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APPLICATION NUMBER:

204640Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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

NDA	204-640	*Submission Date(s)*	March 7, 2012
Proposed Brand Name		Adrenalin	
Generic Name		Epinephrine injection, USP	
Reviewer		Sheetal Agarwal, Ph.D., RAC	
Team Leaders		Satjit Brar, Pharm.D., 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 (NDA 19-430) as well as literature	
Formulation; Strength(s)		Solution for Injection, 1 mg/mL, 30 mL	
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 204-640 requesting approval of 1 mg/mL epinephrine solution in a 30 mL vial, 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 in a 30 mL multiple-dose vial 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. Recently, NDA 204-200 for Adrenalin 1 mg/mL (1 mL presentation, single-use vial) was submitted by the same sponsor and was approved by the Agency on December 12, 2012, to be marketed under the Trade Name, Adrenalin. The 2 major differences in the approved product 1 mg/mL (1 mL presentation) and the product in the current NDA submission, 1 mg/mL (30 mL presentation) are 1) the total volume of presentation, i.e., 1 mL vs. 30 mL and 2) the presence of a preservative, chlorobutanol (0.54%) to enable multiple-dose usage of the 30 mL vial. The sponsor requested for a biowaiver for conducting *in vivo* bioavailability study, which was granted by the ONDQA/Biopharmaceutics team (review in DARRTS dated 12/5/2013).

As with recently approved NDA 204-200, 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.

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 11/25/2013 for current NDA 204-640 and on 10/29/2012 for recently approved NDA 204-200). For a review of some of the relevant published articles outlining epinephrine PK when administered through SC or IM routes, refer to the clinical pharmacology review of NDA 204-200 (in DARRTS dated 11/8/2012). Since the sponsor is proposing to utilize the same package insert as that of recently approved NDA 204-200, the labeling was only reviewed for changes related to addition of the 30 mL presentation as a dosage form in addition to the currently approved 1 mL presentation. As such, there are no major labeling edits from a clinical pharmacology perspective to the proposed package insert for the 30 mL presentation.

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/s/

SHEETAL S AGARWAL
12/06/2013

SATJIT S BRAR
12/07/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-640	**Reviewer:** Assadollah Noory, PhD	
Submission Dates:	August 2, 2013, November 1, 2013		
Division:	Division of Pulmonary, Allergy and Rheumatology Products	**Team Leader:** Tapash Ghosh, PhD	
Applicant:	JHP Pharmaceuticals, LLC	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	Adrenalin®	**Date Assigned:**	November 7, 2013
Established Name:	Epinephrine Injection, USP	**Date of Review:**	November 25, 2013
Indication:	Treatment of severe acute anaphylactic reactions, (b) (4)	**Type of Submission:** Original New Drug Application – 505(b)(2)	
Dosage form/ strengths	Solution for Injection/ 1 mg/mL, 30 mL		
Route of Administration	(b) (4) IM injection		
Type of Review:	Biowaiver Request		

SUBMISSION:

The proposed drug product is a sterile solution for injection intended to be administered via the intramuscular (IM) or subcutaneous (SC) route of administration. The proposed drug product is packaged in a 1 ml single dose vial without preservative and 30 ml multi-dose vial with preservative ((b) (4)% chlorobutanol). This application is an electronic NDA, filed as a 505(b)(2) application. The reference listed drugs (RLD) is EpiPen®. The Applicant is requesting a waiver of the requirement to provide evidence of in-vivo bioavailability for both route of administration (IM, SC) of the proposed drug product. On October 9, 2013 in the filing communication letter the Agency requested the following:

As per 21 CFR § 320.22 (b)(1), FDA shall waive the requirement for the submission of data demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. However, since your product contains chlorobutanol and the reference listed drug (RLD) does not, provide justification with supportive data (e.g., published literature, study data, etc.) demonstrating that the presence of chlorobutanol will not have any impact on the pharmacokinetics, efficacy, and safety of your product. Also provide a side-by-side summary table comparing your proposed product vs. the reference product (including description, formulation, pH, osmolality, tonicity

etc.).

BIOPHARMACEUTICS INFORMATION: The applicant responded to the IR in a communication dated November 1, 2103. The excerpts from that response is reviewed and discussed below:

The applicant provided a summary table comparing their proposed **Adrenalin® 30 mL Vial** product to the reference listed product shown in the following table.

