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APPLICATION NUMBER:

204640Orig1s000

MEDICAL REVIEW(S)

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/s/

PETER R STARKE
12/12/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204-640
Priority or Standard	Standard
Submit Date(s)	August 2, 2013
Received Date(s)	August 2, 2013
PDUFA Goal Date	June 2, 2014
Division / Office	DPARP/OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	November 25, 2013
Established Name	Epinephrine injection, USP, 1mg/mL
(Proposed) Trade Name	Adrenalin [®]
Therapeutic Class	Non-selective alpha and beta adrenergic agonist (catecholamine)
Applicant	JHP Pharmaceuticals, LLC
Formulation(s)	Solution for injection, 30 mL multiple- dose vial
Dosing Regimen	IM or SC Injection
Proposed Indication(s)	Anaphylaxis (the indication of mydriasis during ophthalmologic surgery is not appropriate for this multiple-dose presentation)
Intended Population(s)	No age restrictions

MEDICAL OFFICER REVIEW			
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)			
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
Sept. 14, 2012	Sept. 14, 2012	N-000, SD-1	Original NDA submission for NDA 204-640, split from NDA 204-200
<i>Sept. 20, 2012</i>			<i>Refuse to file letter</i>
August 2, 2013	August 2, 2013	SD-2	PDUFA fee paid, NDA 204-640 reopened
August 14, 2013	August 14, 2013	SD-3	CMC data
Sept. 16, 2013	Sept. 16, 2013	SD-4	Annotated labeling
Sept. 17, 2013	Sept. 17, 2013	SD-5	Administrative information for Module 1, including requests for waivers of bioequivalence and pediatric studies
Sept. 20, 2013	Sept. 20, 2013	SD-6	Administrative information for Module 1, including financial disclosure information, LOA, form 3674, etc.
October 17, 2013	October 17, 2013	SD-9	Updated labeling (formatting issues addressed per filing letter request)
October 23, 2013	October 23, 2013	SD-10	Proprietary name review request (Adrenalin)
November 1, 2013	November 1, 2013	SD-11	Support for request for biowaiver

RECOMMENDED REGULATORY ACTION	
NDA/SUPPLEMENTS:	<input checked="" type="checkbox"/> APPROVAL
	<input type="checkbox"/> COMPLETE RESPONSE
OTHER ACTION:	<input type="checkbox"/>

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This application is approvable from a clinical perspective.

1.2 Risk Benefit Assessment

This is a 505(b)(2) application submitted by JHP Pharmaceuticals for the use of the currently marketed but unapproved 30 mL multiple-dose vial presentation of Adrenalin® (epinephrine injection, USP), 1mg/mL (1:1000), for the emergency treatment of allergic reactions (Type 1), including anaphylaxis [‘anaphylaxis’].

Adrenalin is currently marketed by JHP in both 1 mL (single-use) and 30 mL (multiple-dose) vials.¹ The two presentations differ in inactive ingredients: both contain sodium metabisulfite as an antioxidant, although the concentrations differ. Additionally, the 30 mL presentation contains chlorobutanol as a preservative.

This application relies on the Agency’s previous findings of efficacy and safety for EpiPen for the treatment of anaphylaxis, and also cross-references to the approved 1 mL single-use vial Adrenalin product, which was approved on December 7, 2012. For the 1 mL vial presentation of Adrenalin, the Agency made the determination that the risk/benefit is favorable for two indications: the emergency treatment of allergic reactions (Type 1), including anaphylaxis [which includes severe allergic reactions (b) (4) (b) (4)], and ophthalmic use for induction and maintenance of mydriasis during intraocular surgery [‘mydriasis’].

The presence of chlorobutanol in the 30 mL vial presentation does not affect the risk/benefit assessment for this presentation for indication of anaphylaxis, which remains favorable. Another epinephrine product, Twinject / Adrenaclick, contains chlorobutanol, and the Agency has extensive experience with this ingredient in concentrations similar to the one in this product. Additionally, the clinical experience with epinephrine is extensive and sufficient to determine that the presence of chlorobutanol in this product will not affect the efficacy, safety, dose, drug interactions, or use in special populations of the product when the product is used for the treatment of anaphylaxis. However, the presence of chlorobutanol in the multiple-dose 30 mL vial presentation makes the risk/benefit for the 30 mL vial presentation unacceptable for the mydriasis indication. Therefore, the applicant has only asked for approval of the severe allergic reactions / anaphylaxis indication for the 30 mL vial presentation, and this is appropriate and acceptable.

¹ Note: The volume referred to throughout this review is the fill volume of epinephrine solution in the vial, and not the volume that the vial can hold [including dead space] which is 36 mL.

