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APPLICATION NUMBER:

204200Orig1s000

204200Orig2s000

SUMMARY REVIEW

SUMMARY REVIEW FOR REGULATORY ACTION

Date	Friday December 7, 2012
From	Lydia Gilbert-McClain, MD, FCCP Deputy Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Subject	Summary Review
NDA#	204-200
Applicant Name	JHP Pharmaceuticals, LLC
Date of Submission	March 7, 2012
PDUFA Goal Date	January 7, 2013
Proprietary Name/Established (USAN) Name	Adrenalin (epinephrine injection, USP)
Dosage forms/Strength	Injection 1 mg/mL
Proposed Indication (s)	<ol style="list-style-type: none"> 1. Emergency treatment of allergic reactions (Type I) including anaphylaxis (b) (4) 2. *Induction and maintenance of mydriasis during intraocular surgery
Recommended Action	Approval (with revisions to indication statement)

Materials Reviewed/Consulted OND Action Package, including:	Names of Discipline reviewers
Medical Officer Review	Peter Starke, MD
Cross Discipline Team Leader Review	Theresa Michele, MD
Pharmacology/Toxicology Review	Jane Sohn, PhD, Timothy Robison, PhD
CMC Review	Ying Wang, PhD; Xiaobin Shen, PhD, Prasad Peri, PhD
ONDQA-Biopharmaceutics Review	Kareen Riviere, PhD
Clinical Pharmacology review	Sheetal Agarwal, PhD; Suresh Doddapaneni, Ph.D
DPDP Review	Roberta Szydio; Christine Corser
Product Quality - Microbiology	Erika Pfeiler, PhD
OSE/DMEPA	Jung Lee, RPh; Lissa Owens, Teena Thomas

DPDP = Division of Professional Drug Promotion Review

DSI = Division of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

CDTL = Cross Discipline Team Leader

* Reviewed by the Division of Transplant and Ophthalmology Products (DTOP)

1. Introduction

JHP Pharmaceuticals LLC (JHP) submitted a 505(b)(2) application for Adrenalin® (epinephrine injection, USP) 1 mg/mL (1:1000) for marketing approval for epinephrine injection for the emergency treatment of allergic reactions and anaphylaxis, and for intraocular use during eye surgery to induce and maintain mydriasis. The reference product for this 505(b)(2) application is EpiPen®, an epinephrine auto-injector product marketed by Meridian Pharmaceuticals for the emergency treatment of allergic reactions including anaphylaxis. The application was submitted on March 7, 2012 and because of the two different indications, it was administratively split into 2 submissions as follows:

- Original 1 submission for the proposed indication of emergency treatment of allergic reactions including anaphylaxis reviewed by DPARP.
- Original 2 submission for the proposed indication of induction and maintenance of mydriasis during ocular surgery reviewed by the division of transplant and ophthalmology products (DTOP).

DTOP granted the Original 2 submission for the mydriasis indication a priority review (6 month review clock - PDUFA due date of September 7, 2012) because there are no approved epinephrine products for the mydriasis indication. The Original 1 submission for the allergic reactions and anaphylaxis indication was reviewed under the standard 10-month review clock (PDUFA due date January 7, 2013) because there are other approved epinephrine products on the market for the emergency treatment of allergic reactions and anaphylaxis. During the 6-month review cycle for the Original 2 submission (mydriasis indication), JHP submitted a major amendment to the application on August 17, 2012 to address CMC approvability issues. This submission by JHP resulted in an extension of the original 6-month PDUFA clock and the PDUFA due date for the Original 2 submission (mydriasis indication) is December 7, 2012. With this extension, DPARP adjusted the review timelines to take a regulatory action on the same date as DTOP. This summary review focuses only on the DPARP indication of emergency treatment of allergic reactions and anaphylaxis and provides a brief summary of the salient issues for this application and the basis for the regulatory decision. References to the mydriasis indication under review in DTOP will be made as necessary.

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

Epinephrine solution in vials for injection is a marketed unapproved product. 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 submitted a preIND meeting request on March 2011 to discuss submission of a 505(b) (2) application for Adrenalin®. The label for the currently marketed product included multiple indications in addition to anaphylaxis and mydriasis. The Agency determined that (b) (4)

(b) (4)

the anaphylaxis indication using the intramuscular (IM) and subcutaneous routes (SC) of administration will not need to be supported by additional clinical data, as these routes of administration are already approved. JHP was advised that they could reference an approved auto-injector product in their 505(b) (2) application. JHP submitted the application requesting approval for (b) (4) SC, and IM routes of administration for anaphylaxis (b) (4) in the indication. (b) (4)

The application included (b) (4) a 1 mg/mL presentation in a 3 mL single use vial (b) (4)

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 3 mL single use clear glass vial. Each 1 mL solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.0 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.

All facilities inspections and DMFs are acceptable and there are no outstanding DMF or facilities issues. The microbiology attributes of the product are adequate. The product is sterilized (b) (4). The submitted data support an expiry of 15 months when stored at controlled room temperature (20 to 25°C; 68 to 77°F).

During the review cycle, 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.

(b) (4)

The sponsor submitted 9-month and 12-month stability updates along with other information to the NDA on August 17, 2012, 3 weeks before the PDUFA date for the DTOP priority review application. This submission was considered a major amendment by ONDQA therefore, the review clock for DTOP was extended (by 3 months) to December 7, 2012. The submission of this new data did not affect the PDUFA clock for DPARP as the 10-month goal date is January 7, 2012.

The sponsor has satisfactorily addressed the deficiencies raised by the CMC review team. The agreed upon specifications for impurities are outlined in this table taken from the CMC reviewer Dr Ying Wang's CMC review amendment dated November 15, 2012:

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

Test	Acceptance Criteria at Stability
(b) (4)	

With these specifications, the CMC team is recommending approval. JHP will conduct a post marketing commitment to address the possible causes (b) (4) in the formulation, and process improvements to mitigate the levels of impurities (b) (4). I concur with CMC's recommendation for approval.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies were not necessary to support approval of this application. The sponsor did conduct a 14 day IV toxicology study to evaluate the safety of (b) (4) and there were no dose-limiting findings attributable to (b) (4) *in vivo*. However, pharmacology/toxicology safety margins are not applicable in determining adequate specifications for impurities in this product. The initially proposed specifications would have allowed for an extremely high level of impurities in the drug product which could be a safety concern for the proposed anaphylaxis indication, as the level of impurities are indicative of a product quality issue.

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 and inactive ingredients in the same concentration as the EpiPen® auto-injector. Furthermore, epinephrine solution has a long documented history of use through intramuscular and subcutaneous routes of administration for the emergency treatment of anaphylaxis.

6. Clinical Microbiology

A clinical microbiology review was not needed for this application. The product quality microbiology assessment was adequate.

7. Clinical/Statistical- Efficacy

Clinical trials were not performed for this application. Historically, clinical trials were not required to support the approval of the reference product EpiPen ® autoinjector which relied on the literature and the extensive clinical experience with epinephrine for the treatment of anaphylaxis. All other epinephrine auto-injectors that were approved subsequent to EpiPen®, (Twinject®, Adrenaclick®, and AUVI-Q®) also relied on the published literature and the past clinical use experience with epinephrine.

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 application 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.