Attribute	**EpiPen® Auto-Injector**	**Adrenalin® 30 mL Vial**
Description	Clear, colorless sterile solution in a pre-filled auto-injector	Clear, colorless sterile solution in a 30 mL multi-dose vial
Strength	0.3 mg/0.3 mL, 1:1000	1 mg/mL (1:1000)
Dosage Form	Injection	Injection
Routes of Administration	IM and SC	IM and SC
Indication	Anaphylaxis	Anaphylaxis
Formulation Concentrations (mg/mL)	Epinephrine 1.0 Sodium Chloride (b) (4) Sodium Metabisulfite HCl WFI	Epinephrine 1.14 Sodium Chloride 9.0 Sodium Metabisulfite 1.5 HCl (b) (4) WFI (b) (4) Chlorobutanol 5.4
pH range	2.2 – 5.0	2.2 – 5.0
Osmolality	≈230 mOsm/kg	≈355 mOsm/kg
Tonicity	Not determined	Not determined
Storage	20° to 25°C	20° to 25°C
Dosage	*Patients 30 kg or more:* 0.3mg (0.3 mL) fixed dose *Patients 15 to 30 kg:* 0.15 mg (0.3 mL)	*Adults/Children 30 kg or more:* 0.3 to 0.5 mg (0.3 to 0.5 mL) *Children less than 30 kg:* *0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL)*

*estimate based on expected quantity required to neutralize epinephrine base and adjust pH to range.

The applicant provided a list of approved injectable products that contain chlorobutanol as preservative, shown below.

Brand	**Generic name**	**Route**	**Percent chlorobutanol**
Aquasol A®	vitamin A palmitate	IM	(b) (4)
Delestrogen®	estradiol valerate injection	IM	
Delatestryl®	testosterone enanthate	IM	

Isoniazid	isoniazid injection, USP	IM	(b) (4)
Dolophine®	methadone hydrochloride Injection, USP	IM/SC/IV	
Novocain®	procaine hydrochloride	IM/SC	
Pitocin®	oxytocin injection	IM/IV	
Pyridoxine	pyridoxine hydrochloride injection	IM/IV	
Syntocinon®	oxytocin injection	IM/IV	
Thiamine	thiamine hydrochloride injection	IM/IV	
Twinject®	epinephrine injection	IM/SC auto-injector	

[a]Source = drug product Labels
IM =
intramuscular IV
= intravenous SC
= subcutaneous

Additionally the applicant provided the following information from the literature demonstrating the inter subject variability following intramuscular and subcutaneous administration of epinephrine.

Product	Dose and Route	C_{max} (CV%) (ng/mL)	AUC (CV%) (ng.hr/mL)	T_{max} (%CV) (minutes)	Reference
EP[a]	0.5 mg SC	0.85 range 0.14 - 1.52	NR	range 15-120min	Heilborn et al (1986)
EpiPen®	0.3 mg IM[b]	0.486 (50.8%)	0.536 (36.6%)	range 5-60min (75%)	Edwards et al (2013)
Auvi-Q®	0.3 mg IM[b]	0.520 (63.1%)	0.466 (42.2%)	range 5-60min (75%)	

[a] EP source = Adrenaline, (b) (4), 1 mg/mL (CHLOROBUTANOL content unknown)
[b] The publication states IM, but the Product Labels indicate IM/SC for these auto-injectors
EP = epinephrine
(vials) IM =
intramuscular
NR = not reported
SC = subcutaneous

In summary, the applicant concludes that:

- EpiPen® (chlorobutanol-free) and Twinject® (containing (b) (4) chlorobutanol) have the same recommended efficacious dose and have the same safety profile. These same efficacious doses have been used for several years with no known reports of differences in responses to IM and SC treatment for anaphylaxis, and no reports of differences in adverse effects.

- Pharmacokinetic studies for epinephrine given by regular IM injection or auto-injection (SC/IM) show much variation between methods of injection, as well as high individual to individual

variation within the same product. Therefore, any potential effect of chlorobutanol on systemic absorption will very likely be within the variability normally seen with SC and IM injections of epinephrine.

- Chlorobutanol has been, and still is, used as a preservative for many approved and unapproved drugs, including unapproved epinephrine that has been used for many years. There is no evidence that the addition of chlorobutanol to a drug changes its PK, efficacy or safety profile.