Both presentations will carry the Trade / Proprietary Name 'Adrenalin'. This is acceptable to the review team, although final agreement on acceptability of the proposed Trade Name has not been received from the Division of Medication Error Prevention and Analysis (DMEPA) as of the time of completion of this review. The two products will also have unified labeling, which is also acceptable. The differences in indications for the two presentations will be handled by specific labeling, particularly in the Indications and Dosage and Administration sections.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

1.5 Pediatric Issues

None. This application does not trigger PREA because the 1 mL presentation of Adrenalin is already approved, and this presentation contains no new active ingredients, indications, routes, dosage forms, or dosing regimens.

The previous Adrenalin application triggered PREA for the both the mydriasis and anaphylaxis indications. However, all age ranges were considered to be covered by the data submitted to the application, and therefore the PREA requirements were considered fulfilled. The 30 mL vial presentation will also be labeled for the entire pediatric age range, although because of the preservative, the indication will be restricted to anaphylaxis.

2 Introduction and Regulatory Background

2.1 Introduction

This is a 505(b)(2) application submitted by JHP Pharmaceuticals, LLC (JHP) for the use of the currently marketed but unapproved, multiple-dose 30 mL vial presentation of Adrenalin[®] (epinephrine injection, USP), 1mg/mL (1:1000), for the emergency treatment of severe allergic reactions (Type 1), including anaphylaxis ['anaphylaxis'].

Adrenalin is currently marketed by JHP in both 1 mL (single-use) and 30 mL (multiple-dose) vials. The two presentations differ in inactive ingredients: both contain sodium metabisulfite as an antioxidant, but only the 30 mL presentation contains chlorobutanol

as a preservative. The concentration of sodium metabisulfite differs in the two presentations.

Originally, the sponsor submitted a single 505(b)(2) NDA application for both presentations under NDA 204-200. The application had been requested by the Agency as part of an initiative to remove unapproved drugs from the market by requesting the submission of new drug applications for marketed unapproved products, as set forth in the Compliance Policy Guide (CPG) for Marketed Unapproved Products, issued in 2006.² Two indications were sought: emergency treatment of severe allergic reactions, including anaphylaxis [which includes severe allergic reactions (b) (4)], and induction and maintenance of mydriasis during intraocular surgery [‘mydriasis’]. The application referenced the literature for both indications, as well as the Agency’s previous findings of safety and efficacy of EpiPen[®] Auto-Injector (epinephrine injection, USP) (NDA19-430) [for anaphylaxis]³ to support the following presentations and indications:

For the 1 mL and 30 mL presentations: the emergency treatment of allergic reactions (Type 1), (b) (4).

For the 1 mL presentation only: ophthalmic use for induction and maintenance of mydriasis during cataract surgery.

During the review of NDA 204-200, the 30 mL vial presentation was transferred to a separate NDA (NDA 204-640) because of the presence of chlorobutanol as a preservative and the volume of liquid, both of which make the 30 mL vial presentation inappropriate intraocular use. The presence of chlorobutanol as a preservative presents a safety concern with ophthalmic use, and the volume of liquid can lead to medication errors when diluting for ophthalmic use. Hence, the two presentations differ with respect to their indications. However, it was determined that the second application would invoke a second user fee, at which time the applicant decided not to pay the user fee. Therefore, NDA 204-640 was not accepted by the Agency, and a refuse to file letter was issued on September 20, 2012. NDA 204-200 for the 1 mL presentation was approved for both indications on December 12, 2012, to be marketed under the [previous] Trade Name, Adrenalin.

The applicant has now decided to reopen the application and pay the user fee for NDA 204-640, for review of the 30 mL vial presentation of Adrenalin for the anaphylaxis indication. As a 505(b)(2) application his NDA application references the listed drug EpiPen (NDA 19-420, Mylan), and cross-references JHP’s previous application for the Adrenalin 1 mL single-use vial presentation (NDA 204-200), which was approved for both indications on December 12, 2012.

² <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf>

³ EpiPen[®] and EpiPen[®] Jr. Auto-Injectors are manufactured by Meridian Medical Technologies[™], Inc. (MMT) of Columbia, Maryland, for Dey Pharma, L.P. of Napa, California, and marketed by MMT. MMT is a wholly owned subsidiary of King Pharmaceuticals[®], Inc., which was acquired by Pfizer in March 2011. EpiPen[®] and EpiPen[®] Jr are registered trademarks of Mylan, Inc. licensed exclusively to its wholly-owned affiliate, Dey Pharma, L.P.

Since the presence of chlorobutanol in the multiple-dose 30 mL vial presentation makes the risk/benefit for the presentation unacceptable for the mydriasis indication, the applicant has only asked for approval of the severe allergic reactions / anaphylaxis indication for the 30 mL vial presentation, and this is appropriate and acceptable.