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 applicant submitted a label in the Physician's Labeling Rule (PLR) Format. A joint review was conducted with DTOP since both indications (mydriasis and anaphylaxis) would be reflected in one label. The label underwent multiple revisions during the labeling review with input from DTOP reviewers, SEALD, DPDP, and the various divisions in OSE. Of note, Section 14.1 "Clinical Studies" does not include a section on anaphylaxis. This was intentionally done to avoid any potential advantage of one epinephrine product over another. The use of epinephrine for anaphylaxis is based on extensive use history and is accepted practice. The most recently approved epinephrine auto-injector product (AUVI-Q®) does not have a Section 14 "Clinical Studies" in the label. Because the Adrenalin® label is carrying 2 indications, the Full Prescribing Information (PI) will have a section 14, which provides a description of the clinical trials (from the literature) that support the mydriasis indication. All labeling issues are resolved. The Initial U.S. Approval date of 1939 is based on the following information: Epinephrine was first marketed by Parke Davis in 1901. As such, it is a pre-1938, pre-DESI drug. The first NDA application for epinephrine was for Adrenalin in oil, NDA (b) (4) 'approved' February 3, 1939. However, this product did not survive the DESI process (DESI 366). The first *products* approved after receiving a DESI designation of "Effective" were combinations with Lidocaine and Marcaine; both of which had supplements approved in 1972. In establishing 1939 as the date to use, the division obtained input from the SEALD team and the Office of Regulatory Policy (ORP). ORP stated that "*the Initial U.S. Approval Date for (1) products not removed from the market due to the DESI process and (2) products removed from the market due to the DESI process (found not effective) and subsequently additional efficacy data was submitted after the DESI process to permit marketing is the date on which an NDA containing epinephrine was first approved, even if that predated an effectiveness determination.*"

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 commitment:

1. Evaluate formulation and process improvements to reduce the levels of impurities with Adrenalin (epinephrine injection). In your evaluation, conduct at least one study to determine the possible cause(s) of (b) (4) formation and take appropriate measures to minimize the level of this impurity. Using the results from these investigations, re-evaluate the acceptance limits for (b) (4) and (b) (4) and lower the limits for these impurities. As part of an interim report, include your evaluation of the formulation/process improvements undertaken to mitigate the level of impurities, in particular (b) (4) and (b) (4), as well as a summary of all technical work performed using the results of the conducted study(ies). The interim report should also include a proposed development plan for future batches which will ensure consistency and reliability of product quality.

The timetable JHP submitted on December 7, 2012, states that they will conduct this study according to the following schedule:

Final Protocol Submission:	January 2013
Interim Report Submission:	April 2013
Study/Trial Completion:	March 2014
Final Report Submission:	May 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
12/07/2012

NDA 204200 /Original 2
 Adrenalin (epinephrine injection) 1mg/mL
 Proposed indication: induction and maintenance of mydriasis

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 204200
Related IND	IND 111712
Related NDA	NDA [REDACTED] (b) (4)
Applicant Name	JHP Pharmaceuticals
Date of Submission	March 7, 2012
Date of Receipt	March 7, 2012
Review Type:	Priority
Date of Major Amendments:	August 21 and September 6, 2012
PDUFA Goal Date	December 7, 2012
Proprietary Name / Established (USAN) Name	Adrenalin® epinephrine injection USP
Formulation	Ophthalmic injection for intraocular use during cataract surgery
Presentation	Glass vial containing 1 ml of solution of 1 mg/mL (1:1000) epinephrine in 3 mL vial
Use	Diluted in 100mL to 1000mL of irrigating solution
Proposed Indication(s)	Induction and maintenance of mydriasis
Action for Application	<i>Approval</i>

COMMENT:

Please see regulatory summary regarding the role of two OND Divisions in the review of the two indications (anaphylaxis and mydriasis) in this application. This review only addresses the indication for the induction and maintenance of mydriasis submitted to the Division of Transplant and Ophthalmology Products (DTOP), the subject of NDA 204200/ "Original 2."

NDA 204200 /Original 2
 Adrenalin (epinephrine injection) 1mg/mL
 Proposed indication: induction and maintenance of mydriasis

Material Reviewed/Consulted OAP Action Package, including:	Names of discipline reviewers
Medical Officer Review	Wiley Chambers 9/5/2012
CDTL Review	Bill Boyd 9/6/2012
Deputy Division Director Review	Wiley Chambers, 9/7/2012
CSO Labeling Review	Leanna Kelly, Judit Milstein 4/27/2012
Medical Reviews from DPARP	n/a to mydriasis indication
Statistical Review	Yunfan Deng, Yan Wang 8/6/2012
Pharmacology/Toxicology Review	Conrad Chen, Lori Kotch 8/17/2012
P/T Team Leader Review	Timothy Robison, DPARP 11/16/2012
Clinical Pharmacology Review	Sheetal Agarwal, Philip Colangelo 8/17/2012, 11/8/2012
Biopharmaceutical Review, ONDQA BA/BE Waiver request	Kareen Riviere, Angelica Dorantes 8/13/2012, 11/13/2012
Product Quality Manufacturing Reviews ONDQA/Division III, Branch VIII	Ying Wang, Xianbin Shen, Prasad Peri 8/14/2012 Rapti Madurawe, Terrance Ocheltree 9/7/2012 Ying Wang, Prasad Peri 11/15/2012
ONDQA Division II/Branch V	Balajee Shanmugam, Rapti Madurawe 4/12/2012
Product Quality Microbiology Reviews	Erika Pfeiler, Bryan Riley 8/8/2012
OC/Facilities Inspection	Acceptable (see CMC review)
OSI/DGCPC	n/a
OSE/DMEPA Proprietary Name Review	Lissa Owens, Lubna Merchant, Kellie Taylor, Carol Holquist 7/17/2012 Lissa Owens, Lubna Merchant 11/15/2012
Conditionally Acceptable Letter	Carol Holquist 7/17/2012
OSE/DMEPA Labeling Review	Jung Lee, Jamie Wilkins Parker, Scott Dallas, Carol Holquist 9/6/2012, 11/21/2012
OPDP/DPDP (formerly DDMAC)	Christine Corser 9/6/2012 (for DTOP) Roberta Szydlo 11/9/2012 (for DPARP)
Pediatric Review Committee	George Greeley (Email) 6/6/2012
Extension letter	Judit Milstein 9/7/2012 (DTOP)
NDA User Fee telecon minutes	Carol Hill 8/23/2012 (DPARP)

OND=Office of New Drugs, DPARP=Division of Pulmonary, Allergy and Rheumatology
 Products
 CDTL=Cross-Discipline Team Leader
 ONDQA/DNDQAII = Office of New Drug Quality Assessment/Division of New Drug Quality
 Assessment II/ Branch V
 OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
 (formerly Division of Scientific Investigation (DSI))
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion;
 formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

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1. Summary and Recommendations

Adrenalin® (epinephrine injection, USP) is proposed for the indication of induction and maintenance of mydriasis during ocular cataract surgery.¹ The application was submitted as a 505(b)(2) application and relies on literature data for the clinical and non-clinical information. Adrenalin is a marketed albeit unapproved product. The applicant, JHP, wrote that Adrenalin has been marketed continuously for over 100 years, first by Parke-Davis, then King Pharmaceuticals, and now JHP. JHP reports they distribute Adrenalin in the United States and (through a partner, Erfa) in Canada. Between October 2007 and November 2011, over 2 million vials or ampoules (1 mg/mL) have been sold.

Published clinical studies evaluating induction and maintenance of mydriasis during surgery demonstrated that Adrenalin at concentrations ranging from 1:100,000 to 1:1,000,000 was effective. Epinephrine maintained a significantly greater degree of mydriasis compared to placebo, and the pupil diameter remained greater than 5 mm during surgery.² In some studies, patients in both arms received topical agents before surgery to dilate the pupil, and the additional contribution of intraocular epinephrine to mydriasis was evaluated compared to placebo. Before use, epinephrine is diluted in balanced salt solution and used as an irrigating fluid during surgery or the diluted solution is instilled intracamerally to achieve mydriasis. The Indications and Usage section, and the Dosing and Administration section of labeling will provide the following information:

1.2 Mydriasis during Intraocular Surgery

Induction and maintenance of mydriasis during intraocular surgery.

2.2 Induction and Maintenance of Mydriasis during Intraocular Surgery

Adrenalin® must be diluted prior to intraocular use. Dilute 1 mL of Adrenalin® 1 mg/mL (1:1000) in 100 to 1000 mL of an ophthalmic irrigation fluid to create an epinephrine concentration of 1:100,000 to 1:1,000,000 (10 mcg/mL to 1 mcg/mL). Use the irrigating solution as needed for the surgical procedure.

After dilution in an ophthalmic irrigating fluid, Adrenalin® may also be injected intracamerally as a bolus dose of 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).

