safety and efficacy were also not performed for approval of EpiPen, relying on the literature and 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 this literature, all major

guidelines for the treatment of anaphylaxis recommend epinephrine as first-line therapy for the treatment of anaphylaxis².

As noted by Dr. Starke in his clinical review, the DESI process also indirectly supports the efficacy of epinephrine for the treatment of anaphylaxis. Although epinephrine pre-dates the DESI process, first generation antihistamines, which were reviewed under DESI, were given an indication for “adjunctive treatments to epinephrine for the treatment of anaphylaxis,” implying that epinephrine is also effective for this indication.

7.1. Dose selection

7.1.1. Route of administration

The applicant has proposed dosing for anaphylaxis via (b) (4) routes: subcutaneous (SC), intramuscular (IM) (b) (4)

Dosing via the SC and IM routes are consistent with approved dosing for the RLD, Epi-Pen. Absorption via the SC route is more variable and may be slower. As such, the recommended route of administration for use by medical providers is IM³, but the SC route also has a long clinical history of successful use. For self administration, slower onset with more prolonged activity may be beneficial in order to allow medical help to arrive, and needle length may preclude IM administration depending on body habitus. Thus, both the SC and IM routes of administration are supported.

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. Injection into the buttock is not recommended because there have been reports of gas gangrene infections with *Clostridium perfringens* after dosing into this area, possibly secondary to stool contamination of this area and potential for anaerobic conditions created by epinephrine-induced vasoconstriction. Administration into small areas such as the digits has the potential to cause necrosis due to local vasoconstriction. Warnings regarding route of administration (buttocks, digits) will be included in the product label.

(b) (4)

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.

Kemp SF, Lockey RF, et al., 2008. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy.* 63(8): 1061-1070.

Sampson HA, Muñoz-Furlong A, et al., 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 117(2): 391-397.

³ 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.



7.1.2. Dose and dosing frequency

The sponsor proposes weight-based dosing as follows:

- Adults and Children ≥ 30 kg (66 lbs): 0.3 to 0.5 mg (0.3 to 0.5 mL) IM (or SC) into anterolateral thigh every 5 to 10 minutes as necessary.
- Children 30 kg (66 lbs) or less: 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), IM (or SC) into anterolateral thigh every 5 to 10 minutes as necessary.

Given the linear pharmacokinetics of epinephrine, weight-based dosing is reasonable and is consistent with the latest anaphylaxis guidelines.³ The recommended upper bound of 0.5 mg for adults and 0.3 mg for children (age not defined) is primarily based on the side effects and adverse reactions (particularly cardiac and nervous system), which become more difficult to tolerate and/or potentially more serious at higher doses. This dose is higher than that approved for the RLD and other epinephrine auto-injectors, which are limited by potential side effects in an unmonitored non-medical setting.

Given the short half-life, the instruction for repeated dosing every 5-10 minutes as needed is appropriate. The number of doses is based on clinical effect. Unlike epinephrine auto-injectors, which are limited to 2 doses, there is no upper limit for the number of doses. For the purposes of calculating toxicology safety margins in the product label, the clinical team recommends 3 doses, which is somewhat arbitrary, but has literature support from case series suggesting that the majority of patients receive either 1 or 2 doses.⁴

⁴ Rudders SA, Banerji A, et al., 2010. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. *Pediatrics*. 125(4): e711-718.

Manivannan V, Campbell RL, et al., 2009. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Ann Allergy Asthma Immunol*. 103(5): 395-400.

7.2. Anaphylaxis

No randomized placebo or active controlled clinical trials have been conducted to support the safety and efficacy of Adrenalin® in anaphylaxis.

One prospective, uncontrolled trial⁵ evaluated a protocol for the treatment of sting anaphylaxis using a controlled infusion of intravenous (IV) epinephrine (1 mL diluted in 100 mL of IV fluids to a concentration of 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 two 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.

Case series of fatal anaphylaxis suggest that death occurs most frequently among patients for whom epinephrine is not given promptly after onset of symptoms. In most cases, this appears to result because patients did not have access to epinephrine for self-administration or used it incorrectly rather than lack of epinephrine use in a health-care setting.⁶

8. Safety

Adrenalin is a marketed unapproved product. Since October 1, 2007, when JHP acquired the license for Adrenalin from King Pharmaceuticals, the applicant states that sales figures suggest that there have been approximately (b) (4) 1 ml doses sold in the United States and Canada. The most common adverse event reports per the sponsor's post-marketing database include stress cardiomyopathy, tachycardia, ventricular tachycardia, myocardial ischemia, coronary vasospasm, cardiac arrest, increased blood pressure, hypotension, and chest pain. Adverse reactions related to site of administration include gas gangrene when injected into the buttocks and digital necrosis when injected into the fingers.

Based on the literature, common adverse reactions associated with epinephrine are pallor, tremor, anxiety, palpitations, dizziness, and headache. More serious adverse effects include arrhythmias (including fatal ventricular fibrillation), cerebral hemorrhage related to rapid

⁵ Brown SGA, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J.* 2004;21:149-154.

⁶ Pumphrey RSH, 2000. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy.* 30(8): 1144-1150.

Pumphrey RSH and Gowland MH, 2007. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol.* 119(4): 1018-1019.

Sampson HA, Mendelson L, et al., 1992. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med.* 327(6): 380-384.

Bock SA, Muñoz-Furlong A, et al., 2007. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol.* 119(4): 1016-1018.

elevations in blood pressure, angina, and myocardial infarction. Adverse effects may be more common in patients with a cardiac history, pregnant women, and the elderly. (b) (4)

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

10. Pediatrics

This application will trigger PREA for the anaphylaxis indication because of the proposed new (b) (4) dosing regimen. Since only one clinical trial is available from the literature to support the anaphylaxis indication, the supports for all ages come from pharmacologic and physiologic experiments in animals and in humans, as well as over 110 years of clinical experience with the drug for a variety of indications in all age groups. The underlying disease process and the pharmacologic and physiologic effects of the drug are considered the same for all age groups.

Several pharmacokinetic and pharmacodynamic studies have been conducted evaluating dosing, PK, and PD effects of epinephrine in children⁷. (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. The application was discussed at the Pediatric Review Committee (PeRC) meeting on June 12, 2012. 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, the PeRC agreed with the Division that the pediatric assessment for this drug is considered to have been fulfilled in all age groups.

11. Other Relevant Regulatory Issues

11.1. Ethics and data integrity

No clinical trials were submitted as part of this NDA. As such financial disclosure does not apply. No Division of Scientific Investigation (DSI) audits were requested or performed.

