CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204200Orig1s000
204200Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-200 Original 1	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	March 7, 2012		
Divisions:	DPARP	**Team Leader:** Angelica Dorantes, Ph.D.	
Sponsor:	JHP Pharmaceuticals	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Adrenalin®	**Date Assigned:**	March 19, 2012
Generic Name:	Epinephrine Injection	**Date of Review:**	November 13, 2012
Indication:	Treatment of severe allergic reactions (anaphylaxis)	**Type of Submission:** 505(b)(2) NDA Application	
Formulation/strengths:	Parenteral / 1 mg per mL		
Route of Administration:	IM and SC		

SUMMARY

On March 7, 2012, JHP Pharmaceuticals submitted a 505(b)(2) New Drug Application for Adrenalin® (epinephrine injection, USP) 1 mg/mL. In this NDA, the Applicant is seeking the approval of different indications; therefore, it includes the Original 1-Submission (Standard) and the Original 2-Submission (Priority), which are being handled by the Clinical Divisions, DPARP and DTOP, respectively.

- The Original 1 submission involves the proposed indication of allergic reactions (anaphylaxis).
- The Original 2 submission involves the proposed indication of maintenance of mydriasis during cataract surgery.

This review relates only to the Original 1-Submission section that includes a BA/BE waiver request for the proposed product (Adrenalin® 1 mg/mL) for the intramuscular (IM) and subcutaneous (SC) routes of administration. (The review of the Original 2-Submission by this reviewer can be founds in DARRTS dated 08/13/2012.) To support the biowaiver request, the Applicant provided a quantitative and qualitative comparison of the formulation, strengths, and needle dimensions for the proposed product and the reference product (EpiPen® Auto-injector), which is approved for IM and SC routes of administration. The proposed drug product primarily differs from the approved reference in that it will be used solely in the clinical setting. The proposed product will be administered by needle injection and it is intended to be used by a medical professional in a medically supervised setting, whereas the RLD, EpiPen® Auto-Injector, is specifically intended to be used by patients who have been determined to be at risk in the non-medically supervised setting at the first sign of symptoms. For these reasons, although the overall indication will be the same (treatment of anaphylaxis), the dosage and administration for this product will differ substantively from the approved auto-injector products.

The focus of this Biopharmaceutics review is on the evaluation and acceptability of the biowaiver request for the IM and SC routes. (b) (4)

RECOMMENDATION

A waiver from conducting an *in vivo* bioequivalence study is granted for the Adrenalin® IM and SC routes of administration due to 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,

Kareen Riviere, Ph.D.
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Office of New Drug Quality Assessment

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cc: Richard Lostritto, Ph.D.

ASSESSMENT OF BIOPHARMACEUTIC INFORMATION

1. Background

Drug Substance

Epinephrine is a naturally occurring hormone and neurotransmitter that is a nonselective agonist of adrenergic receptors. It is soluble in water at neutral and acidic pHs. The stucture is epinephrine is shown in Figure 1.

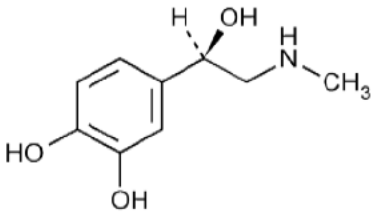


Figure 1. Chemical structure of epinephrine.

Drug Product

Adrenalin® currently marketed by JHP Pharmaceuticals, LLC (JHP) is the same Adrenalin® initially manufactured and marketed by Parke-Davis around the turn of the twentieth century (pre-1938 drug). The drug product has been commercially available for over 100 years, with a formulation similar to the current formulation described in Table 1.

Table 1. Adrenalin® Drug Product Formulation

Ingredient	Function	1 mL	
		mM	mg/mL
			(b) (4)
NaCl	Tonicity agent	(b) (4)	9.00
Sodium Metabisulfite (as Sodium Bisulfite)	Anti-oxidant		1.00
HCl	(b) (4		(b) (4)
Epinephrine USP Synthetic			

The drug substance is (b) (4) administered as a solution.

2. Biowaiver Request

As per 21 CFR 320.21(a), all NDA applicants are required to include in the NDA either evidence measuring the in vivo bioavailability of the drug product that is the subject of the NDA or information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

Intramuscular and Subcutaneous Routes

The Applicant requested a waiver of in vivo bioequivalence studies for the intramuscular (IM) and subcutaneous (SC) routes. They claim that the proposed drug product is in the same dosage form (b) (4) as the reference listed drug, EpiPen® by Meridian Medical Technology. Tables 2 and 3 summarize the supportive information provided by the Applicant for a BA/BE waiver for IM and SC routes of administration.

Table 2. Comparison of the Epinephrine Formulation in Adrenalin® and EpiPen®

Ingredient	Adrenalin® (b) (4) (mg/mL)	EpiPen® Auto-injector (mg/mL)
Epinephrine	1:1000	1:1000
Sodium Metabisulfite	1	(b) (4)
Sodium Chloride (b) (4	9 (b) (4	
Hydrochloric Acid		
Water for Injection		

Table 3. Comparison of Adrenalin® and EpiPen® Products

Parameters	RLD - EpiPen® Meridian Medical Technology	Proposed 505(b)(2) NDA JHP Pharmaceuticals, LLC
Drug Name:	EpiPen® (epinephrine injection)	Adrenalin® (epinephrine injection)
Conditions of Use	Treatment of anaphylaxis	Treatment of anaphylaxis
Dosage Form	Injection	Injection
Route of Administration	Intramuscular Subcutaneous	Intramuscular Subcutaneous
Strengths	0.3 mg/0.3 mL (1:1000)	1 mg/mL (1:1000)
Presentations	2 mL solution per Auto-Injector	1 mL (b) (4)
Mode of Delivery (needle dimension)	1/2" to 5/8"	1/2" to 5/8"