Inspect visually for particulate matter and discoloration prior to administration. Do not use if the solution is colored or cloudy, or if it contains particulate matter.

Adverse events associated with the ocular use of epinephrine were also reviewed. In animal trials, direct intraocular injection of the undiluted 1:1000 solution (1 mg/mL) with sodium

¹ The application also included the indication for emergency treatment of allergic reactions (Type I) including anaphylaxis which was reviewed in the Division of Pulmonary, Allergy and Rheumatology Products. Approved labeling will include both indications. This review focuses on the mydriasis indication.

² A size of 5 mm or greater is relevant for several reasons, including because this makes the insertion of the intraocular lens, which is generally 5 mm in size, possible.

bisulfite 0.1% caused corneal endothelial cell damage.³ When the epinephrine was diluted 5 fold (1:5000), the endothelial damage did not occur. In another preclinical study, cats received different amounts and concentrations of epinephrine (0.1 mL of 0.02% epinephrine hydrochloride up to 0.5 mL of 0.1% epinephrine hydrochloride) containing 0.02% sodium bisulfite intraocularly and there was no difference in endothelial cell counts compared to baseline cell counts.⁴ The endothelial toxicity is considered to be due to the presence of sodium metabisulfite (as sodium bisulfite) in the formulation. The compound is added as an antioxidant

(b) (4)

In the published clinical studies for this indication, adverse events attributable to epinephrine were rarely reported. JHP also submitted a summary of adverse events reported to the company, which included a range of ocular adverse events, and OSE provided post-marketing reports for review. The medical officer notes that the types of events reported (including endophthalmitis, toxic anterior segment syndrome, blurred vision, cataract formation, corneal disorder or opacity, etc.) can be seen associated with ocular surgery regardless of epinephrine use.

In several of the published clinical trials reviewed for this indication, patient heart rate (HR) and blood pressure (BP) were monitored. There were no reported differences in HR and BP between the treatment and placebo groups. This finding is not unexpected given the low amount of epinephrine in the dilute solution used intraocularly and the resulting lack of systemic toxicity. On the other hand, parenteral use of epinephrine has been associated with various adverse reactions, and these are included in the labeling as part of the approval of the anaphylaxis indication under NDA 204200/Original 1.

The major challenge with this application has been the concern about the proposed potency of the product (b) (4) and the proposed specification for total impurities/degradants at expiry (b) (4) raised by the CMC review staff.⁶ This concern led to a complete response recommendation by the ONDQA reviewers during the initial review, and an extension of the PDUFA goal date based on additional information submitted in August and September 2012, warranting review. During the extension period, ONDQA and JHP exchanged additional information and held additional teleconferences to discuss the product quality issues. In November 2012, JHP was able to reach agreement with the proposed CMC requests regarding amount (b) (4) and degradants at expiry (b) (4) 15 months), as well as requests for a post-marketing commitment (PMC) to characterize the manufacturing process. Based on this information, ONDQA reviewers revised their recommendation to approval of the NDA. A detailed summary of the CMC issues and their resolution is provided in Section 3. CMC/Product Quality Microbiology of this document.

³ DS Hull, CHemotti MT, Edelhofer HF, Van Horn DL, Hyndiuk RA. Effect of epinephrine on the corneal endothelium. *Am J Ophthalmol* 1975; 79(2):245-50.

⁴ RJ Olson, R Kolodner, P Riddle, H Escapini. Commonly used intraocular medications and the corneal endothelium. *Arch Ophthalmol* 1980; 98:2224-6.

⁵ JM Rowland and DE Potter. Steric structure activity relationships of various adrenergic agonists: ocular and systemic effects. *Current Eye Research* 1981; 1:25-35.

⁶ Some of the DPARP reviews cite higher impurity levels and lower potency levels

(b) (4)

NDA 204200 /Original 2
Adrenalin (epinephrine injection) 1mg/mL
Proposed indication: induction and maintenance of mydriasis

Product labeling, including carton and container labels for the 3 mL vial, containing 1 mL of 1 mg/mL (1:1000) epinephrine has been finalized by both DPARP, DTOP, and consulting groups. The trade name Adrenalin is acceptable. Manufacturing facilities are acceptable.

1.1 Deficiencies

None, the application will be approved.

1.2 Post-Marketing Studies:

See Section 13.3 for details about post-marketing requirements/commitments.

1.3 Other Issues

None

2. Background

2.1 NDA Submission and User Fee Overview

The original NDA 204200 for Adrenalin® (epinephrine injection USP) was submitted on March 7, 2012, and assigned to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), and the Division of Transplant and Ophthalmology Products (DTOP).

1. DPARP was assigned review of the anaphylaxis indication and this was designated as NDA 204200/Original 1 and DTOP was assigned the mydriasis indication and this was designated as NDA 204200/Original 2.
2. DPARP determined that the anaphylaxis indication would be reviewed under a standard 10-month clock because other epinephrine products have been approved for this indication (EpiPen® NDA 19430, Twinject® NDA 20800),⁷ and the PDUFA goal date was January 7, 2013.
3. DTOP determined that the mydriasis indication would be reviewed under a 6-month priority review clock because there are currently no approved epinephrine products for mydriasis indication. On initial review of the efficacy information, epinephrine was able to maintain mydriasis during ocular surgery and provided a benefit in addition to the topical products used for mydriasis. The PDUFA Goal Date for DTOP was September 7, 2012.

Then it was noted that NDA 204200 contained (b) (4)
1 mg/mL (1:1000) of epinephrine injection (b) (4)

⁷ Auvi-Q (epinephrine injection, USP) Auto-Injector, NDA 201739, was approved on August 10, 2012, following a tentative approval date of July 29, 2011.



2.2 Regulatory Timelines and Summary

Adrenalin® was the subject of a pre-NDA teleconference on July 5, 2011, archived under pIND 111712. Most of the discussion focused on the CMC, [REDACTED] (b) (4) and requested information from JHP to support the safety of the proposed specifications. There was discussion of possible indications and Divisions that would review these. The minutes of the meeting and the DPARP clinical filing review document that the recommendation to seek FDA approval was made by the Office of Compliance (OC) in a letter sent to JHP on July 23, 2009 when the API, epinephrine, was in US Customs. OC requested that JHP provide the history/lineage of the Adrenalin product and its relation to the Parke-Davis product marketed before June 25, 1938. Once the information was provided, US Customs released the API and OC urged JHP to submit a new drug application.

Despite the two different PDUFA goal dates, initially there was discussion that DTOP and DPARP would work in concert to complete the review of the application by the earlier of the two PDUFA dates (September 7, 2012). This process was discontinued once the CMC reviewers identified concerns about impurities [REDACTED] (b) (4). The ONDQA reviewers recommended a complete response based on the original NDA review completed in early August 2012. JHP submitted additional information August 21 and September 6, 2012. This information indicated the need for further evaluation of the differences between registration and historic stability batches and raised questions about the manufacturing process controls, analytical methods, stability data, and specifications and proposed shelf-life that needed to be addressed. Therefore ONDQA recommended an extension of the review clock. The extension letter was issued September 7, 2012. The revised PFUDA goal date was December 7, 2012.

During the review extension period, ONDQA sent several information request letters and JHP provided submissions with responses to the inquiries. ONDQA and JHP held a number of teleconferences which enabled JHP to reach agreement on acceptable specifications for the epinephrine product and enabled ONDQA to make a recommendation of approval. DTOP and DPARP finalized labeling with JHP, so that one package insert with both indication and one carton/container label for the 1 mg/mL (1:1000) epinephrine product is being approved.

3. CMC/Product Quality Microbiology

See complete CMC reviews by Drs. Wang, Shen and Peri.