⁷ Fisher DG, Schwartz PH, et al., 1993. Pharmacokinetics of exogenous epinephrine in critically ill children. Crit Care Med. 21(1): 111-117.

Simons FER, Gu X, et al., 2002. EpiPen Jr. versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. J Allergy Clin Immunol. 109(1): 171-175.

Simons FER, Roberts JR, et al., 1998. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 101(1 Pt 1): 33-37.

11.2. Proprietary name review

The Division of Medication Error Prevention and Analysis (DMEPA) to conducted a review of the proposed proprietary name, Adrenalin, under which this product has been marketed for over 100 years. Per the review dated July 17, 2012, there are no objections to the proposed trade name.

12. Labeling

JHP submitted a label in the Physician's Labeling Rule (PLR) format that contains information based on the unapproved label for epinephrine with indications not submitted in this application removed. To create a single label for the product containing information on both submitted indications (mydriasis and anaphylaxis), DPARP worked with DTOP on labeling. The label was reviewed by appropriate disciplines of both Divisions in addition to consults by the Office of Prescription Drug Promotion (OPDP) and the Division of Medication Error Prevention and Analysis (DMEPA). Because much of the information provided in the sponsor's label was outdated, extensive revisions were undertaken to provide more streamlined up to date information. The final label is consistent with labeling for the currently approved epinephrine auto-injector products (including the most recently approved, Auvi-Q), taking into account the additional indication of mydriasis and differences between this product and products intended for self-administration by the patient.



As of the date of this review, the sponsor has accepted all of the FDA proposed changes to the label, and the label is in the process of final editing.

13. Recommendations/Risk Benefit Assessment

13.1. 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 [redacted] (b) (4) [redacted] which may result from allergic reactions to insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis."

13.2. Risk benefit assessment

Epinephrine is the treatment of choice for anaphylaxis and has been demonstrated to be immediately life-saving, with over 110 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. Likewise, the risk of allergy in patients allergic to sulfites should not preclude use for treatment of anaphylaxis. The risk/benefit assessment is similar for all age groups, although it is noted that elderly patients, patients with a cardiac history, and pregnant women may be more sensitive to effects of epinephrine.

13.3. Recommendation for Postmarketing Risk Evaluation and Management Strategies

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

13.4. Recommendation for other Postmarketing Requirements and Commitments

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

- *The sponsor will investigate [REDACTED] (b) (4) and will take necessary measures to minimize this impurity. The sponsor commits to provide an interim report by April 1, 2013 summarizing the following:*
 - *Technical work conducted*
 - *Evaluation of potential formulation/process improvements*
 - *Recommended development plan forward*

Following the submission of this report, the sponsor will contact the Agency to seek further guidance and agreement on the data requirements to support proposed manufacturing and specification change(s).

13.5. Recommended comments to applicant

There are no additional comments to the applicant.

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/s/

THERESA M MICHELE
11/29/2012

Cross-Discipline Team Leader Review NDA 204200, Original - 2

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|--|---|
| Date | September 6, 2012 |
| From | William M. Boyd, M.D. |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 204200 |
| Supplement# | |
| Applicant | JHP Pharmaceuticals, LLC |
| Date of Submission | March 7, 2012 |
| PDUFA Goal Date | September 7, 2012 |
| | |
| Proprietary Name / Established (USAN) names | Adrenalin (epinephrine injection, USP) 1 mg/mL |
| Dosage forms / Strength | Solution containing 1 mg/mL |
| Proposed Indication(s) | Induction and maintenance of mydriasis during intraocular surgery |
| Recommended: | Recommended for Approval |

1. Introduction

Adrenaline (epinephrine injection, USP) has been available on the market for over 100 years. The product has been continuously marketed under the Adrenalin trademark by Parke-Davis, King Pharmaceuticals, and JHP Pharmaceuticals. In addition to the emergency treatment of severe allergic reactions, epinephrine injection has been accepted in the medical community for a variety of uses, including resuscitation from cardiac arrest, hemostasis, and for maintaining mydriasis during cataract surgery.

The treatment for cataract is removal of the opacified crystalline lens and replacement with an artificial intraocular lens (IOL). The most commonly performed surgical procedure first breaks up and emulsifies the opacified lens using an instrument containing a small ultrasonic probe (phacoemulsification), and the emulsified material is suctioned out with simultaneous irrigation, using the same instrument. Regardless of the surgical technique used, the pupil must be well dilated (mydriasis) throughout the procedure to allow the surgeon to see clearly into the eye. Pre-operative eye drops are used to induce mydriasis prior to surgery but are not always sufficient to maintain it.

The addition of epinephrine to the irrigation fluid used to extract the emulsified lens (or injection of epinephrine directly above the iris at the start of the surgery) has been commonly used to induce and maintain mydriasis for the duration of the surgery.

Epinephrine containing sodium bisulfite has been associated with corneal endothelial damage when used at undiluted concentrations (1 mg/mL).

This is a 505(b)(2) application which lists EpiPen, held by Meridian, as the reference listed drug.

2. Background

A Pre-Investigational New Drug Application (PIND) file was opened on March 11, 2011, for this product (PIND 111712).

The FDA granted a pre-IND meeting request on March 24, 2011. JHP provided the background materials for the meeting held on June 3, 2011, and requested a teleconference in lieu of a face-to-face meeting.

The New Drug Application for Adrenalin (epinephrine injection, USP) 1 mg/mL submitted March 7, 2012, contained two proposed indications:

- Original 1- Emergency treatment of severe acute anaphylactic reactions (b) (4)
- Original 2- Induction of mydriasis during cataract surgery.

As the two indications sought in the original submission are reviewed by separate review Divisions¹, this NDA was administratively split into two originals as described above. The mydriasis indication received a priority review designation (six month review clock); there are no approved drug products for the induction and maintenance of mydriasis during cataract surgery that can be given after an incision is made into the cornea.