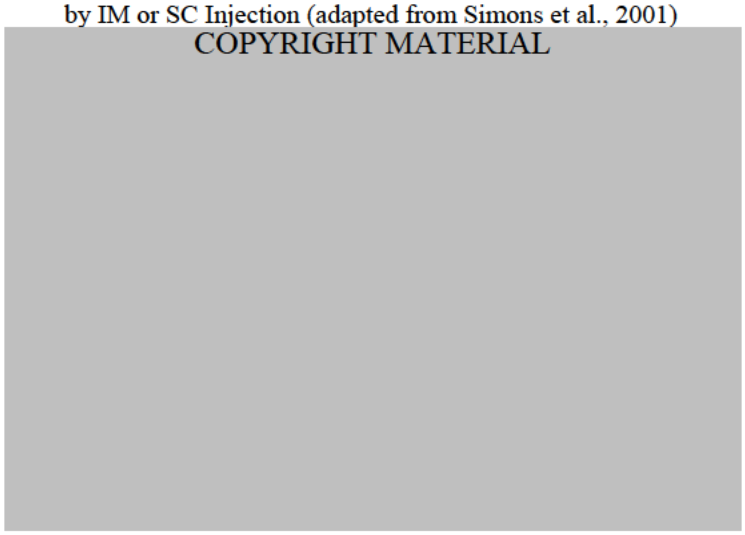
Reviewer's Assessment:

Based on 21 CFR 320.22 and scientific considerations, a waiver may be granted if the drug product under evaluation meets the following criteria:

1. ***It is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution;***
2. ***Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application;***
3. ***Administered via similar delivery mode as demonstrated by delivery device parameters (i.e. total needle length, exposed needle length, needle gauge, injection duration, injection volume, and injection force) as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.***

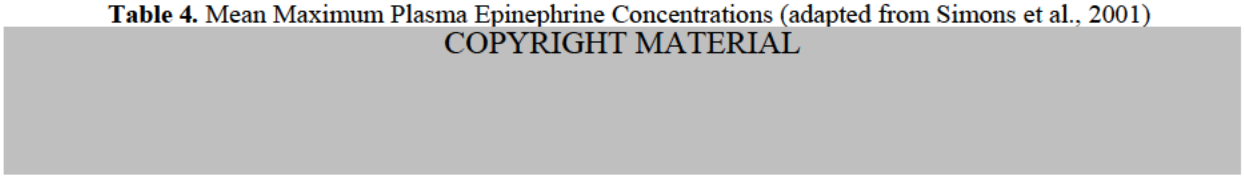
The proposed drug product is intended solely for administration by injection. Also, the proposed drug product does contain the same active and inactive ingredients in the same concentration as the RLD. Additionally, the Applicant provided information comparing the needle gauge for the proposed product and the RLD. They did not provide information comparing the total needle length, exposed needle length, injection duration, injection volume, and injection force for the proposed product and the RLD. However, the Applicant referenced a published article with data from a prospective, randomized, blinded, placebo-controlled, 6-way crossover study conducted by Simons et al. that shows that the 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. The Cmax of Epipen, the RLD, is relatively similar to that of epinephrine administered intramauscularly in the thigh (refer to Figure 2 and Table 4 below). Furthermore, the formulation of the proposed product is comparable to the epinephrine formulations investigated in the above mentioned published study.

Figure 2. Mean Plasma Epinephrine Concentrations after administration of 0.3mg dose of Epinephrine by IM or SC Injection (adapted from Simons et al., 2001)



T, Thigh; A, upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of 0.9% saline solution (0.3 mL) in the upper arm. The plasma epinephrine concentrations shown were calculated by averaging (mean ± SEM) the epinephrine concentrations at each sampling time for each route and each site of injection.

Table 4. Mean Maximum Plasma Epinephrine Concentrations (adapted from Simons et al., 2001)



Therefore, a biowaiver is granted for the Adrenalin® IM and SC routes of administration due to 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 relatively 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.***

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/s/

KAREEN RIVIERE
11/13/2012

ANGELICA DORANTES
11/13/2012

CLINICAL PHARMACOLOGY REVIEW FOR ADRENALIN, NDA 204200 (ORIGINAL 1)

NDA	204200 Original 1	*Submission Date(s)*	March 7, 2012
Proposed Brand Name		Adrenalin	
Generic Name		Epinephrine injection, USP	
Reviewer		Sheetal Agarwal, Ph.D.	
Team Leaders		Suresh Doddapaneni, Ph.D (DPARP)	
OCP Division		Division of Clinical Pharmacology-2	
OND Divisions		Division of Pulmonary, Allergy and Rheumatology Products and Division of Topical and Ophthalmic Products	
Sponsor		JHP Pharmaceuticals	
Submission Type		505 (b) (2) NDA referencing Epipen® as well as published articles in literature	
Formulation; Strength(s)		1 mg/mL solution to be administered IM, SC (b) (4) (upon dilution)	
Proposed Indication		Hypersensitivity reactions: severe acute anaphylactic reactions (b) (4)	
Proposed Dosing Regimen		Flexible depending on the need determined by the physician	

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1.0 Executive Summary

1.1 Recommendation:

Office of Clinical Pharmacology/Division of Clinical Pharmacology-2, has reviewed NDA 204200 requesting approval of 1 mg/mL epinephrine solution, and finds the proposed drug product acceptable from a Clinical Pharmacology perspective.

1.2 Phase 4 commitments:

From the Clinical Pharmacology perspective, no Phase 4 commitment is applicable to this NDA.

1.3 Summary of important Clinical Pharmacology findings:

The NDA for Adrenalin (epinephrine injection, USP) 1 mg/mL was submitted under 505 (b) (2) regulations. This solution for injection has been marketed, unapproved, since the early 1900s, under the brand name Adrenalin trademark by Parke-Davis, King Pharmaceuticals, and JHP Pharmaceuticals.

In this NDA, the sponsor is seeking the approval of different indications; therefore, it includes the Original 1-Submission (Standard) and the Original 2-Submission (Priority), which is being handled by the Clinical Divisions, DPARP and DTOP, respectively.
• The Original 1 submission involves the proposed indication of allergic reactions (anaphylaxis).
• The Original 2 submission involves the proposed indication of maintenance of mydriasis during cataract surgery.

