CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207534Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW FOR NDA 207-534

NDA	207-534	*Submission Date(s)*	5/28/14
Proposed Brand Name		Symjepi	
Generic Name		Epinephrine injection, USP	
Reviewer		Sheetal Agarwal, Ph.D., RAC	
Team Leaders		Satjit Brar, Pharm.D., Ph.D	
OCP Division		Division of Clinical Pharmacology-2	
OND Divisions		Division of Pulmonary, Allergy and Rheumatology Products and Division of Topical and Ophthalmic Products	
Sponsor		Adamis	
Submission Type		505 (b) (2) NDA referencing Epipen (NDA 19-430) as well as literature	
Formulation; Strength(s)		0.3 mg in a pre-filled, single-dose syringe	
Proposed Indication		treatment of severe allergic reactions (anaphylaxis)	
Proposed Dosing Regimen		Flexible depending on the need determined by the physician. The product is intended for self or caregiver administration in the medically unsupervised, emergency setting.	

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1.0 Executive Summary

1.1 Recommendation:

Office of Clinical Pharmacology/Division of Clinical Pharmacology-2, has reviewed NDA 207-534 requesting approval of 0.3 mg / 0.3 mL epinephrine solution in a 0.3 mg in a pre-filled, single-dose syringe, 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 Epinephrine injection, USP, in a 0.3 mg in a pre-filled, single-dose syringe, was submitted under 505 (b) (2) regulations. Epinephrine injection is intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

As with recently approved NDAs 204-640 and 204-200, no clinical pharmacology studies were conducted by the sponsor in support of this 505 (b) (2) NDA. The sponsor's request for a biowaiver from conducting an *in vivo* bioavailability study with their product was reviewed and approved by the ONDQA/Biopharmaceutics team. 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. Labeling edits from a clinical pharmacology perspective will be provided to the review team.

Overall, the information provided in the NDA is acceptable from a clinical pharmacology perspective.

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/s/

SHEETAL S AGARWAL
02/26/2015

SATJIT S BRAR
02/26/2015

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 207534**	**Proposed Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Epinephrine**
Medical Division	**DPARP**	**Drug Class**	**Endogenous molecule**
OCP Reviewer	**Sheetal Agarwal, Ph.D., RAC**	**Proposed Indication(s)**	**Emergency treatment of allergic reactions (Type I) including anaphylaxis**
OCP Team Leader	**Satjit Brar, PharmD., Ph.D.**	**Dosage Form**	**0 3 mg/0.3 mL epinephrine for injection, USP, pre-filled syringe**
Other discipline reviewers	-	**Dosing Regimen**	**Flexible depending on the need determined by the physician**
Date of Submission	**5/28/14**	**Route of Administration**	**IM/SC**
Estimated Due Date of OCP Review		**Sponsor**	**Adamis**
Medical Division Due Date	**2/21/15**	**Priority Classification**	**S**
PDUFA Due Date	**5/28/15**		

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:				

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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	**X**			**ONDQA/Biopharm will review the request for biowaiver**
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	

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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	
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 Adamis for their currently marketed, unapproved 0.3 mg/0.3 mL epinephrine for injection, USP, pre-filled is fileable. The proposed indication

is for emergency treatment of allergic reactions (Type I) including anaphylaxis. This product is a manual injector as opposed to currently marketed auto-injector epinephrine products for the same indication. The reference drug for this NDA is EpiPen (NDA 19430). No studies have been conducted with the product. A request for biowaiver from conducting BA/BE studies has been submitted in the NDA which will be reviewed by the ONDQA/Biopharm review team.

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
07/11/2014

SATJIT S BRAR
07/13/2014