The product is currently marketed by JHP in two different marketing configurations, a 1 mL single use vial and a 30 mL multiuse vial. The formulation of these two configurations is different (b) (4)

3. Product Quality

DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Adrenalin
- b) Non-Proprietary Name: Epinephrine
- c) Code Name/# (ONDQA only): N/A

¹ Original 1 – managed by Division of Pulmonary, Allergy and Rheumatology Drug Products (DPARP)
Original 2 – managed by Division of Transplant and Ophthalmology Products (DTOP)

d) Chem. Type/Submission Priority
 Chem. Type: 5

PHARMACOLOGIC CATEGORY: Sympathomimetic catecholamine

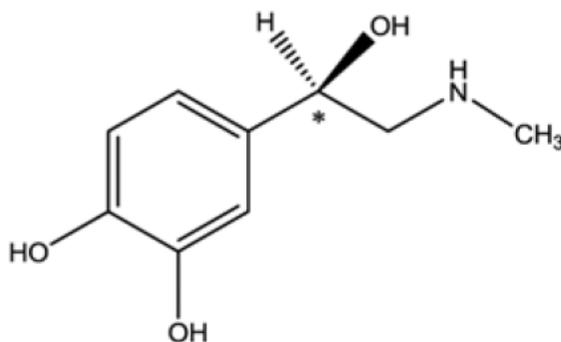
DOSAGE FORM: Injection (solution containing 1 mg/mL)

STRENGTH/POTENCY: 1 mg/mL

ROUTE OF ADMINISTRATION: Intraocular

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R) (USP)
 (-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol (CAS)
 R-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (BP)



Molecular Formula

C₉H₁₃NO₃

Relative Molecular Mass

183.20

Formulation (b) (4)

| Ingredient | Grade | Function | Batch Quantity | Unit Formula |
|---------------------------|-------|-------------------|----------------|--------------|
| Epinephrine | USP | Active | (b) (4) | (b) (4) |
| Sodium Chloride | USP | Tonicity adjustor | | 9.0 mg |
| Sodium Metabisulfite | NF | Antioxidant | | 1.0 mg |
| (b) (4) Hydrochloric Acid | USP | (b) (4) | | (b) (4) |
| Water for Injection | USP | (b) (4) | | (b) (4) |

Drug Product Specifications:

| Test | Specification 1 mL Release | Specification 1 mL Stability (b) (4) |
|----------------------------------|-------------------------------|---|
| Description | (b) (4) | |
| Assay | | |
| (b) (4) | | |
| Individual Unidentified Impurity | | |
| Total Impurities | | |
| Identification | | |
| pH | | |
| Sodium Bisulfite | | |
| Total Acidity | | |
| Color & Clarity | | |
| Sterility | | |
| Particulate Matter | | |
| Bacterial Endotoxin | | |

Reviewer's Comments: *In this reviewer's opinion, the proposed specifications are acceptable. Due to the small volume and expected dilution prior to use, it is unlikely that the current specifications will lead to any ocular harm* (b) (4)

A teleconference was held with representatives from ONDQA, DTOP, and JHP on Friday, August 31, 2012. ONDQA requested (b) (4) *in the preceding table. See ONDQA proposed specification table below:*

| ONDQA Recommended Acceptance Criteria for the Drug Product (1 mL) | |
|---|----------------------------------|
| Test | Acceptance Criteria at Stability |
| (b) (4) | |

Based on that conversation, JHP re-submitted specifications on September 5, 2012. In this reviewer's opinion, these specifications from JHP found below are acceptable.

Table 3. Adrenalin 1 mg/mL Proposed Stability Specifications

| Impurity | Acceptance Criteria at Stability |
|----------|----------------------------------|
| (b) (4) | |

As of the date of this review, the ONDQA reviewer recommends a Complete Response (b) (4) (see table titled "ONDQA Recommended Acceptance Criteria for the Drug Product (1 mL)" above).

4. Nonclinical Pharmacology/Toxicology

From the original Division of Transplant and Ophthalmology Products Pharmacology/Toxicology Review dated 8/17/2012:

The nonclinical safety assessment of Adrenalin for ocular use relied on reports obtained from the literature. All of the effects seen in animals were due to the expected pharmacologic and supra-pharmacologic actions of epinephrine. No unexpected nonclinical effects of epinephrine have been reported. Ocular studies with commercially available epinephrine formulations have shown adverse effects on the cornea, including increased corneal thickness, increased corneal epithelial cell density and morphological changes. Published nonclinical studies have shown that these effects are due to a combination of the dose of sodium sulfite (antioxidant in the formulation) to the eyes and the low pH of buffered epinephrine formulations. However, this

will not be an issue in the ocular use of Adrenalin since the 1:1,000 formulation will be diluted by at least 100-fold before use and the concentration of Na sulfite after dilution will not cause significant effects on cornea. The use of Adrenalin for the induction of mydriasis during cataract surgery, as described in the labeling, is recommended from the nonclinical perspective.

Subcutaneous administration of epinephrine to rabbits at a dose of 1.2 mg/kg/day (~19,000-fold the human highest intraocular dose) on gestational days 3 to 9 produced an increased incidence of arrested fetal development and structural teratogenicity (gastroschisis). Subcutaneous administration of epinephrine to mice at a dose of 1 mg/kg/day (~4,000-fold the human highest intraocular daily dose) on gestational days 6 to 15 produced delayed skeletal ossification. These effects were not observed in mice at a dose of 0.5 mg/kg/day (2,000-fold the human highest intraocular daily dose). Subcutaneous administration of epinephrine to hamsters at a dose of 0.5 mg/kg/day (~3,000-fold the highest intraocular human dose) on gestational days 7 to 10 resulted in decreased litter size and delayed skeletal ossification. Behavioral effects were reported in the offspring of rats receiving subcutaneous administration of 0.4mg/kg epinephrine (~3,000-fold the human highest intraocular daily dose) on gestational days 7-12. (The above dose human dose multiples are based on an intraocular human dose of 1 µg / 50 kg individual).

Epinephrine has also been shown to affect fertility. Decreased implantation was shown in female rats administered epinephrine subcutaneously at 0.4mg/kg/day (~3,000-fold the human highest intraocular daily dose) on gestational days 1 to 6; female rabbits administered epinephrine subcutaneously at 1.2 mg/kg/day (~19,000- fold the human highest intraocular daily dose) on gestational days 3 to 9; and female hamsters administered epinephrine subcutaneously at 0.5mg/kg/day (3,000-fold the human highest intraocular daily dose) on gestational days 7 to 10.

The approval of Adrenalin for induction and maintenance of mydriasis during intraocular surgery is recommended.

A second, separate Pharmacology/Toxicology Review dated 6/1/2012 was completed by the Division of Pulmonary, Allergy and Rheumatology Drug Products (DPARP) regarding the indication for the treatment of anaphylaxis in adults and pediatric patients (all ages by the intramuscular (IM), subcutaneous (SC) (b) (4) routes).

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review:

Office of Clinical Pharmacology/Division of Clinical Pharmacology 4, has reviewed NDA 204200, Original-2, for Adrenalin® (epinephrine injection, USP) 1 mg/mL (b) (4) and finds the proposed drug product acceptable from a Clinical Pharmacology perspective.