This review relates only to the Original 1- Submission section. Review of Original 2 submission by this reviewer can be found in DARRTS dated 08/17/2012.

No Clinical Pharmacology studies were conducted by the sponsor in support of this 505 (b) (2) NDA. Primary support for this NDA comes from several referenced published articles documenting a long (over 100 years) history of use of epinephrine at a variety of doses and routes of administration depending on the severity of the anaphylaxis reaction. The NDA is also a 505 (b) (2) NDA referencing previously approved auto-injector product dispensing epinephrine, i.e., EpiPen® (NDA 19-430). The NDA for EpiPen® was also approved as a 505(b)(2) NDA referencing published studies in literature for providing support of safety and efficacy of use of epinephrine in emergency anaphylactic situations.

The sponsor's proposed drug product primarily differs from the approved reference in the way it will be be used in a clinically setting. Sponsor's product Adrenalin is intended to be used by a medical professional in a medically supervised setting, whereas the epinephrine auto-injector, EpiPen®, is specifically intended to be used (by patients who have been determined to be at risk) in the non-medically supervised setting at the first sign of symptoms. For these reasons, although the overall indication will be the same (treatment of anaphylaxis), the dosage and administration for this product will differ substantively from the approved auto-injector products. Refer to the clinical review by the medical officer, Dr. Peter Starke (DPARP), for a review of literature articles provided in support of safety, efficacy and dosing of the product as labeled (in DARRTS dated 10/29/2012). From a Clinical Pharmacology perspective, since epinephrine solution has a long documented history of use through the intramuscular (IM) and subcutaneous (SC) routes in emergency anaphylactic situations and clinical review team finds

the safety and efficacy of the final labeled dosing of Adrenalin through SC and IM routes acceptable in a medical setting, there is no need for additional PK data through these routes.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The NDA for Adrenalin (epinephrine injection, USP) 1 mg/mL was submitted under 505 (b) (2) regulations referencing Agency's summary of findings for safety and efficacy of approved product, EpiPen® (NDA 19-430). Epinephrine solution for injection has been marketed, unapproved, since the early 1900s, under the brand name Adrenalin trademark by Parke-Davis, King Pharmaceuticals, and JHP Pharmaceuticals.

Currently approved epinephrine products for anaphylaxis indication include the following drug-device combinations marketed as 'auto-injectors':

a. Epipen® and Epipen Jr. (NDA 19-430) approved on Dec 22, 1987
b. Twinject® (NDA 20-800) approved on May 30, 2003
c. Auvi-Q® (NDA 201739) approved on Aug 10, 2012

All these 3 products are 'auto-injector' presentations indicated for emergency treatment of allergic reactions (Type I) including anaphylaxis. Each of the 3 products comes in 2 strengths, i.e., 0.15 (0.3 mL, 1:2000) and 0.3 mg (0.3 mL, 1:1000). The dosing regimen for the 3 products is also the same, i.e., auto-injector 0.3 mg to be used in patients greater than or equal to 30 kg (66 lbs) and auto-injector 0.15 mg to be used patients 15 to 30 kg (33 lbs – 66 lbs).

The sponsor has submitted a 505 (b) (2) NDA application referencing both literature (supporting proposed doses, indications and populations) as well as previously approved product Epipen® to support their NDA. Refer to the clinical review in DARRTS (dated 10/29/2012) by the medical officer, Dr. Peter Starke, for a review of literature articles provided in support of safety, efficacy and dosing of the product as proposed to be labeled.

It is important to note that sponsor's product differs from the currently approved epinephrine auto-injector products (EpiPen, Twinject, Auvi-Q) in that it 1) is a drug product only, whereas the auto-injectors are drug-device combinations, and 2) is intended to be used by a medical professional in a medically supervised setting, whereas the epinephrine auto-injectors are specifically intended to be used (by patients who have been determined to be at risk) in the non-medically supervised setting at the first sign of symptoms. For these reasons, although the overall indication will be the same (treatment of anaphylaxis), the dosage and administration for this product will differ substantively from the approved auto-injector products.

From a Clinical Pharmacology perspective, since epinephrine solution has a long documented history of use through the intramuscular (IM) and subcutaneous (SC) routes in emergency anaphylactic situations and clinical review team finds the safety and efficacy of the final labeled dosing of Adrenalin through SC and IM routes acceptable in a medical setting, there is no need for additional PK data through these routes.

(b) (4)

(b) (4)

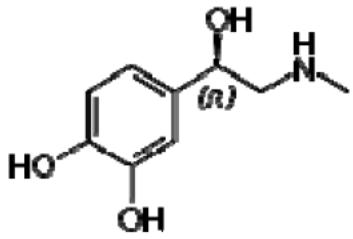
In addition, another relevant piece of the regulatory history for Adrenalin is that it is currently marketed in two sizes, 1 mL and 30 mL volumes, the two presentations differing in inactive ingredients: both contain sodium metabisulfite as an antioxidant (b) (4)

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

(b) (4)

pinephrine is soluble in water at neutral and acidic pHs. Epinephrine degrades through three common pathways: oxidation, sulfonation, and racemization.

Chemical structure of epinephrine:



Molecular Formula: C9H13NO3

Molecular Weight: 183.20

Chemical Name: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, *or* (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Epinephrine binds to both α-and β-adrenergic receptors, producing a complex range of physiological effects which can vary with dose, route, and speed of administration, but may have potent beneficial effects in patients with anaphylaxis. Via α1 adrenergic receptors, epinephrine mediates vasoconstrictor

effects on the small arterioles and precapillary sphincters in most body organ systems. This vasoconstriction decreases mucosal edema, which in turn prevents and relieves upper airway constriction, and increases blood pressure, preventing and relieving vasodilatory shock. β1 adrenergic effects include increased heart rate and force of cardiac contractions, and β2 effects lead to increased bronchodilation and decreased release of histamine, tryptase and other pro-inflammatory mediators from mast cells and basophils.

Based on literature articles provided by the sponsor, for the treatment of anaphylaxis epinephrine has been administered via SC, IM, and IV and inhalation routes. Epinephrine 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.