3.1 Product Quality

Adrenalin® (epinephrine injection, USP) is provided in a concentration of 1 mg/mL (1:1000). It is supplied as a 1mL solution in a 3 mL Single-Use Vial. The quantitative composition of the 1mg/mL product in the 3 mL vial is presented below (applicant's Table 2.3.P.3.3)

Component	Grade	Batch Quantity	Unit Dose	Function
Epinephrine	USP	(b) (4)	(b) (4)	Active
Sodium Chloride	USP		9.0 mg	Tonicity Agent
Sodium Metabisulfite (as bisulfite)	NF		1.0 mg	(b) (4)
Hydrochloric Acid	USP		(b) (4)	
Water for Injection	USP			

In the application, JHP included stability data up to 18 months for historic (previously manufactured) batches and included (b) (4) levels were not measured. JHP also provided 6 month stability data for 3 new registration batches placed on stability between March and May, 2011 in both inverted and upright orientation. These batches were tested for both (b) (4) levels.

The degradation reactions and resulting degradants (b) (4) are shown in Figure 1.

Figure 1. Degradation Reactions (b) (4) 8



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 Proposed indication: induction and maintenance of mydriasis

The shelf-life limits for specifications proposed by JHP are shown in the table below.

Test	Release Limit	Shelf-Life Limit	Justification
Description			(b) (4)
Assay			(b) (4)
Impurity: Individual Unid.			(b) (4)
Total Impurities			(b) (4)
Identification			(b) (4)
pH			(b) (4)
Sodium Bisulfite (1 mL)			(b) (4)
Total Acidity			(b) (4)
Color & Clarity			(b) (4)
Sterility			(b) (4)
Particulate Matter			(b) (4)
Bacterial Endotoxin			(b) (4)

ONDQA reviewed the proposed limits and considered them unacceptable. (b) (4)

(b) (4)

(b) (4)

During the original NDA review, the CMC reviewers working with DPARP finalized their review in DARRTS and recommended a complete response be issued (see review dated August 14, 2012). During internal discussion, it was recommended that a Discipline Review letter be issued to let the applicant know the scope of the deficiencies. No Discipline Review letter was issued; an IR letter requesting information on impurities, in process controls, analytic methods and revised acceptance criteria for impurities was issued (September 18, 2012).

The DTOP clinical reviewer recommended the application should be approved despite the CMC recommendations, and summarized why the potency and impurity limits were not considered of concern for the mydriasis indication. These reasons included that epinephrine has been marketed for over 100 years, clinical trials supported its safety and efficacy, and the degradants/ impurities had been qualified. Potency was stated not to be a concern given that the product is typically diluted prior to use, and the effect is seen visually during the surgery, and the needed duration of effect is during the procedure, which usually takes less than one hour to complete. Epinephrine was effective in dilutions up to 1:1,000,000. JHP set the shelf-life limit (b) (4). The application (published clinical studies) did not provide information on the potency and impurities of the epinephrine products used in the clinical trials.

Before the original PDUFA goal date, there was discussion whether to approve this product for the mydriasis indication only, but this approach was considered less desirable and would also potentially lead to more confusion than addressing the CMC concerns and reaching agreement on a product with potency and specifications considered acceptable by ONDQA and both Divisions. Because the applicant had submitted one product for the two indications, the goal was to see if the CMC issues could be addressed and resolved.

On August 17, 2012, JHP submitted 9-month and 12-month stability updates for the three registration stability batches (b) (4). The registration batches showed (b) (4). Based on review of the new registration batch stability data, the CMC reviewers working with DTOP noted that the primary reason for the complete response recommendation was the failure to assure adequate drug product quality (b) (4). Therefore the Agency held another teleconference with JHP Pharmaceuticals on Aug 31, 2012, during which the stability data and the drug product specification were again discussed (b) (4). On September 6, 2012, JHP submitted a new proposal for drug product specifications with additional justification for the revised acceptance criteria. This new information indicated further evaluation was warranted to reassess the manufacturing process controls, analytical methods, stability data, specifications and proposed shelf-life. Therefore, this information was filed as a major amendment and the PDUFA goal date for NDA 204200 was extended to December 7, 2012. Efforts were focused on resolving the CMC deficiencies.

The applicant submitted amendments on October 15 and November 9, 2012 which were reviewed and resulted in the recommendation by ONDQA that the application is adequate for approval. The proposed expiry of 15 months when stored at controlled room temperature (20 – 25°C; 68 – 77°F) was granted.

Some of the observations noted by the CMC reviewer:

- 1)  (b) (4)
- 2) Analytic method deficiencies for the drug substance testing have been adequately addressed by JHP.
- 3) JHP accepted the new  (b) (4) limits  (b) (4) proposed by ONDQA. These are shown in the table below from the CMC review, November 15, 2012.

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

Test	Acceptance Criteria at Stability
(b) (4)	

Table from JHP submission dated November 9, 2012 to NDA 204200

Based on these discussions between ONDQA and JHP, the applicant provided the following specifications on November 9, 2012:

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 Adrenalin (epinephrine injection) 1mg/mL
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Adrenalin 1 mL Specifications

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

Furthermore, the applicant was asked to conduct a post-marketing study, and agreed to this in their submissions dated November 9, November 27 and December 7, 2012 (See Section 13.3).

Summary Comments:

After completing the review of the original NDA, the CMC reviewers summarized the CMC deficiencies and recommended a complete response on August 14, 2012. The major deficiency was the proposed level of total degradants/impurities in the product at expiry (b) (4)

(b) (4)
Other deficiencies were identified by the reviewers, but it was noted during internal discussion that these additional issues could be addressed as PMCs.

From the clinical perspective, the reviewers stated there are no concerns about potency or safety for the mydriasis indication because of the following:

- *Doses ranging from 1:25,000 to 1:1,000,000 are still shown to be effective for mydriasis.*
- *The product is given intracamerally, directly to the site of desired action, and can be either given as bolus or continuous irrigation.*
- *The effect – mydriasis – dilation and maintenance of dilation is visible to the surgeon.*
- *The effect is needed for the duration of surgery, which can range from 15 minutes, generally around 45 minutes, and on rare occasions to 3 hours.*
- *From a safety perspective, the “degradants” have been qualified in nonclinical studies and as noted above, the solution is further diluted before administration, so the level of impurities is even lower than in the vial.*

However, the clinical studies submitted to support the safety and efficacy of epinephrine did not identify the specific age of the product used, whether it was at release or close to expiry, and therefore the amount (b) (4) in these products was not known. In addition, the ONDQA reviewers working with DTOP noted that there were inconsistencies in the historic batches, in the registration batches and the proposed specifications which needed to be addressed before approval. Finally, DPARP was reviewing the anaphylaxis indication for this product and had expressed concerns about potential problems if the potency of the product were low. Although the possibility of approving this product for only the mydriasis indication was discussed, it was preferable to work with the applicant and reach agreement on the CMC issues.

Therefore, ONDQA and JHP continued discussion of the degradants/impurities and analytic methods, as documented in the Information Request letters and responses by JHP. These exchanges are summarized in the November 15, 2012 CMC review. As a result of these discussions, the applicant was able to agree to revised specifications and will conduct further evaluation of the manufacturing process and levels of impurities.

The ONDQA CMC reviewers recommend approval of the application from their perspective based on resolution of the deficiencies and a PMC.

3.2 Product Quality Microbiology

The Product Quality Microbiology reviewers noted that this (b) (4) glass vial is filled (b) (4). The microbiological attributes of the manufacturing process, process controls, process validation, media fill, specifications and analytical procedures are adequate and the application can be approved from their perspective.

A recommendation is included at the end of the review (b) (4)

3.3 Biopharmaceutics – BA/BE Waiver

The Biopharmaceutics reviewers from ONDQA determined that a BA/BE waiver under 21 CFR 320.22(e) is appropriate and the application can be approved from their perspective.

Comment:

Following review of the original application, the amendments, and based on the additional discussions between ONDQA and JHP, all CMC reviewers (drug substance/drug product), Product Quality Microbiology reviewers and Biopharmaceutics reviewers recommended approval of the application from their perspective.

4. Nonclinical Pharmacology/Toxicology

See Pharmacology/ Toxicology review by Drs. Chen and Kotch.

The applicant relied on literature and also performed four new animal studies: two rat IV studies, as well as an Ames assay and chromosome aberration study in CHO cells intended to qualify the impurities.