This review relates only to the Original 2- Submission section for the ophthalmology indication. No Clinical Pharmacology studies were conducted by the sponsor in support of this 505 (b) (2) NDA. For the mydriasis indication, the NDA is a 505 (b) (2) NDA referencing EpiPen® (NDA 19430) for chemistry and nonclinical data as well as literature for studies related to its safety and efficacy. Refer to the clinical review by the medical officer, Dr. Wiley Chambers (DTOP), for a review of literature articles provided in support of safety, efficacy and dosing of the product as labeled.

From a Clinical Pharmacology perspective, no PK data is needed for the drug product for the mydriasis indication as the final drug concentration to be exposed to the ocular tissue is very low, and significant epinephrine absorption into the systemic circulation is not expected. Even if some systemic absorption of epinephrine takes place, it is not expected to raise any safety concerns from a clinical perspective as epinephrine is an endogenous molecule. In addition, the safety and efficacy of this product for the ocular indication is supported by clinical studies that will be reviewed by Dr. Wiley Chambers (DTOP).

6. Sterility Assurance

From the original drug substance Product Quality Microbiology Review:

Recommended for approval on the basis of product quality microbiology.

The drug product is a sterile aqueous 1 mg/ml solution packaged in (b) (4) glass vial. The product is sterilized (b) (4)

The manufacturing process for the drug product can be broken down into (b) (4) steps. (b) (4)

(b) (4) A batch of the 1 ml presentation of the product is approximately (b) (4) vials.

Table 2. Description of the drug product container closure system. From 3.2.P.7.

| Components Detail | Manufacturer | DMF # |
|-------------------|--------------|-------|
| (b) (4) | | |

Specifications state that the drug is sterile and the endotoxin limit is (b) (4) EU/ml. The pH range for the drug is 2.2-5.0.

The long-term, post-approval stability protocol includes holding at 25°C/60% RH and sampling for endotoxins and sterility at 0, 18, and 24 months. The applicant commits to pacing the first three batches in the long-term stability program, as well as adding one production batch to the program annually.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review:

The main support for efficacy is from the following publications:

| Study | Authors | Title | Doses Studied | Number of Patients |
|-------|------------------------------------|---|---|--|
| 1 | Liou and Chen, 2001 | Maintenance of Mydriasis with One Bolus of Epinephrine Injection During Phacoemulsification | 0.1 mL injection, 1:25,000; 1:50,000; 1:100,000; 1:200,000; 1:400,000 | 70 patients; Mean Age 69 (55-83); 10 control; 11 group 1; 13 group 2; 10 group 3; 14 group 4; 12 group 5 |
| 2 | Corbett and Richards, 1994 | Intraocular adrenaline maintains mydriasis during cataract surgery | 1:1,000,000 epinephrine in intraocular irrigation fluid | 70 patients; Mean Age 75 |
| 3 | Gimbel, 1988 | The Effect of Treatment with Topical Nonsteroidal Anti-inflammatory drugs with and without Intraoperative Epinephrine on the Maintenance of Mydriasis during Cataract Surgery | 1:1,666,667 epinephrine in intraocular fluid; 6 treatment groups; Ocufer plus epinephrine, Ocufer without epinephrine; Indocid plus epinephrine, Indocid without epinephrine; Placebo with epinephrine; Placebo without epinephrine | 216 patients randomly distributed between 6 groups (approx 36 per group) |
| 4 | Liou and Chen, 1998 | The Effect of Intracameral Adrenaline Infusion on Pupil Size, Pulse Rate, and Blood Pressure During Phacoemulsification | 1:1,000,000 epinephrine in intraocular irrigation fluid | 42 eyes (30 with 0.25 mL added to 250 mL BSS Plus), 12 control eyes (BSS Plus) |
| 5 | Backstrom and Behndig, 2006 | Redilation with intracameral mydriatics in phacoemulsification surgery | 1:1,666,667 epinephrine in intraocular fluid in epinephrine group. Additional 150 microliters of 1.5% in Intracameral mydriatic (ICM) group | 80 patients; Mean Age 76; 30 eyes epi+ ICM; 30 eyes epi + no-ICM; 10 eyes no-epi + ICM; 10 eyes no-epi + no-ICM. |
| 6 | Duffin, Pettit and Straatsma, 1983 | Maintenance of Mydriasis with Epinephrine During Cataract Surgery | 1:16,000 to 1:96,000 | 55 patients, Mean Age 72 (range 55 to 93) |

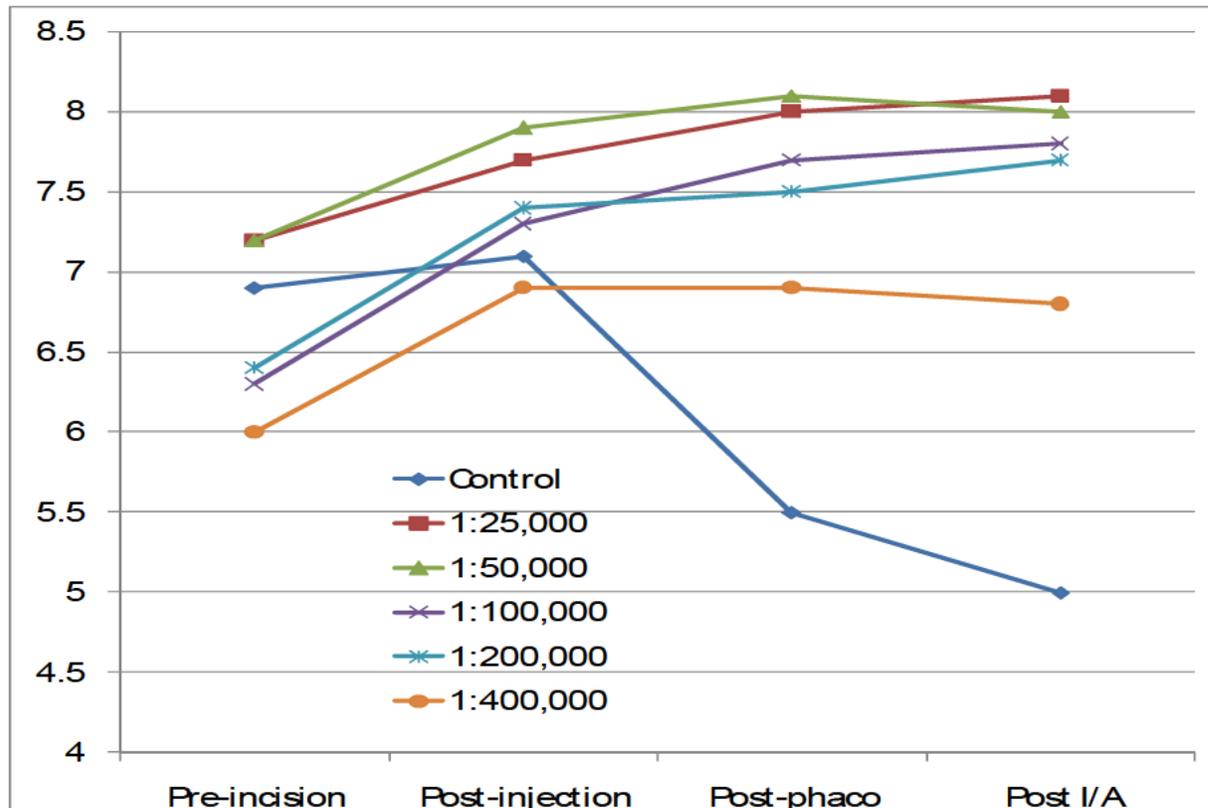
Analysis of Primary Endpoint(s)