For ophthalmic use during cataract surgery, epinephrine is administered intraocularly/intracameraly, where its action on α1 adrenergic receptors in the iris produce mydriasis.

Proposed Indications:

Hypersensitivity reactions: severe acute anaphylactic reactions (b) (4)

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Several dosing regimens via different dosing routes (b) (4) have been proposed by the sponsor as indicated below.

Hypersensitivity Reactions: Anaphylaxis Intramuscular/Subcutaneous	(b) (4)
	(b) (4)

As of October 26, 2012 the following dosing scheme is being considered as acceptable for the anaphylaxis indication:

(b) (4)

[redacted] (b) (4)

Inspect visually for particulate matter and discoloration prior to administration. Do not use if the solution is pinkish or darker than slightly yellow, or if it contains particulate matter.

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 to 0.5 mL) of undiluted Adrenalin administered IM or SC in the anterolateral aspect of the thigh, up to a maximum of 0.5 mg (0.5 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) of undiluted Adrenalin administered IM or SC in the anterolateral aspect of the thigh, up to a maximum of 0.3 (0.3 mL) mg, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects. "

For the final dosing scheme approved for this product, refer to the final approved package insert.

2.1.5 What are the to-be-marketed formulations?

Adrenalin 1 mg/mL (1:1000). The vial size for Adrenalin 1mg/mL is listed as 3 mL in the NDA. The composition of the vial is represented below:

Ingredient	Function	1 mL	
		mM	mg/mL
[redacted] (b) (4)			
NaCl	Tonicity agent	(b) (4)	9.00
Sodium Metabisulfite (as Sodium Bisulfite)	Anti-oxidant		1.00 (b) (4)
HCl	(b) (4)		
Epinephrine USP Synthetic	Active Ingredient		

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

As indicated previously, no clinical pharmacology and clinical studies have been conducted in the support of this NDA, the NDA is a 505 (b) (2) NDA referencing literature and previously approved products and literature for approval.

2.2.2 What are the known PK characteristics of epinephrine and its metabolites?

Pharmacokinetics: When administered intramuscularly (IM) or subcutaneously (SC), epinephrine has a rapid onset and short duration of action. After oral administration, epinephrine is rapidly conjugated and oxidized in the gastro-intestinal mucosa and liver.

A review of some published studies that reported pharmacokinetic (PK) parameters of epinephrine when administered IM, SC or IV in adults and in children was conducted and is summarized in Appendix 1 at the end of this review. Although, these studies provide some PK information of epinephrine, their overall utility in quantitative terms as it relates to the proposed indication and associated dosing regimen for anaphylaxis indication via IM and SC routes is limited. Some of the limitations were that data was obtained in subjects when they are not in an allergic state, epinephrine levels were not corrected for baseline levels, and data was obtained with a single administration of a 0.3 mg IM or SC dose.

Metabolism: After injection, epinephrine is rapidly inactivated in the liver. It is either methylated by catechol-O-methyltransferase to metanephrine; or, alternatively, oxidatively deaminated by monoamine oxidase to 3,4-dihydroxyphenyl glycolaldehyde and then reduced to 3,4-dihydroxyphenylethylene glycol or oxidized to 3,4-dihydroxy-mandelic acid.

2.3 Intrinsic Factors

2.3.1. What is the pediatric plan?

The indication of anaphylaxis will trigger PREA because of the new route of administration and dosing regimen. However, since this drug has a documented clinical experience of over 110 years o for a variety of indications in all age groups and the pharmacologic and physiologic effects of the drug are considered the same for all age groups, the medical reviewer, Dr. Peter Starke recommends that the pediatric assessment be considered fulfilled for all age groups (see his review in DARRTS dated 10/29/2012). The application was discussed at the Pediatric Review Committee (PeRC) meeting on June 12, 2012. The PeRC agreed that the pediatric assessment for this drug will be considered to have been fulfilled in all age groups for both anaphyaxis and mydriasis indications.

3. Labeling Recommendations

The sponsor's proposed label was significantly modified by the Agency. Since the label is still undergoing several changes, the reader is requested to see the final approved label after the approval of the drug product. From a Clinical Pharmacology perspective, the following labeling language is recommended for section 12 (Clinical Pharmacology) which includes both the anaphylaxis and mydriasis indications (if approved for both):

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha and beta-adrenergic receptors.

12.2 Pharmacodynamics

Through its action on alpha-adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension.

Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation and helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis.

Epinephrine also alleviates pruritus, urticaria, and angioedema and may relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

12.3 Pharmacokinetics

(b) (4)

The extent of human systemic exposure at the labeled intraocular dose has not been evaluated, however, significant systemic concentrations or plasma exposure of epinephrine are not expected when administered intraocularly.

Appendix 1: A review of published PK studies involving epinephrine:

ADULTS:

1. **"Epinephrine absorption in adults: Intramuscular versus subcutaneous injection." Simons et al., 2001**

Study design and formulations/doses of epinephrine employed: Prospective, randomized, blinded, placebo-controlled, 6-way crossover study of intramuscular versus subcutaneous injection of epinephrine in young men. Participants were asked to come to the Health Sciences Clinical Research Centre Allergy Laboratory on 6 different mornings. The visits were scheduled at least 1 week apart; each visit lasted 3.5 to 4 hours. One injection was given at each visit. During the course of the study, each participant received 4 injections of epinephrine 0.3 mg (0.3 mL) and 2 injections of saline solution (0.9% NaCL, 0.3 mL) through use of a variety of injection routes and sites. Epinephrine USP 1:\000,0.3 mg (0.3 mL) was injected either IM into the vastus lateralis muscle or the deltoid muscle or SC in the deltoid region. Epinephrine 0.3 mg (0.3 mL) was injected IM into the vastus lateralis muscle through use of an EpiPen. Saline solution (0.3 mL) was injected IM into the deltoid muscle or SC in the deltoid region. To ensure blinding, all injections were given by a nurse not otherwise involved in the study, and at each visit both the thigh and upper arm sites were covered after the injection.

Study population: Healthy allergic men age 18 to 35 years. Thirteen men (26 ± 2 years; weight, 85 ± 5 kg [range, 62-114 kg]; body mass index, 36.6 ± 4.6 [range, 20-64]) completed the study.