Literature searches covered pharmacological and toxicological effects, related to pharmacologic and supra-pharmacologic actions of epinephrine. Effects on fertility, pregnancy, fetal development, genotoxicity and carcinogenicity were searched.

Dr. Kotch writes that 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 1:1000 formulation will be diluted by at least 100-fold before use and the concentration of sodium sulfite after dilution will not cause significant effects on cornea.

Comment: The Pharmacology/Toxicology (P/T) reviewers in DTOP recommend approval from the Pharmacology/Toxicology perspective, and discussed labeling proposals with the P/T reviewers in DPARP. Their labeling revisions are included in Sections 8.1 and 13 of labeling.

5. Clinical Pharmacology/Biopharmaceutics

See Clinical Pharmacology review by Drs. Agarwal and Colangelo.

No trials were submitted, and the review states that no PK data are needed as the product is given directly in the eye, ocular exposure is low and systemic exposure is not expected. Should any absorption occur, it is not expected to raise concerns as the amount would be very low and

epinephrine is an endogenous catecholamine. The reviewers noted that the applicant requested and was granted a BA/BE waiver for this product.

Dr. Agarwal writes that epinephrine binds to both α - and β -adrenergic receptors (stimulant), producing a complex range of physiological effects which can vary with dose, route, and speed of administration. Epinephrine mediates vasoconstrictor effects on the small arterioles and precapillary sphincters in most body organ systems via α_1 adrenergic receptors. This vasoconstriction decreases mucosal edema, which in turn prevents and relieves upper airway constriction, and increases blood pressure, preventing and relieving vasodilatory shock. The β_1 adrenergic effects include increased heart rate and force of cardiac contractions, and β_2 effects lead to increased bronchodilation and decreased release of histamine, tryptase and other pro-inflammatory mediators from mast cells and basophils.

For ophthalmic use during cataract surgery, epinephrine is administered intraocularly/intracamerally, where its action on α_1 adrenergic receptors in the iris produce mydriasis.

- Adrenalin® after dilution can be used intracamerally for adults and pediatric patients to induce and maintain mydriasis. One milliliter of Adrenalin® may be added to 100 to 1000 milliliters of an ophthalmic irrigating fluid to create a low concentration of 1:100,000 to 1:1,000,000 [10 mcg/mL to 1 mcg/mL] of epinephrine.
- Adrenalin® after dilution in an ophthalmic irrigating fluid may also be injected intracamerally as a bolus dose of 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).

A study by Fell⁹ reports on adrenaline and noradrenaline concentrations measured in 13 patients undergoing cataract surgery who received intraocular irrigation with epinephrine 1:500,000. Plasma concentrations of epinephrine before, during, and after irrigation were not significantly different.

Comment: The reviewers recommend approval from the Clinical Pharmacology perspective, and provide labeling revisions to Clinical Pharmacology section of labeling.

6. Clinical Microbiology/Immunology

Not Applicable

7. Clinical/Statistical-Efficacy

See clinical review by Drs. Chambers and Boyd, and biostatistics review by Drs. Deng and Wang.

⁹ Fell D, AP Watson, N Hindocha. Plasma concentrations of catecholamines following intraocular irrigation with adrenaline. *Br J Anaesth* 1989;62(5):573-5.

The statistical reviewers examined three publications¹⁰ reporting on the efficacy of epinephrine during cataract surgery and concluded the data support the indication of **maintenance** of mydriasis, and recommend not including p-values in labeling because raw data from trials were not available for review.

Comment: Although the indication is extended to include both induction and maintenance of mydriasis based on the published data summarized below, there are no p values included in the labeling.

The clinical reviewers summarized six clinical trials that included information on **induction and maintenance** of mydriasis. In these studies, patients usually received preoperative topical drops to induce mydriasis. Epinephrine was then used intracamerally by infusion or irrigation and shown to further dilate the pupil (primarily if the pupil diameter was less than 6 mm), and maintain that dilation, as summarized below.

By way of background, progressive pupillary constriction occurs during cataract surgery: after incision, during capsulotomy, during subsequent phacoemulsification and irrigation/aspiration of the lens content and implantation of the IOL. It is considered that manipulation of the iris results in release of prostaglandins which constrict the iris sphincter, causing progressive miosis during surgery.

(1) **Liou and Yang (1998)** state that pupillary constriction during phacoemulsification (phaco) and irrigation/aspiration (I/A) is found to be the major cause of iris damage, incomplete cortex removal and posterior capsule rupture, and note that cataract surgery is easier to perform if mydriasis is maintained. They studied 42 patients, randomized to receive 1:1,000,000 epinephrine (n=30) vs. control (n=12). One surgeon performed all the cataract surgeries. As noted in Table 1 from the publication, pupil size was similar at baseline, and statistically larger (approximately 2 to 2.5 mm) in the epinephrine arm vs. control arm after phaco and I/A. In addition, because most cataract patients are elderly, questions about systemic adverse reactions were examined; there were no significant effects on heart rate or blood pressure with this dilution.

TABLE 1.
Pupil Size Changes Between Control and Study Groups

Pupil size	Before phaco	Before I/A	After I/A
Study group	8.06±0.637	8.00±0.633	8.03±0.623
Control group	7.79±0.567	5.96±1.3396	5.54±1.3635
p Value	0.206	< 0.00001	< 0.00001

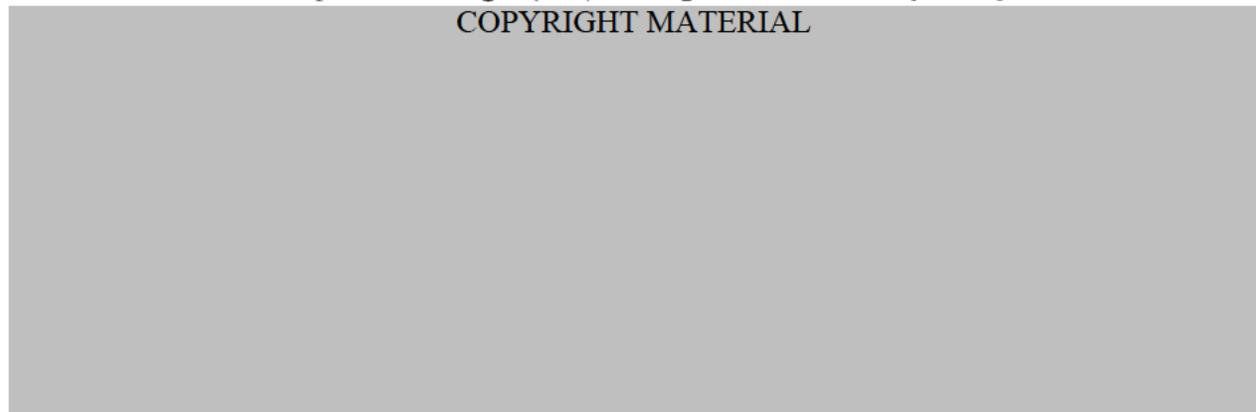
¹⁰ Corbett, MC and AB Richards. Intraocular adrenaline maintains mydriasis during cataract surgery. in *Br J Ophthalmology* 1994; 78:95-98.

Liou S-W and C-Y Yang. The effect of intracameral adrenaline infusion on pupil size, pulse rate, and blood pressure during phacoemulsification *J Ocular Pharmacol Ther.* 1998; 14(4):357-361.

Liou S-W and C-C Chen. Maintenance of mydriasis with one bolus of epinephrine injection during phacoemulsification *J Ocular Pharmacol Ther.* 2001; 17(3):249-253.

(2) **Liou and Chen (2001)** evaluated 60 patients randomized to 5 concentrations of epinephrine given as an intraocular bolus and showed that all maintained significantly higher mydriasis compared to control. They noted that there was no significant difference in pupil size among the 5 different epinephrine groups, thus all dilutions were effective. Measurement of HR and BP showed no significant difference between epinephrine and control groups. The first author is the same as in the 1998 article (above); in this article the authors report that patients received 0.5% tropicamide at 30, 10, and 5 minutes before surgery.