- Chlorobutanol has no known or theoretical attributes that would result in the exacerbation of local or systemic adverse effects that may occur after IM or SC injections of epinephrine.

Reviewer's Comments: The proposed multi-dose Adrenalin® contains 0.54% chlorobutanol which has been used in some currently marketed products without safety concern. It is noted that the osmolality of the proposed product 355 mOsm/kg makes the product little hypertonic. Both the issues were discussed with the medical reviewer (Dr. Peter Starke) and no concern was noted by him.

Therefore, based on the information provided by the applicant along with comparison between the formulations, and considering the functions and expected lack of serious adverse effect due to addition of chlorobutanol in the proposed drug product, a waiver of conducting an *in-vivo* bioavailability study for the proposed drug product **Adrenalin® 30 mL Vial** for IM and SC administration is granted.

RECOMMENDATION:

Based on the information provided by the applicant along with comparison between the formulations, and considering the functions and expected lack of serious adverse effect due to addition of chlorobutanol in the proposed drug product, a waiver of conducting an *in-vivo* bioavailability study for the proposed drug product **Adrenalin® 30 mL Vial** for IM and SC administration is granted.

The Office of New Drug Quality Assessment Completed the review of Biopharmaceutics portion of this NDA and recommends NDA 204-640 to be approved.

Signature	**Signature**
Assadollah Noory, Ph.D.	Tapash Ghosh, Ph.D.
Biopharmaceutics Reviewer	Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

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/s/

ASSADOLLAH NOORY
12/05/2013

TAPASH K GHOSH
12/05/2013

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 204640**	**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**
OCP Team Leader	**Satjit Brar**	**Dosage Form**	**Emergency treatment of anaphylaxis**
Other discipline reviewers	**-**	**Dosing Regimen**	**Flexible depending on the need determined by the physician**
Date of Submission	**August 2, 2013**	**Route of Administration**	**IM/SC**
Estimated Due Date of OCP Review		**Sponsor**	**JHP Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**S**
PDUFA Due Date	**June 2, 2014**		

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 -				

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

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				
Total Number of Studies				

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			x	

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

	review to begin?				
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 requirements for approvability of this product?			x	
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.

Reviewer comments: This is a 505(b)(2) application submitted by JHP Pharmaceuticals, LLC (JHP) for the currently marketed but unapproved, multiple-use 30 mL vial presentation of Adrenalin (epinephrine injection, USP), 1mg/mL (1:1000). The proposed indication is for the emergency treatment of severe allergic reactions (anaphylaxis), (b) (4). Adrenalin is currently marketed by JHP in

both 1 mL (single-use) and 30 mL (multiple-use) vials. The two presentations differ with respect to the presence and concentrations of inactive ingredients, both contain sodium metabisulfite as an antioxidant, although the concentrations differ, and the 30 mL presentation also contains chlorobutanol as a preservative. The 1 mL presentation of Adrenalin was recently approved (December 12, 2012) by the FDA under NDA 204200 for anaphylaxis as well as mydriasis indications. For the present NDA (b) (4), the sponsor has referenced both recently approved NDA 204200 (Adrenalin 1 mL presentation) as well as EpiPen (NDA 19430). No studies have been conducted with the 30 mL vial presentation and submitted in the NDA. For the recently approved NDA 204200, a biowaiver from conducting BA/BE studies was considered reasonable by the ONDQA/Biopharmaceutics team (see Dr. Kareen Riviere's Biopharm review of NDA 204200 in DARRTS dated 11/13/2012).

At the filing meeting for the current NDA (b) (4), the ONDQA/Biopharmaceutics team indicated that they will be sending a comment to the sponsor asking them to request a biowaiver for NDA (b) (4) since no studies have been conducted with this product, and also to justify the biowaiver request. From a clinical pharmacology perspective, the only difference between the 30 mL vial presentation and the recently approved 1 mL vial presentation is that the 30 mL presentation is a multiple-use product, as such previously reviewed information for NDA 204200 for the 1 mL presentation which included a review of PK parameters when Adrenalin is administered SC or IM, can be applied to the current NDA as well and no additional clinical pharmacology related information is warranted at this time.

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

None.

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/s/

SHEETAL S AGARWAL
09/17/2013

SATJIT S BRAR
09/17/2013