PK sampling: Before injection and at 5, 10, 15, 20, 30, 40, 60, 90, 120, and 180 minutes afterwards.

Bioanalytical method: Plasma samples were frozen at -20°C until analyzed for epinephrine through use of a validated high-performance liquid chromatograph-electrochemical detector method with a limit of quantitation of 5 pg/mL, linear calibration curves over the range 25 to 1000 pg/mL, and a coefficient of variation of 3% at 1000 pg.7 Pharmacokinetic and statistical data analyses were performed through use of WinNonLin (Scientific Consulting Inc, Apex, NC) and PC-SAS (SAS Institute Inc, Cary, NC), respectively.

PK data: Mean plasma epinephrine concentrations versus time are shown in Fig I. There was a 9- to 14-fold range in peak plasma epinephrine concentrations (Cmax) among doses and routes of injection, a 2-fold variation in body weight, and a 3-fold variation in body mass. Mean Cmax was significantly higher *(P* < .01) after epinephrine IM injection into the thigh, either from an ampule or an EpiPen, than after epinephrine IM or SC injection into the upper arm, or after saline solution IM or SC injection into the upper arm (Table I).

Reviewer's comments: This study was reviewed as it provides preliminary support for labeling of epinephrine to be dosed through the thigh as a preferred site of IM injection. PK data as shown in Table I below, indicates that absorption of epinephrine through thigh is higher than through arm at the same nominal dose. Although epinephrine levels are not baseline-corrected, qualitatively the plasma concentrations appear to be much higher when epinephrine is injection through the thigh vs. through the arm.

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FIG 1. COPYRIGHT MATERIAL
COPYRIGHT MATERIAL

TABLE I. Mean maximum plasma epinephrine concentrations

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2. **"Adrenaline: relationship between infusion rate; plasma concentration, metabolic and haemodynamic effects in volunteers". Ensinger et al., 1992**

Study design and formulations/doses of epinephrine employed: 2 mL of commercially available adrenaline (1 mL solution containing 1.2 mg adrenaline hydrochloride equivalent to 1 mg free base of adrenaline; 4 mg chlorobutanol; 0.53 mg sulphite) were diluted to 50 mL with 0.9% saline. Adrenaline was infused at five nominal infusion rates (0.01, 0.06, 0.1, 0.14, 0.2 µg/kg/min) each for the duration of 30 min, for the purpose of constructing cumulative dose response curves.

Study population: Eight normal young men were studied (age 22-27 years, height 175-189 cm, weight 67-85 kg).

PK sampling: Arterial blood samples were taken before the start of the infusion and at the 28th min of each infusion period to determine the concentration of adrenaline, noradrenaline, sodium, potassium, NEFA, glucose, lactate, insulin, c-peptide and glucagon. The infusion was stopped after 150 min and further readings of the cardiovascular parameters and blood samples were taken at intervals of 14,30,60 and 90 min after the end of the infusion.

PK data: Adrenaline was infused at five nominal infusion rates of 0.01, 0.06, 0.1, 0.14 and 0.2 µg/kg/min. The resulting arterial adrenaline plasma concentrations were correlated to the infusion rate (Table 1, Fig.

1). Infusions of adrenaline in increasing rates from 0.01 to 0.2 µg/kg/min resulted in a linear increase in plasma concentration.

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Reviewer's comments: (b) (4) ***the study was reviewed as it showed that when dosed at an infusion rate of 0.01 to 0.2 µg/kg/min, epinephrine plasma concentrations increase with increasing dose indicating linear pharmacokinetics of epinephrine between these doses, in adults. It should be noted that the epinephrine levels that are reported are not corrected for baseline epinephrine levels.***

CHILDREN:

1. **"Epinephrine absorption in children with a history of anaphylaxis" Simons et al., 1998**

Study design and formulations/doses of epinephrine employed: Randomized, single-blind, single-dose, parallel-group pilot study in 17 children who received either a **SC injection** of 0.01 mL/kg epinephrine hydrochloride solution (maximum, 0.3 mL [0.3 mg]) in the form of Adrenaline (1 mg/mL ampule; Parke-Davis, Scarborough, Ontario, Canada) or an **IM injection** of 0.3 mL (0.3 mg) with the EpiPen Auto-Injector (Allerex Laboratory, Ltd., Kanata, Ontario, Canada).

Study population: Children 8 ± 1 years, 27 ± 2 kg in the IM group and 32 ± 3 kg in the SC group, having a history of severe allergies and systemic anaphylaxis

PK sampling: Before injection and at 5, 10, 15, 20, 30, 40, 60, 90, 120, and 180 minutes afterwards. Both endogenous and exogenous plasma epinephrine concentrations were measured. The preinjection baseline (presumably endogenous) plasma epinephrine concentrations found (285 +/- 32 to 339 +/- 115 pg/mL) were higher than those found in 10 healthy adult control subjects studied concurrently in our laboratory, in whom baseline endogenous plasma epinephrine concentrations ranged from 141 +/- 22 pg/mL to 173 +/- 34 pg/mL on two different study days. On one of these study days, the ten adult control subjects were monitored for 120 minutes without receiving any epinephrine injections, and during that time their endogenous plasma epinephrine concentrations peaked at 237 +/- 33 pg/mL.

Bioanalytical method: Blood samples were centrifuged at 4° C. Plasma was transferred into an appropriately labeled polypropylene tube with screw cap, frozen promptly in an upright position, and stored at –20° C until analysis. After thawing the plasma, solid/liquid-phase extraction was performed, with an efficiency of 75% to 80%. Epinephrine concentrations were measured with a high-performance liquid chromatography (HPLC) reverse-phase system (Waters Corp., Milford, Mass.) with electrochemical detection.13 With modification of this assay, it was possible to detect as little as 5 pg/ml (0.025 nmol/ml) of epinephrine. Calibration curves were linear over the range 25 to 1000 pg/ml (0.125 to 5 nmol/ml) with a coefficient of variation of 3% at 1000 pg and 10% at 25 pg.