Analysis of Primary Endpoint – Pupil Size

Published literature includes adequate and well controlled studies demonstrating the safety and efficacy of epinephrine when injected intracamerally or added to balanced salt solution during intraocular surgery.

Intracameral epinephrine has been widely used for decades. The company provided literature references of adequate and well controlled studies to support their position that epinephrine when added to an ophthalmic irrigating solution was safe and efficacious. While the company did not provide a systematic plan for reviewing the literature, independent searches have the literature have failed to provide any inconsistencies in the studies provided by the applicant. Representative studies have been included in this review. Studies 1-4 and 6 were included in the applicant's original submission. Study 5 was identified during additional Medline searches.

Study 1: Liou SW and Chen CC. Maintenance of Mydriasis with One Bolus of Epinephrine Injection During Phacoemulsification. *J Ocular Pharmacology*. 2001; 17:249-253.



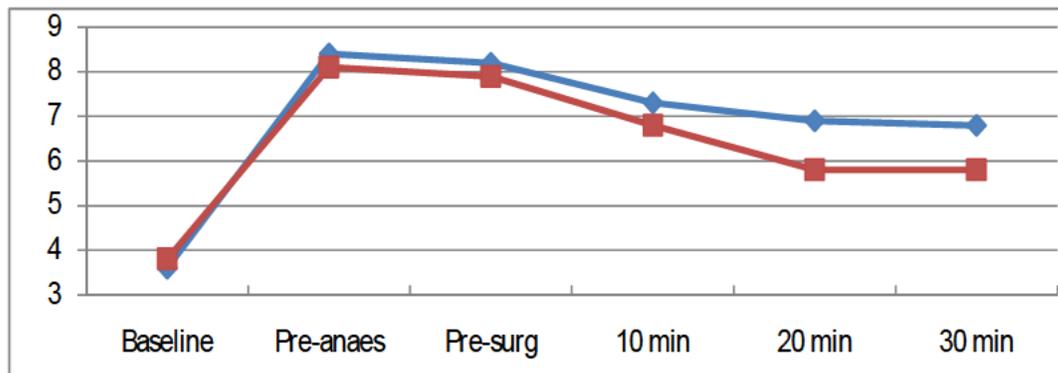
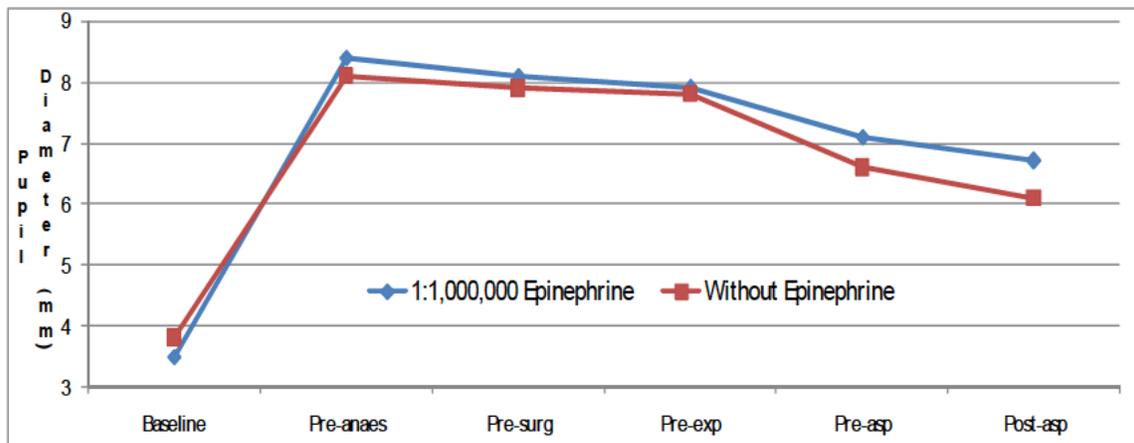
| | Pre-incision | Post-incision | Post-phaco | Post I/A |
|---------------|--------------|---------------|------------|----------|
| Control Group | 6.9 ± .5 | 7.1 ± .5 | 5.5 ± .4 | 5.0 ± .4 |
| 1:25,000 | 7.2 ± .5 | 7.7 ± .5 | 8.0 ± .6 | 8.1 ± .6 |
| 1:50,000 | 7.2 ± .6 | 7.9 ± .7 | 8.1 ± .8 | 8.0 ± .5 |
| 1:100,000 | 6.3 ± .4 | 7.3 ± .5 | 7.7 ± .7 | 7.8 ± .6 |
| 1:200,000 | 6.4 ± .5 | 7.4 ± .6 | 7.5 ± .7 | 7.7 ± .6 |
| 1:400,000 | 6.0 ± .6 | 6.9 ± .6 | 6.9 ± .9 | 6.8 ± .2 |

While all concentrations were effective, there is a small difference due to concentration. Increased pupil size allows for increased surgical visibility.

Study 2: Corbett MC and Richards AB. Intraocular adrenaline maintains mydriasis during cataract surgery. *Br J Ophthalmol.* 1994; 78:95-98.