The applicant has submitted CMC and administrative data, but no clinical data. This is acceptable, since the Agency has already made the decision that the risk/benefit of epinephrine, including EpiPen and the 1 mL vial of Adrenalin, is favorable for the treatment of anaphylaxis. The reader is referred to the reviews of NDA 204-200 for clinical support for the NDA and for other background information.

It should also be noted that, although the application does not qualify for a shortened review timeline, the applicant has requested a shortened review timeline for this application. Based on a standard review timeline, the PDUFA goal date is June 2, 2014. However, the Division plans to take an early action on the application, and has set February 2, 2014 (6 month clock) as the goal date for the application.

2.2 Regulatory Background

Adrenalin in 30 mL vials is a marketed unapproved presentation of epinephrine. The original application submitted by JHP for both presentations was requested by the Agency as part of an initiative to remove unapproved drugs from the market by requesting submission of new drug applications for marketed unapproved products, as set forth in the Compliance Policy Guide (CPG) for Marketed Unapproved Products, issued in 2006. Please see the Introduction to this review (Section 2.1) and the clinical reviews of NDA 204-200 for full details.

2.3 Product Information

Please see the Introduction to this review (Section 2.1) and the clinical reviews of NDA 204-200 for full details.

2.4 Tables of Currently Available Treatments for Proposed Indications

NDA 204-200 for Adrenalin (epinephrine injection, USP), 1mg/mL (1:1000) in a 1 mL vial presentation was approved for two indications, mydriasis and anaphylaxis, in December 2012.

There are also a number of epinephrine-containing disposable, prefilled automatic injection devices approved for immediate patient self (or caregiver) administration to treat life-threatening allergic reactions, including anaphylaxis, in people who are at risk for or have a history of serious allergic reactions. They contain one (EpiPen, Adrenaclick, and Auvi-Q) or two (Twinject) doses of epinephrine, depending upon the product. The epinephrine products approved for anaphylaxis are shown in Table 1.

Table 1. Approved Epinephrine Products for Treatment of Anaphylaxis

Product	NDA	Packaging and Dose	Strength* and Dispensed Volume	Indication(s)
EpiPen® EpiPen® Jr	19-430	Single dose of 0.3mg Single dose of 0.15 mg	0.3 mg: 1:1000 0.3mL 0.15 mg: 1:2000 0.3mL	Treatment of life-threatening allergic reactions, including anaphylaxis, in people who are at risk for or have a history of serious allergic reactions
Twinject®	20-800	2 doses per injector, containing: 0.3 mg or 0.15 mg	0.3 mg: 1:1000 0.3mL 0.15 mg: 1:1000 0.15mL	
Adrenaclick™ and authorized generic	20-800	Single-dose version of Twinject, containing 0.3 mg or 0.15 mg		
Auvi-Q™	201-739	Single dose of 0.3mg Single dose of 0.15 mg	0.3 mg: 1:1000 0.3mL 0.15 mg: 1:1000 0.15mL	
Adrenalin	204-200	1 mL vial	1:1000	Anaphylaxis Induction and maintenance of mydriasis during cataract surgery
*Strength of Epinephrine Injection (1:1000 = 1 mg/mL)				

2.5 Availability of Proposed Active Ingredient in the United States

2.5.1 Single-ingredient epinephrine products for injection

Epinephrine is a pre-1938 [and pre-1906] drug that has been marketed under the trade name Adrenalin® since the turn of the 20th Century. The drug product, Adrenalin®, was originally marketed by Parke-Davis, sold to Parkedale Pharmaceuticals, Inc. (a wholly owned subsidiary of King Pharmaceuticals, Inc.) on February 27, 1998, and sold to JHP on July 14, 2007.

Products previously marketed in the United States for the treatment of anaphylaxis include: Epi EZ Pen [and Epi EZ Pen Jr] and Ana-Kit®. Meridian Medical Technologies, the maker of EpiPen, marketed Epi EZ Pen and Epi EZ Pen Jr (single doses of 0.3 and 0.15 mg) for a short period of time in the mid to late 1990s (NDA 19-430). The product differed from EpiPen in that it was a manually-triggered, pen-like epinephrine injection device; otherwise it was similar to the EpiPen devices. Ana-Kit (epinephrine injection, USP, 1:1000, manufactured by Hollister-Stier Laboratories) contained multiple doses of epinephrine in an Ana-Guard® syringe, co-packaged with an oral antihistamine (chlorpheniramine). The product was discontinued in 2001 after the supplier of epinephrine, Wyeth Pharmaceuticals, stopped production (<http://www.wildmed.com/blog/discussion-on-epi-pen-prescription-increase/>, accessed 4/30/2012). In 2004, Hollister-Stier received FDA approval for a successor product, Twinject (NDA 20-400), and in 2006, Verus Pharmaceuticals bought the rights to

Twinject [now owned by CorePharma] and Ana-Kit. However, Ana-Kit and/or Ana-Guard are still marketed in Europe by various companies, including Bayer Schering Pharma, Hollister Stier, and Milex Products (<http://www.telefonica.net/web2/insect/POSI.html#MM5>, accessed 4/30/2012).