PK data: In nine children who received epinephrine subcutaneously, the mean maximum plasma epinephrine concentration (+/- SEM) was 1802 +/- 214 pg/mL, achieved at a mean time of 34 +/- 14 minutes (range, 5 to 120 minutes). Only two of the nine children achieved maximum plasma concentrations by 5 minutes. In eight children who received epinephrine intramuscularly, the mean maximum plasma concentration was 2136 +/- 351 pg/mL, achieved at a mean time of 8 +/- 2 minutes, which was significantly faster than the mean time at which maximum plasma concentrations were achieved after subcutaneous epinephrine injection ($p < 0.05$). Six of the eight children achieved maximum plasma concentrations by 5 minutes. The terminal elimination half-life was 43 +/- 15 minutes.

Reviewer's comments: This pilot study was reviewed as it provides preliminary PK data of epinephrine when dosed IM or SC in children. The study involves dosing of 0.3 mg epinephrine to children via an auto-injector product or via a solution. The injection sites for the injections are not mentioned for both the routes, i.e., thigh or arm or any other site. Although the epinephrine solution was administered SC by a medical professional, the children injected the auto-injector product themselves and it is not clear if the route of administration was IM or SC. However the authors have assumed that the auto-injector route of administration was IM. The study showed that epinephrine plasma concentrations were slightly higher with the auto-injector (assumed to be IM) as compared to the SC solution. In addition,

time to achieve maximal concentrations is shorter with the auto-injector product as compared with the SC solution. The half life of epinephrine is reported to be 43 min with IM epinephrine, however since the exogenously administered epinephrine is not tagged with a radioactive moiety, the reported half life cannot be assumed as true half-life as significant endogenous levels of epinephrine are reported to exist in the volunteers. In this study, the epinephrine baseline concentrations were reported as mean, but the final epinephrine plasma concentrations in individuals were not baseline-corrected.

2. **"Pharmacokinetics of exogenous epinephrine in critically ill children" Fisher et al., 1993**

Study design and formulations/doses of epinephrine employed: This study was prospective, without intervention or control groups. All patients in the pediatric ICU at either Memorial Miller Children's Hospital or the University of California, Irvine, Medical Center, who were monitored for ~4 hrs, and who received a constant infusion of epinephrine, were eligible for enrollment. Solutions of epinephrine (Parke-Davis, Kalamazoo, MI) were made by the pharmacy at both hospitals using 5% or 10% dextrose in water. All infusions were administered using an infusion pump (AS 20S, Baxter Healthcare, Hookset, NH) at infusion rates of 0.5 to 11.0 *Mu* hr.

Study population: The patients' ages ranged from 0.5 to 16 yrs with a median age of 5 yrs. Their weights ranged from 8.5 to 84.1 kg. Four of the six patients were male.

PK sampling: Paired arterial blood samples were obtained 20 to 30 mins apart during a constant **infusion** of epinephrine, the first sample being drawn after 60 mins of a documented constant rate and stable hemodynamic status. A sample of the epinephrine infusion solution was also collected for determination of the epinephrine concentration.

PK data: Plasma epinephrine concentrations during steady-state infusions of 0.03 to 0.2 µg/kg/ min ranged from 670 to 9430 pg/mL (3660 to 51,490 pmol/L), with a mean of 4360 ± 3090 pg/mL (23,810 ± 16,870 pmol/L) and were linearly related to dose. Epinephrine clearance rates ranged from 15.6 to 79.2 mUkg/min (mean 29.3 ± 16.1) and were not dependent on steady-state plasma concentrations.

Reviewer's comments: (b) (4) ***the study was reviewed as it showed that when dosed at an infusion rate of 0.03 to 0.2 µg/kg/ min, epinephrine plasma concentrations increase with increasing dose indicating linear pharmacokinetics of epinephrine between these doses, in children. It should be noted that the epinephrine levels that are reported are not corrected for baseline epinephrine levels.***

Appendix 2: A review of published PK studies involving epinephrine:

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies to be reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				

III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**More than 15**	**4**	**Sponsor has not conducted any clinical studies. Literature information has been submitted to support safety and efficacy of the product. 505b2 reference EpiPen® is approved for SC and IM routes.** (b) (4) **The 4 articles that were reviewed constitute some adult and pediatric data with epinephrine solution administered IM, SC and IV. The studies are not robust and data will not be included in the label.**
Total Number of Studies		**More than 15**	**4**	

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/s/

SHEETAL S AGARWAL
11/05/2012

SURESH DODDAPANENI
11/08/2012

NDA	204200, Original 2	*Submission Date(s)*	March 7, 2012
Proposed Brand Name	Adrenalin®		
Generic Name	Epinephrine injection, USP		
Reviewer	Sheetal Agarwal, Ph.D.		
Team Leader	Philip Colangelo, Pharm.D, Ph.D		
OCP Division	Division of Clinical Pharmacology 4		
OND Divisions	Division of Transplant and Ophthalmic Products (DTOP)		
Sponsor	JHP Pharmaceuticals		
Submission Type	505 (b) (2) NDA referencing Epipen® as well as literature		
Formulation; Strength(s)	1 mL (b) (4)		
Indication	1 mg/mL ophthalmic solution: Induction and maintenance of mydriasis during intraocular surgery		
Proposed Dosing Regimen	• 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).		

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation:

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.

1.2 Phase 4 commitments:

From the Clinical Pharmacology perspective, no Phase 4 commitment is applicable to this NDA.

1.3 Summary of important Clinical Pharmacology findings:

The NDA for Adrenalin® (epinephrine injection, USP) 1 mg/mL (b) (4) was submitted on March 7, 2012 under 505 (b) (2) regulations. This solution for injection has been marketed, unapproved, since the early 1900s, under the brand name Adrenalin® trademark by Parke-Davis, King Pharmaceuticals, and JHP Pharmaceuticals.

In this NDA, the Applicant is seeking the approval of different indications; therefore, it includes the Original 1-Submission (Standard) and the Original 2-Submission (Priority), which is being handled by the two Clinical Divisions, DPARP and DTOP, respectively.
• The Original 1 Submission involves the proposed indication of allergic reactions (anaphylaxis).
• The Original 2 Submission involves the proposed indication of induction and maintenance of mydriasis during cataract surgery.