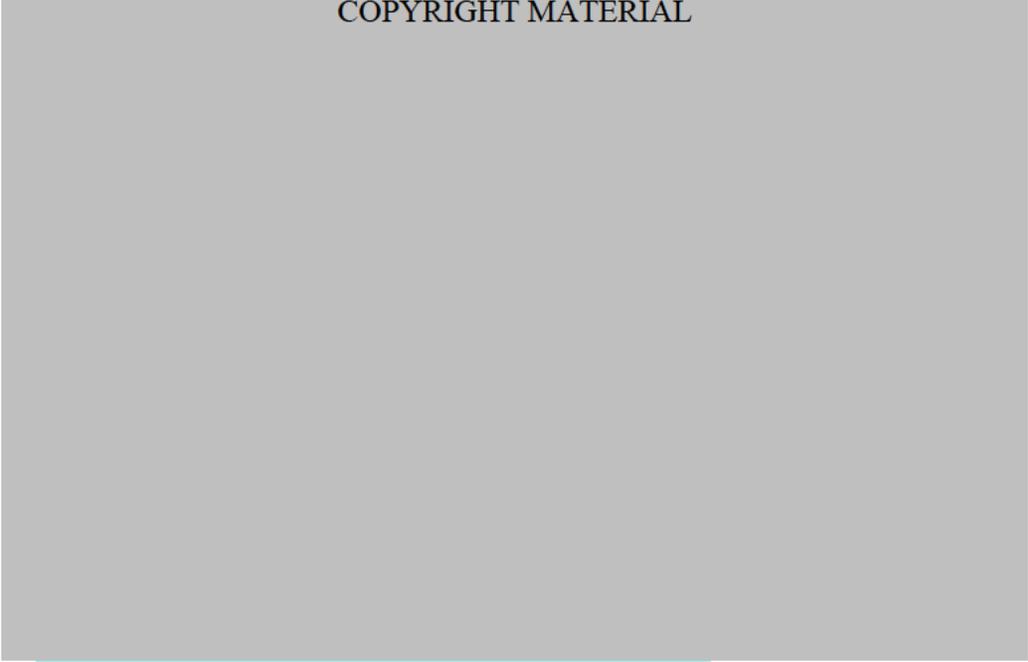
TABLE 1.
Pupil Size Changes (mm) Among Control and Study Groups
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(3) **Corbett et al (1994)** randomly allocated 70 patients to receive irrigations with epinephrine 1:1,000,000 (n=27) vs. placebo (n=43) during ECCE.¹¹ All patients received four drops of both cyclopentolate 1% and phenylephrine 10% during the 1 hour preceding surgery. The authors state that 5 mm minimum diameter is required to reduce the difficulty of the surgery, and that one advantage of giving adrenaline in the irrigation fluid, as opposed to a bolus, is that it continues to enter the eye while the stimulus to miosis persists. In this publication, the baseline values of pupil diameter are included in the figure below, and show that before the use of topical drops, the baseline diameter is between 3mm – 4 mm, is then dilated with the use of topical drops, and then the diameter is maintained during the surgical procedure, compared to the group without adrenaline.

¹¹ <http://www.surgeryencyclopedia.com/Ce-Fi/Extracapsular-Cataract-Extraction.html> Extracapsular cataract extraction (ECCE) is a category of eye surgery in which the lens of the eye is removed while the elastic capsule that covers the lens is left partially intact to allow implantation of an intraocular lens (IOL). This approach is contrasted with intracapsular cataract extraction (ICCE), an older procedure in which the surgeon removed the complete lens within its capsule and left the eye aphakic (without a lens). The patient's vision was corrected after intracapsular extraction by extremely thick eyeglasses or by contact lenses. There are two major types of ECCE: manual expression, in which the lens is removed through an incision made in the cornea or the sclera of the eye; and phacoemulsification, in which the lens is broken into fragments inside the capsule by ultrasound energy and removed by aspiration.

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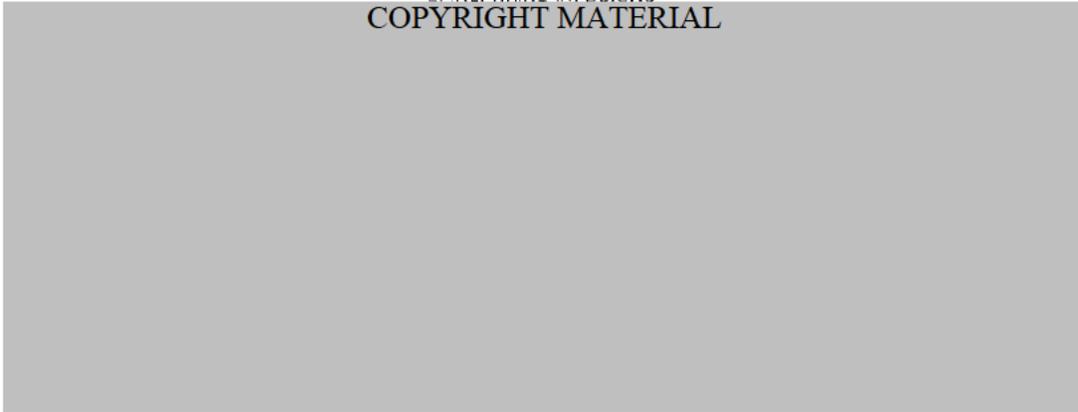


(4) Duffin et al (1983)¹² assessed pupillary diameter in 55 patients undergoing extracapsular cataract extraction (ECCE), including anterior capsulotomy, expression of the lens nucleus and mechanical irrigation/aspiration of lens cortex. The study was done at UCLA, California. Mean patient age was 72 years (range 55-93), 23 were males and 22 were females. Thirty seven patients received preoperative topical phenylephrine 2.5%, 18 patients received phenylephrine 10%, and all received cyclopentolate 1%. Patients were assigned to five epinephrine concentrations (diluted in balanced salt solutions) in this prospective, randomized, double blind trial. Epinephrine volume of 0.1mL was infused into the anterior chamber. The authors report there was no significant difference in mydriatic response to the concentrations tested, when diameter was measured 1 minute after administration under standard illumination of an operating microscope, compared to pre-operative size. They report that 25% of patients did not dilate further, while 42% increased pupil area by less than 20% - the pupils that responded poorly were usually greater than 6 mm in diameter. The variable that correlated with re-dilation of the pupil during surgery was pupil size before epinephrine injection. By regression analysis it was determined that smaller pupils (<6 mm) dilated much better than larger ones (>6 mm). The authors note that they did not measure diameter over time and therefore do not report on duration of action.

¹² Duffin RM, TH Pettit. BR Straatsma. Maintenance of mydriasis with epinephrine during cataract surgery. *Ophthalmic Surgery* 1983;14:41-45.