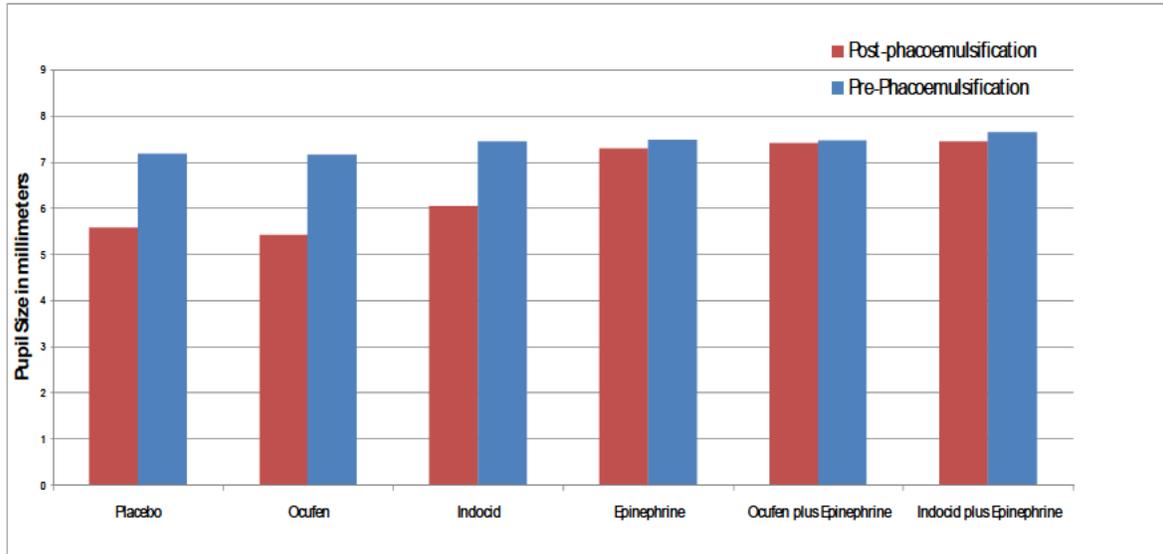
Pre-defined endpoint: Percentage of patients with pupil less than 5 millimeter

| Time or stage of surgery | Without Epinephrine | With Epinephrine |
|--------------------------|---------------------|------------------|
| Total number of patients | 43 | 27 |
| Before expression | None | None |
| Before aspiration | 7 (16%) | None |
| After aspiration | 9 (21%) | 2 (7%) |
| 10 min | 4 (9%) | 1 (4%) |
| 20 min | 9 (21%) | 1 (4%) |
| 30 min | 9 (21%) | 3 (9%) |



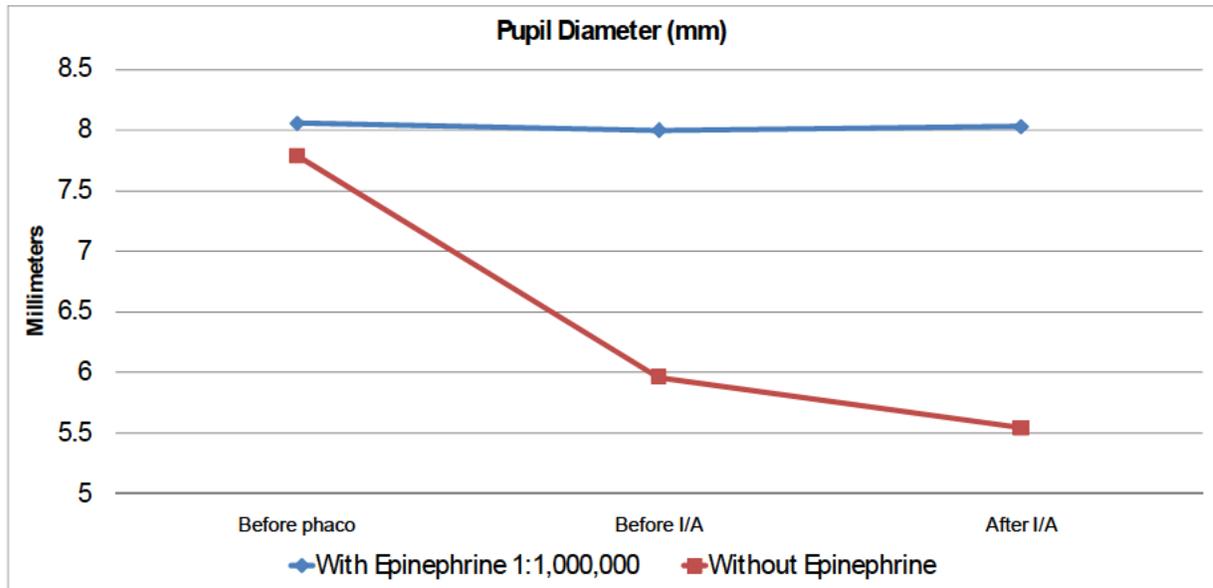
As noted above, pupil dilation is maintained to a greater extent by the use of epinephrine at the critical times of the operation, at a 1,000,000 dilution. Increased pupil size allows for increased surgical visibility.

Study 3: Gimbel HV. The Effect of Treatment with Topical Nonsteroidal Antiinflammatory Drugs with and without Intraoperative Epinephrine on the Maintenance of Mydriasis during Cataract Surgery. *Ophthalmol.* 1989; 96:585-588.