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).

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The NDA for Adrenalin® (epinephrine injection, USP) 1 mg/mL [redacted] (b) (4) was submitted under 505 (b) (2) regulations. This solution for injection has been marketed, unapproved, since the early 1900s, under the brand name Adrenalin®.

Currently approved epinephrine products include Epipen® (NDA 19-430) and Twinject® (NDA 20-800) auto-injectors for emergency treatment of allergic reactions (Type I) and numerous epinephrine containing anesthetic solutions (e.g., Marcaine® and Xylocaine®) indicated for the production of local anesthesia.

For the anaphylaxis indication, the current application is submitted as a 505 (b) (2), referencing both literature [redacted] (b) (4) as well as approved products Epipen® and Twinject® (to support previously approved intramuscular and subcutaneous dosing). Both Twinject® and EpiPen® were approved by the FDA for the treatment of anaphylaxis solely based on the literature without the need for additional clinical trials. For the mydriasis indication, the product has a long history of use just like for the anaphylaxis indication, and as such, for this indication as well, the current application is submitted as a 505 (b) (2), referencing both previously approved epinephirine products as well as published articles. 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.

A pre-IND/pre-NDA teleconference meeting was held on July 5, 2011 to discuss requirements for filing a 505 (b) (2) NDA. At this meeting, the ONDQA/Biopharmaceutics review team provided the following comments to the sponsor that is pertinent to Clinical Pharmacology as well:

"1. The to-be-submitted 505 (b) (2) NDA submission for the proposed drug product should include data from a Bioavailability or Bioequivalence (BA/BE) study comparing the proposed drug product to a RLD product (EpiPen® or Twinject®) [§320.2I (a) (1)]. Or, you may request a BA/BE waiver and provide the supportive data [§320.21 (a)(2)].

2. A BA/BE waiver may be granted for the proposed product for the SC or IM routes if the following supportive information is provided:
• Qualitative/quantitative comparison of formulations;
• Justification for differences in the inactive ingredients, if any;
• A head to head comparison table (proposed product vs. RLD) listing strengths, [redacted] (b) (4) label indications, etc.); and
• Evidence of similar mode of delivery (needle dimensions, etc.) as the RLD product.

[redacted] (b) (4)

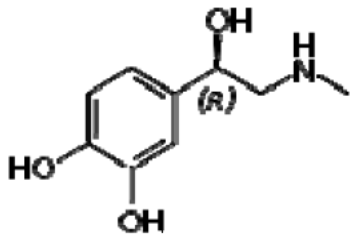
Based on the comments provided, the sponsor requested for a BA/BE waiver for their product for the ophthalmic indication and were granted a biowaiver (see review in DARRTS by Dr. Kareen Riviere dated 8/13/12).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

[redacted] (b) (4)

Epinephrine is soluble in water at neutral and acidic pHs. Epinephrine degrades through three common pathways: oxidation, sulfonation, and racemization.

Chemical structure of epinephrine:



Molecular Formula: C9H13NO3

Molecular Weight: 183.20

Chemical Name: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, *or*
(-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Epinephrine binds to both α-and β-adrenergic receptors, producing a complex range of physiological effects which can vary with dose, route, and speed of administration, but may have potent beneficial effects in patients with anaphylaxis. Via α1 adrenergic receptors, epinephrine mediates vasoconstrictor effects on the small arterioles and precapillary sphincters in most body organ systems. This vasoconstriction decreases mucosal edema, which in turn prevents and relieves upper airway constriction, and increases blood pressure, preventing and relieving vasodilatory shock. β1 adrenergic effects include increased heart rate and force of cardiac contractions, and β2 effects lead to increased bronchodilation and decreased release of histamine, tryptase and other pro-inflammatory mediators from mast cells and basophils.

Based on literature articles provided by the sponsor, for the treatment of anaphylaxis epinephrine has been administered via SC, IM, and IV and inhalation routes. Epinephrine 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.

For ophthalmic use during cataract surgery, epinephrine is administered intraocularly/intracameraly, where its action on α1 adrenergic receptors in the iris produce mydriasis.

Proposed Indications:

Induction and maintenance of mydriasis during cataract surgery

2.1.4 What are the proposed dosage(s) and route(s) of administration?

- 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).

2.1.5 What are the to-be-marketed formulations?

Adrenalin® currently marketed by JHP Pharmaceuticals, LLC (JHP) is the same Adrenalin® initially manufactured and marketed by Parke-Davis around the turn of the twentieth century (pre-1938 drug). The drug product has been commercially available for over 100 years, with a formulation similar to the current formulation described below:

Ingredient	Function	(b) (4) 1 mL	
		mM	mg/mL
	(b) (4)	(b) (4	(b) (4)
NaCl	Tonicity agent		9.00
Sodium Metabisulfite (as Sodium Bisulfite)	Anti-oxidant		1.00 (b) (4)
HCl	(b) (4)		
Epinephrine USP Synthetic	Active Ingredient		

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

As indicated previously, no clinical pharmacology or clinical studies have been conducted in the support of this NDA, the NDA is a 505 (b) (2) NDA referencing literature and previously approved products for approval.

3. Labeling Recommendations

A label was constructed by Dr. Wiley Chambers for the ophthalmic indication for this product (attached). Clinical Pharmacology edits are underlined.

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

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/s/

SHEETAL S AGARWAL
08/17/2012

PHILIP M COLANGELO
08/17/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-200 Original 2	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	March 7, 2012		
Division:	DTOP	**Team Leader:** Angelica Dorantes, Ph.D.	
Sponsor:	JHP Pharmaceuticals	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Adrenalin®	**Date Assigned:**	March 19, 2012
Generic Name:	Epinephrine Injection	**Date of Review:**	August 13, 2012
Indication:	Ophthalmic clinical use: maintenance of mydriasis during cataract surgery	**Type of Submission:** 505(b)(2) NDA Application	
Formulation/strengths:	Opthalmic Solution / 1 mg per mL		
Route of Administration:	Intraocular		

SUBMISSION

On March 7, 2012, JHP Pharmaceuticals submitted a 505(b)(2) New Drug Application for Adrenalin® (epinephrine injection, USP) 1 mg/mL. In this NDA, the Applicant is seeking the approval of different indications; therefore, it includes the Original 1-Submission (Standard) and the Original 2-Submission (Priority), which are being handled by the Clinical Divisions, DPARP and DTOP, respectively.