TABLE 2

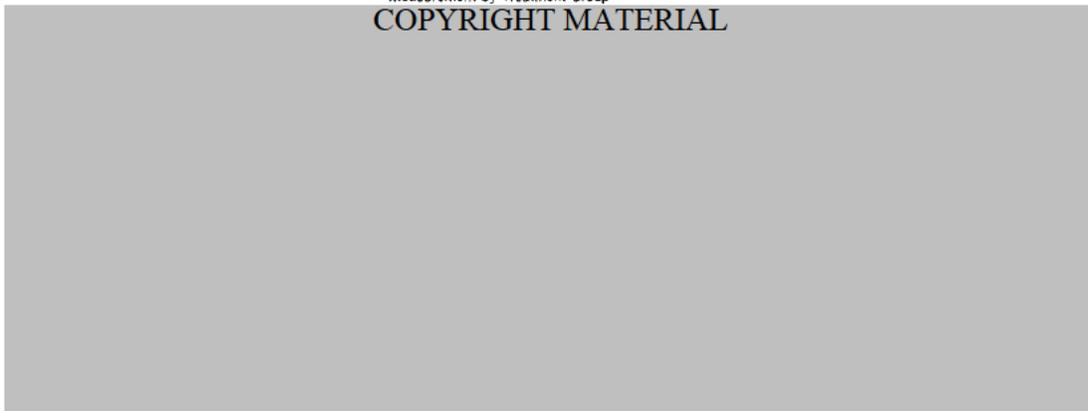
PUPILLARY DILATION WITH INTRAOCULAR
EPINEPHRINE INFUSIONS
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(5) Gimbel (1989)¹³ randomized 216 patients to 6 groups: preoperative topical flurbiprofen or indomethacin with or without epinephrine, epinephrine alone, and placebo. The study was done in Calgary, Canada. Patients received preoperative phenylephrine and cyclopentolate before intraocular lens (IOL) surgery. The author notes that despite good preoperative dilation, progression miosis frequently occurs during surgery, hampering adequate capsulotomy, subsequent phaco and the aspiration of the lens cortex and implantation of the IOL. Surgical trauma releases prostaglandins from the iris and these constrict the iris sphincter. Epinephrine can be instilled intracamerally or by adding to irrigating solution. NSAIDs reduce intraoperative miosis. Epinephrine was used at 0.3 mL of 1:1000 in 500 mL (1:1,666,667). The overall adjusted mean for epinephrine patients was 7.38 mm, compared with 5.68 mm for the patients without epinephrine treatment.

Table 1. Summary of Changes in Mean Pupil Diameter from the Pre-phacoemulsification to Post-phacoemulsification Measurement by Treatment Group

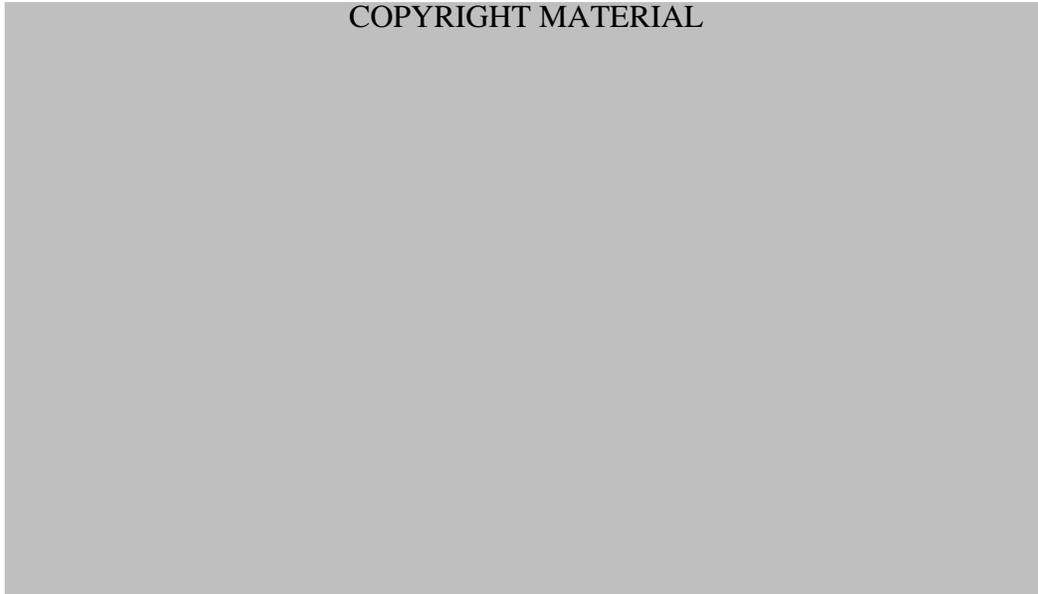
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¹³Gimbel HV. The effect of treatment with topical nonsteroidal anti-inflammatory drugs with and without intraoperative epinephrine on the maintenance of mydriasis during cataract surgery.

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(6) **Lundberg et al (2007)**¹⁴ evaluated 50 patients who received topical mydriatics and then intracameral epinephrine or placebo in irrigating solution.



Independent of epinephrine, Zaczek et al¹⁵ reported that patients with diabetes had more pronounced surgically induced miosis (about 0.5 mm greater constriction), and surgery took longer. The authors note that maintaining mydriasis is essential, and diabetic patients have a weaker response to topical anticholinergic mydriatic drops, and they respond better to a combination of anticholinergic and adrenergic drugs. In this trial, surgery lasted from 6-16 minutes in control patients and 8-20 minutes in diabetics.

8. Safety

Corneal endothelial damage and corneal decompensation have been reported with undiluted epinephrine 1:1000 but not with 1:5000, and this was due to the presence of the sodium bisulfite preservative and not epinephrine.¹⁶ The authors also suggest that osmolarity and pH may be contributing factors. Therefore dilution is important before intracameral use, and this will be included in labeling.

Epinephrine is an α - and β -adrenergic stimulant and systemic administration is associated with tachycardia, palpitations, hypertension, arrhythmias in patients with cardiac morbidity, with fear and anxiety. The concern that ocular use may cause these events in elderly was investigated in several studies (Fiore 1988¹⁷, Yamaguchi 1998,¹⁸ Liou 1998,¹⁹ Liou 2001²⁰), and in these studies

¹⁴ Lundberg B and A Behndig. Intracameral mydriatics in phacoemulsification surgery obviate the need for epinephrine irrigation. *Acta Ophthalmol Scand* 2007; 85:546-550.

¹⁵ Zaczek A and C Zetterstrom. Cataract surgery and pupil size in patients with diabetes mellitus. *Acta Ophthalmol Scand* 1997; 75:429-32.

¹⁶ Hull 1975 and Liou 1998 cited above

¹⁷ Fiore PM, Cinotti AA. Systemic effects of intraocular epinephrine during cataract surgery. *Ann Ophthalmol* 1988; 20(1):23-25.

there were no significant differences in heart rates and blood pressure between patients who received intracameral epinephrine (concentrations between 1:25,000 – 1:1,000,000) and those who did not. In these studies, patients were generally under local anesthesia and were generally monitored continuously during the surgery.

Postmarketing information was provided by JHP and includes a range of reported events which were reported in association with epinephrine use but which are also potential complications of cataract surgery. The reviewer requested OSE to provide AERS reports for intraocular and intracameral use of epinephrine, and received information regarding the following rates.

OSE reported that AERS searches were run using route of administration intraocular and indication for use as cataract operation or cataract conditions, and retrieved 78 reports (after removing duplicates). Of those, 26 involved epinephrine use with lidocaine or bupivacaine as a periorbital block, these were removed, leaving a total of 52 cases. The vast majority (42) involved epinephrine admixed with BSS. The reported events included:

- endophthalmitis – 15
- 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 decompensated cornea. The reports were provided to the clinical reviewer who reviewed the cases and noted that these adverse events were confounded and could be associated with the surgical procedure and/or other products used during the surgery.

9. Advisory Committee Meeting

There were no efficacy and safety issues raised by this application to bring before the Advisory Committee. Epinephrine is not a new molecular entity.

10. Pediatrics

The application and the mydriasis indication were presented before PeRC on June 6, 2012 (email from George Greeley, PRM of PMHS dated June 25, 2012). The application is based on published literature that describes the use in maintaining mydriasis in cataract surgery. Pediatric

¹⁸ Yamaguchi H and Y Matsumoto. Stability of blood pressure and heart rate during ocular epinephrine irrigation. *Ann Ophthalmol* 1988; 20(2):58-60.

¹⁹ Liou 1998 cited above

²⁰ Liou 2001 cited above

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efficacy was reported in non-comparative clinical trials and extrapolated from adult efficacy.
The pediatric record printout states: Studies Completed.

11. Other Relevant Regulatory Issues

This is a 505(b)(2) application, the preclinical and clinical information was submitted from the literature.

11.1 Compliance Inspection –

Overall the Office of Compliance found that facilities are acceptable as of August 6, 2012 per email from Linda Ng dated August 9, 2012. A reevaluation date of January 8, 2013 has been set.

11.2 Office of Scientific Investigation (OSI) Audits

This is a 505(b)(2) application based on published literature, therefore an OSI inspection was not applicable.