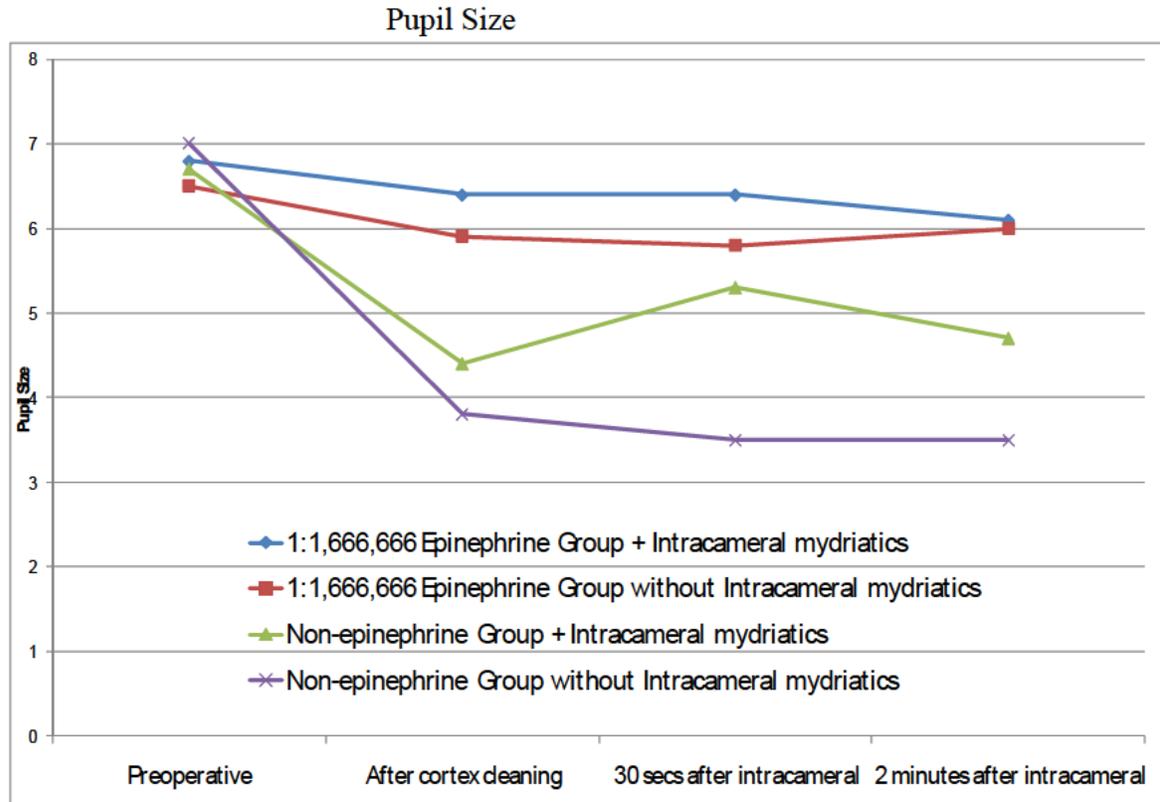
As displayed above, each of the 3 groups which included epinephrine demonstrated statistically significantly larger pupil diameters than the any of the 3 groups which did not include epinephrine. The differences are statistically significant even after a Bonferroni correction for multiplicity. Increased pupil size allows for increased surgical visibility.

Study 4: Liou SW and Yang CY. The effect of Intracameral Adrenaline Infusion on Pupil Size, Pulse Rate, and Blood Pressure During Phacoemulsification. *J Ocular Pharmacology Therapeutics*. 1998; 14(4): 357-361.



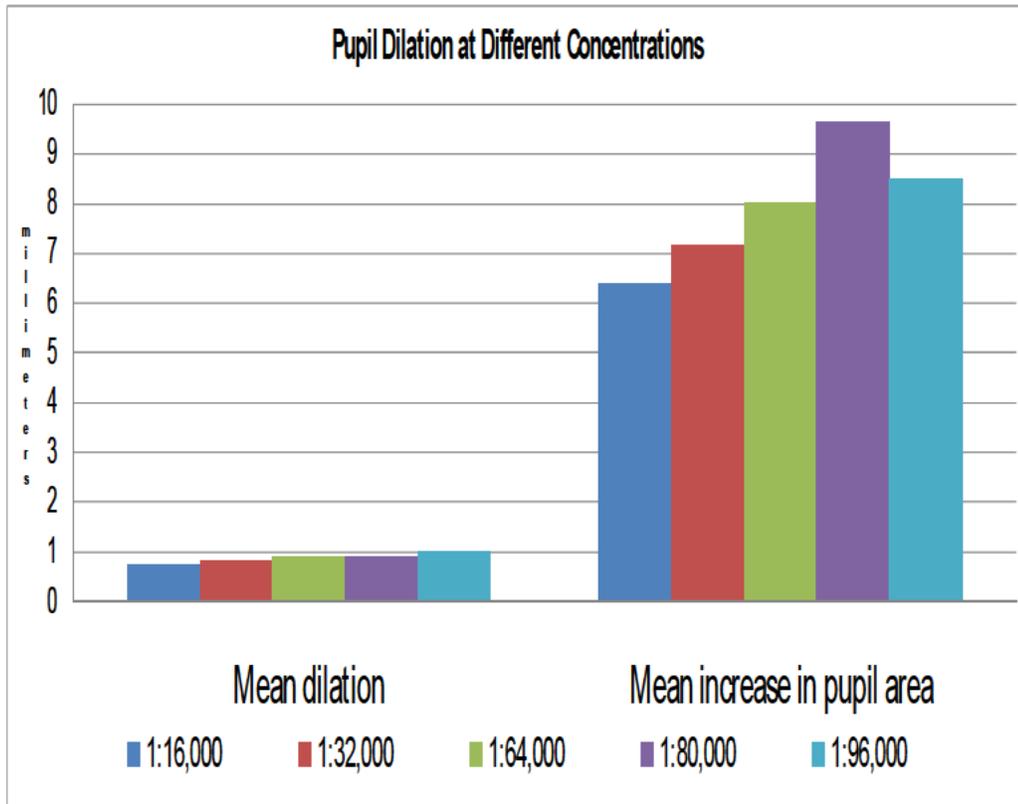
As noted above, pupil dilation is maintained to a greater extent by the use of epinephrine, at a 1,000,000 dilution. Increased pupil size allows for increased surgical visibility.

Study 5: Backstrom G and Behndig A. Redilation with intracameral mydriatics in phacoemulsification surgery. *Acta Ophthalmol Scand.* 2006; 84:100-104.



Pupil size is reported in millimeters. Epinephrine added to the irrigating solution maintained pupil diameter and precluded the need for additional intracameral mydriatics. Increased pupil size allows for increased surgical visibility.

Study 6: Duffin RM, Pettit TH and Straatsma BR. Maintenance of Mydriasis with Epinephrine During Cataract Surgery. *Ophthalmic Surgery*. 1983; 14:41-43.



All concentrations lead to significant increases in pupil size. Increased pupil size allows for increased surgical visibility. Pupil area is reported as square millimeters.

Summary Efficacy Statement

Induction and maintenance of the mydriasis, as the phrase is used in this review and proposed labeling of the drug product is considered one indication. Pupillary dilation in response to direct application of epinephrine intracamerally occurs within seconds but without continued administration rapidly wears off. The phrase “induction and maintenance” is meant to describe an increase in pupillary diameter over the diameter that would have occurred during the entire intraocular surgical procedure as long as the drug product is continuing to be administered.

In randomized, controlled studies, patients undergoing routine cataract extraction were evaluated after receiving intraocular irrigation with or without epinephrine diluted up to 1:1,666,666 (0.6 mcg/mL). Patients have also been evaluated after receiving bolus

intracameral injections of epinephrine diluted between 1:25,000 (40 mcg/mL) and 1:400,000 (2.5 mcg/mL).