- The Original 1 submission involves the proposed indication of allergic reactions (anaphylaxis).
- The Original 2 submission involves the proposed indication of maintenance of mydriasis during cataract surgery.

REVIEW

This review relates only to the Original 2- Submission section. The Original 2- Submission includes literature data to support the safety and efficacy of the ophthalmic indication for the proposed product. A BA/BE waiver request was not included in the NDA for this ophthalmic indication, which requires an intraocular (IO) route of administration.

The focus of this Biopharmaceutics review is the evaluation and acceptability of the information/data supporting the approval of a BA/BE waiver for Adrenalin® using the IO route of administration.

BIOPHARMACEUTICS INFORMATION

Drug Substance

Epinephrine is a naturally occurring hormone and neurotransmitter that is a nonselective agonist of adrenergic receptors. It is soluble in water at neutral and acidic pHs. The stucture is epinephrine is shown in Figure 1.

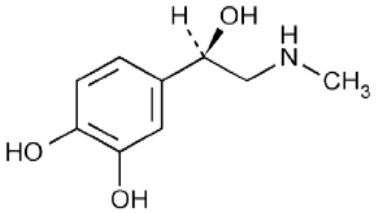

Figure 1. Chemical structure of epinephrine.

Drug Product
Adrenalin® currently marketed by JHP Pharmaceuticals, LLC (JHP) is the same Adrenalin® initially manufactured and marketed by Parke-Davis around the turn of the twentieth century (pre-1938 drug). The drug product has been commercially available for over 100 years, with a formulation similar to the current formulation described in Table 1.

Table 1. Adrenalin® Drug Product Formulation

Ingredient	Function	1 mL	
		mM	mg/mL
	(b) (4	(b) (4	(b) (4)
NaCl	Tonicity agent		9.00
Sodium Metabisulfite (as Sodium Bisulfite)	Anti-oxidant		1.00 (b) (4)
HCl	(b) (4)		
Epinephrine USP Synthetic			

The drug substance is (b) (4) administered as a solution.

BIOWAIVER

As per 21 CFR 320.21(a), all NDA applicants are required to include in the NDA either evidence measuring the in vivo bioavailability of the drug product that is the subject of the NDA or information to permit FDA to waive the submission of evidence measuring in vivo bioavailability. A BA/BE waiver request was not included in the NDA for this indication, which requires an IO route of administration.

Biowaiver Justification: Based on discussions with Dr. Sheetal Agarwal, the Clinical Pharmacology Reviewer from OCP, bioavailability data are not available for the IO route of administration for this drug product since it is delivered locally. Though the Applicant did not conducted any PK studies to demonstrate that Adrenalin® administered intraocularly does not produce systemic levels of epinephrine, the ONDQA Biopharmaceutics Team deduces that the proposed dose of Adrenalin® administered intraocularly (1µg/mL to 10µg/mL) is unlikely to generate measurable levels of epinephrine in the systemic circulation. Thus, it is not feasible to attain bioavailability data for Adrenalin® administered intraocularly at the proposed dose.

Reviewer's Assessment: Acceptable
Since it is not feasible to evaluate the bioavailability of Adrenalin® administered intraocularly at the proposed dose, this Reviewer is of the opinion that a "Good Cause" BA/BE waiver is appropriate for this product.

RECOMMENDATION

A "Good Cause" BA/BE waiver is granted for the Adrenalin® IO route of administration based on 21 CFR 320.22(e). Therefore, from the Biopharmaceutics perspective NDA 204-200/Original 2 - Submission Section for Adrenalin® 1 mg/mL for the IO route of administration is recommended for APPROVAL.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Richard Lostritto, Ph.D.

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/s/

KAREEN RIVIERE
08/13/2012

ANGELICA DORANTES
08/13/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 204200**	**Proposed Brand Name**	**Adrenalin**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Epinephrine**
Medical Division	**DPARP**	**Drug Class**	**Endogenous molecule**
OCP Reviewer	**Sheetal Agarwal**	**Proposed Indication(s)**	**Anaphylaxis and Mydriasis**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**IM/SC (b) (4) solutions: Emergency treatment of anaphylaxis Optical solution: Mydriasis**
Other discipline reviewers	-	**Dosing Regimen**	**Flexible depending on the need determined by the physician**
Date of Submission	**March 7, 2012**	**Route of Administration**	**IM/SC (b) (4): Anaphylaxis Optical: Mydriasis**
Estimated Due Date of OCP Review		**Sponsor**	**JHP Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**S (Anaphylaxis) P (Mydriasis)**
PDUFA Due Date	**Anaphylaxis: January 7, 2013 Mydriasis: September 7, 2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**Many**		**Sponsor has not conducted any studies. Literature information has been submitted to support safety and efficacy of the product. 505b2 reference EpiPen® is approved for SC and IM routes.** (b) (4) [redacted]
Total Number of Studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x		x	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic	x			

	requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Additional Comments: The sponsor has referenced 2 articles in the Clinical Pharmacology section of the proposed label. In addition, they have submitted several articles published over the past 30-40 years in support of their application. The main support for this 505(b)(2) NDA comes from published articles as well as from the approved reference EpiPen®, which was also a 505(b)(2) NDA referencing literature for its approval. A few articles may be reviewed for Clinical Pharmacology information, depending on the level of adequacy of the content of those articles as per current standards, however the main support for this NDA will come from the long history of safety and efficacy of proposed doses and dosing regimen of epinephrine based on published literature (clinical review).

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

/s/

SHEETAL S AGARWAL
04/26/2012

SURESH DODDAPANENI
04/26/2012