11.3 Debarment Certification

JHP Pharmaceuticals LLC certified that they did not and will not use in any capacity the services of any person debarred under Section 306 subpart (b) or (b) of the Generic Drug Enforcement Act of 1992 and the Federal Food Drug and Cosmetic Act in connection with the manufacturing or testing of pharmaceutical products.

11.4 Financial Disclosure

Form 3454 is submitted and notes that JHP has not entered into any financial arrangements with the listed investigators. As noted, this is a 505(b)(2) application based on published literature, and the applicant noted “N/A” under the list of clinical investigators.

11.5 Other Regulatory Issues

None

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by DTOP, DPARP, DMEPA, OPDP/DPDP and OBP, and multiple labeling meetings were held with the reviewers and consultants. (See Appendix A)

- **Package insert (PI):** The PI is written in PLR format, and includes information on both indications. Preliminary format and content comments were reviewed by Leanna Kelly and Judit Milstein. DTOP, DPARP, DMEPA and OPDP provided labeling recommendations that have been addressed. Labeling has been finalized for the two indications.
- **Carton and Container Labels:** The labels have been reviewed by DTOP, ONDQA and DMEPA. The carton/container labels have been finalized.
- **Proprietary Name:** DMEPA concluded that the proposed proprietary name Adrenalin is not vulnerable to name confusion and was not found to be promotional in their review

of July 17, 2012. A letter stating that the name is conditionally acceptable was issued by Dr. Holquist of DMEPA on July 17, 2012. A follow up review dated November 15, 2012 continues to find the proprietary name acceptable.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The Adrenalin NDA 204200 will be approved. All disciplines recommend approval of the mydriasis indication. CMC initially recommended CR in August 2012 based on multiple deficiencies, but with further information exchange and teleconferences, JHP agreed to the product specifications and a PMC requested by ONDQA. As a result, ONDQA recommended approval.

Although initially DPARP indicated they would issue a separate letter, after input from the Associate Directors for Regulatory Affairs from the Offices in which DPARP and DTOP are located, it was agreed that one approval letter for both indications would be issued, and it would contain the single package insert and the carton/container labeling. The letter will be issued by or on the December 7, 2012 PDUFA goal date.

13.2 Risk Benefit Assessment

The safety and efficacy of epinephrine injection USP was based on the review of published preclinical and clinical trials submitted in this 505(b)(2) application. Epinephrine is an adrenergic agonist that has been marketed for over 100 years, and used for multiple uses, including the induction and maintenance of mydriasis during cataract surgery.

Cataract surgery and manipulation of the iris cause miosis of the pupil which complicates phacoemulsification and particularly insertion of the intraocular lens. Clinical trials provided data on efficacy and safety of epinephrine (1:1000) in dilutions up to 1:1,000,000. It was effective in keeping the pupil diameter >5 mm during the surgical procedure. According to CDC, cataract surgery is one of the most common outpatient procedures in the United States; there were 3.1 million procedures in 2006.²¹

Adrenalin (epinephrine injection, USP) is packaged in 3mL single-use vials containing a 1 mL solution of 1 mg/mL (1:1000) epinephrine with instructions for use. The contents of the vial must be diluted before use. The epinephrine is administered either as a bolus (0.1mL), or used for irrigation during the cataract procedure and maintains mydriasis by a direct action on the dilator pupillae of the iris.

Based

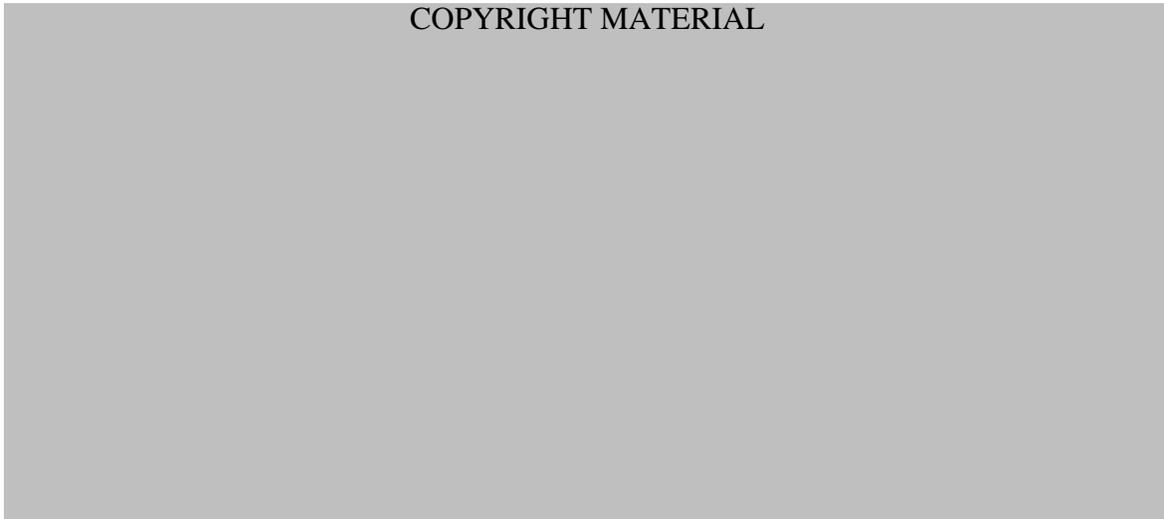
(b) (4)

in a single publication by Rowland the authors reported that the D- and L-forms of epinephrine had nearly identical effect on mydriasis in the rabbit model, as shown in

²¹ US Outpatient surgeries on the rise. January 28, 2009, <http://www.cdc.gov/media/pressrel/2009/r090128.htm>

²² Rowland JM and DE Potter. Steric structure activity relationships of various adrenergic agonists: ocular and systemic effects. Current Eye Research 1981; 1(1):25-35.

Figure 3 from the publication, below. Although it is not clear whether the human iris would react identically, at least in this rabbit study the two forms were both active.



Nonclinical studies demonstrated that epinephrine containing 0.1% sodium bisulfite as an antioxidant is associated with endothelial cell damage; however, when administered in diluted solution of at least 1:5000, corneal endothelial cell injury was not seen in rabbits and monkeys. In cats, epinephrine with sodium bisulfite 0.02% concentration was not associated with endothelial damage. In clinical trials, adverse reactions were rarely reported with epinephrine in the dilute concentrations tested (1:16,000 to 1,000,000). OSE retrieved 78 reports of adverse reactions reported for intraocular use of epinephrine products, these events included endophthalmitis, TASS, vision loss, etc., that can be seen during cataract surgery whether or not epinephrine is present. Intracamerally administered epinephrine was not associated with systemic changes in heart rate and blood pressure, suggesting there is no systemic absorption from the eye, which is not surprising given the 10 to 100 fold dilution before administration in the eye. In summary, the benefits of this product outweigh risks and the application will be approved.

13.3 Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)

ONDQA requested that JHP further evaluate their manufacturing process and determine possible causes for the formation of impurities and ways to minimize these. JHP will perform the following PMC:

Evaluate formulation and process improvements to reduce the levels of impurities with Adrenalin (epinephrine injection). In your evaluation, conduct at least one study to determine the possible cause(s) of (b) (4) formation and take appropriate measures to minimize the level of this impurity. Using the results from these investigations, re-evaluate the acceptance limits for (b) (4) and (b) (4) and lower the limits for these impurities. As part of an interim report, include your evaluation of the formulation/process improvements undertaken to mitigate the level of impurities, in

NDA 204200 /Original 2

Adrenalin (epinephrine injection) 1mg/mL

Proposed indication: induction and maintenance of mydriasis

particular (b) (4) and (b) (4), as well as a summary of all technical work performed using the results of the conducted study(ies). The interim report should also include a proposed development plan for future batches which will ensure consistency and reliability of product quality.

Final Protocol Submission: January 2013

Interim Report Submission: April 2013

Study/Trial Completion: March 2014

Final Report Submission: May 2014

Appendix A

Labeling - attached

12 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/

RENATA ALBRECHT
12/07/2012