In patients with similar pupil diameters at baseline, with or without the use of preoperative mydriatic agents, mydriasis was maintained better in the eyes receiving epinephrine by an average of one to two millimeters in pupil diameter. Pupil constriction to 5mm or less occurred more often in the patients not receiving epinephrine.

8. Safety

From the original Medical Officer Review:

The safety profile was evaluated from the published literature, adverse events reported to the applicant during marketing of the product and a review of MedWatch reports. The potential adverse consequences of intracameral epinephrine when administered as intended (diluted into the ophthalmic irrigating solution) are difficult to evaluate because of the short onset of effect (seconds), short duration of effect (minutes) and the potentially confounding factors associated with using it as an admixture to balanced salt solution in intraocular surgery. There have been very few adverse reports to the Agency after millions of doses of used over decades.

OCULAR SAFETY

As reported by Hull et al [*Am J Ophthalmol.* 1975 Feb;79(2):245-50] commercial epinephrine 1:1000 with its preservative sodium bisulfite damaged corneal endothelial function and ultrastructure in rabbit and monkey eyes with sodium bisulfite the source of the damage. Endothelial damage can be prevented with a 1:5000 dilution of commercially available epinephrine in 0.1% sodium bisulfite or freshly prepared epinephrine bitartrate 1:1000 with a bicarbonate Ringers.

Cakmak et. al. [*Cutaneous and Ocular Toxicology.* 2010; 29(1):41-49] reported the safe use of 1:100,000 dilution of sodium bisulfate preserved epinephrine. Their clinical trial evaluated the effects on the corneal endothelial cells in patients treated with or without 1:100,000 epinephrine and they did not detect any differences.

Bozkurt et. al. [*J Cataract Refract Surg* 2010; 36:1380–1384] performed a randomized clinical trial evaluating the safety of an intracameral 0.2 mL injection of 1:5000 epinephrine. The clinical trial focused on the macular safety and demonstrated no difference with or without epinephrine.

PEDIATRICS

Wilson et al. [*J Cataract Refract Surg* 2007; 33:1325–1327] have reported on the safety of their routine use of epinephrine [0.5 mL in 500 mL of 0.1% epinephrine]. Included in this report is a case of intraoperative floppy-iris syndrome (IFIS) which occurred when the epinephrine was inadvertently left out of the irrigating solution.

POSTMARKETING EXPERIENCE

The Office of Safety Evaluation provided a summary of the reported adverse events associated with the use of epinephrine when administered intracamerally.

78 ocular reports were retrieved (after removing duplicates). Of those, 26 involved epinephrine use with lidocaine or bupivacaine as a periorbital block. The vast majority of intracameral use (42) involved epinephrine admixed with BSS. The reported events included:

- Endophthalmitis – 15
- Toxic Anterior Segment Syndrome (TASS) – 9
- Corneal disorder – 6
- Blurred vision & edema – 6
- Vision loss – 4
- Cataract formation (post-vitreectomy) – 3
- Corneal opacity – 2
- Staph eye infection – 2
- Keratitis – 1
- Failed corneal graft secondary to osmotic shock – 1

There were three cases reporting inadvertent intraocular administration in which the events were vitreous hemorrhage, vision loss, and a decompensated cornea.

The cases have been reviewed. Each of the cases has multiple potentially contributing causes and all events listed above have also been reported with the use of balanced salt solution (BSS) without epinephrine. None of the reported cases suggest that the cause of the adverse event was related to epinephrine use.

Safety Summary Statement

Epinephrine containing sodium bisulfite has been associated with corneal endothelial damage when used at undiluted concentrations (1 mg/mL).

Mean pulse rate and blood pressure showed no significance difference between patients receiving epinephrine and controls and there was no increased incidence of ventricular dysrhythmias in patients receiving epinephrine.

Adrenalin (epinephrine injection, USP) 1 mg/mL has an acceptable, well-documented safety profile when utilized as recommend in the proposed labeling for the product.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for this application for Adrenalin (epinephrine injection, USP) 1 mg/mL.

10. Pediatrics

The safety and effectiveness of Adrenalin have been established in pediatric patients. Use of Adrenalin in pediatric patients is supported by adequate and well controlled studies in adults and uncontrolled studies in pediatric patients.

11. Other Relevant Regulatory Issues

BIostatISTICS

Per the original Biostatistics review:

Based on the results of these three publications, there is evidence to support the efficacy for epinephrine in maintaining mydriasis in cataract surgery. All three papers reported p-values that were less than 0.05 for difference endpoints comparing epinephrine group with placebo control group; however, due to limited information provided in the papers and there are no raw data submitted, the reviewer cannot verify these p-values.

Although the Applicant seeks approval of epinephrine for the induction of mydriasis in cataract surgery, the statistical reviewer recommends the drug be approved for maintenance of mydriasis in cataract surgery instead.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Adrenalin, on July 17, 2012. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional. DMEPA had no objection to the proprietary name, Adrenalin, at this time.

FINANCIAL DISCLOSURE

This is a literature NDA. The applicant has certified that they have entered into no financial arrangements with any clinical investigators associated with this product. There is no evidence to suggest that the results of the literature studies were impacted by any financial payments.

DSI

No Division of Scientific Investigations (DSI) audit was requested. This is a literature NDA.

12. Labeling

NDA 204200 for Adrenalin (epinephrine injection, USP) 1 mg/mL, is recommended for approval for the induction and maintenance of mydriasis during intraocular surgery with the package insert labeling submitted by JHP Pharmaceuticals, LLC, on 9/5/2012 and found in this

CDTL review (see Appendix 1). Carton and container labeling was also submitted on 9/5/12 and is acceptable (see Appendix 1).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 204200 for Adrenalin (epinephrine injection, USP) 1 mg/mL, is recommended for approval for the induction and maintenance of mydriasis during intraocular surgery with the package insert labeling submitted by JHP Pharmaceuticals, LLC, on 9/5/2012 and found in this CDTL review (see Appendix 1).

RISK BENEFIT ASSESSMENT:

The benefits of using epinephrine injection when administered in concentrations between 1:10,000 and 1:1,000,000 inclusive to dilate the pupil during the performance of intraocular surgery outweigh the potential risks associated with the use.

Clinical, Biostatistics, Pharmacology/Toxicology, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

ONDQA has recommended Complete Response for this application based on the applicant's proposed release specifications.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM M BOYD
09/06/2012

WILEY A CHAMBERS
09/06/2012