A number of products are listed in the NDC directory as being identical, related, or similar (IRS) to this product. Table 2 shows a listing of unapproved epinephrine injectable products that have National Drug Code (NDC) numbers listed in the NDC directory as of April 5, 2012. Adrenalin does not show up in this listing, although an NDC number (42023-122) is shown on the labeling for the current Adrenalin products marketed by JHP. The Agency is aware that other manufacturers market other unapproved epinephrine products without NDC numbers. However, products without an NDC number are not shown in the table below because it is difficult to track a product without an NDC number.

Table 2. Unapproved Epinephrine Injectable Products with NDC Numbers

Labeler's Name	Strength	Listed Route of Administration	Marketing Date	NDC #
American Regent, Inc.	1 mg/mL (1:1000)	INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	1990-09-30	0517-1071
	1 mg/mL (1:1000)	INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	1994-03-01	0517-1130
Amphastar Pharmaceuticals, Inc.	0.1 mg/mL (1:10,000)	PARENTERAL	2010-08-25	0548-3316
	1 mg/mL (1:1000)	PARENTERAL	2000-07-01	0548-9061
General Injectables and Vaccines, Inc.	1 mg/mL (1:1000)	INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	2010-07-01	52584-019
McKesson Packaging Services Business Unit of McKesson Corporation	1 mg/mL (1:1000)	INTRACARDIAC; INTRAMUSCULAR; INTRAVENOUS; SUBCUTANEOUS	2010-05-03	63739-467

Source: Table created from search of NDC Directory, last updated 6/11/2012, downloaded 6/15/2012 from <http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm>.

2.5.2 Other epinephrine-containing products

Please see the Introduction to this review (Section 2.1) and sections 2.4 and 2.5.1 above.

2.6 Important Safety Issues With Consideration to Related Drugs

Please see the Introduction to this review (Section 2.1) and the reviews of NDA 204-200 for full details.

2.7 Summary of Presubmission Regulatory Activity Related to Submission

Please see the Introduction to this review (Section 2.1) and the reviews of NDA 204-200 for full details.

2.8 Other Relevant Background Information

Please see the Introduction to this review (Section 2.1) and the reviews of NDA 204-200 for full details.

3 Ethics and Good Clinical Practices

Not applicable (NA)

3.1 Submission Quality and Integrity

NA

3.2 Compliance with Good Clinical Practices

NA

3.3 Financial Disclosures

NA

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The proposed drug product is a sterile, injectable solution containing 30 mL of epinephrine injection, USP, 1 mg/mL (1:1000), packaged in a (b) (4) multiple-dose amber glass vial.

The drug substance is manufactured by [REDACTED] (b) (4). The vials are filled [REDACTED] (b) (4).

There are some issues with the [REDACTED] (b) (4) drug substance manufacturing site and site currently has an unacceptable compliance status. Further, the site will not be ready for re-inspection until [REDACTED] (b) (4). However, epinephrine is medically necessary and may be the subject of a drug shortage. Thus, the Agency's Drug Shortages Branch has indicated that they will exercise regulatory discretion for the application pending re-inspection of the manufacturing site.

The 30 mL vial presentation contains 1.5 mg/mL sodium metabisulfite as an antioxidant (EpiPen contains [REDACTED] (b) (4)) and [REDACTED] (b) (4) of chlorobutanol per mg of epinephrine as an antimicrobial preservative (not present in EpiPen), which is necessary for a multiple-dose vial.

The levels of degradants in this product is an issue, as it is for all epinephrine solution products, because degradant levels build up over time depending upon the product and the storage conditions. The two major degradants are [REDACTED] (b) (4).

[REDACTED] (b) (4)

(b) (4)

Another issue for this product is leachables from the (b) (4) stopper. However, this issue was also raised during the review of the 1 mL vial NDA, and JHP has previously committed to conducting a leachable study and submit the data to the NDA for the 1 mL vial when available. Since this was acceptable for the 1 mL product, the same approach can be applied to this application.

4.2 Clinical Microbiology

There were no microbiological issues noted in this application, and the recommendation from Clinical Microbiology is approval.

4.3 Preclinical Pharmacology/Toxicology

To support the nonclinical pharmacology and toxicology, JHP conducted a literature review supplemented by four studies, two to assess genotoxicity, and two to qualify (b) (4) as an impurity. The studies included 1) an IV bolus 14-day repeat-dose toxicity dose range-finder (DRF) study in rats, 2) an IV bolus 14-day repeat-dose toxicity pivotal study in rats, 3) a bacterial mutagenicity study, and 4) a CHO cell chromosomal aberration study. The two repeat-dose toxicity studies included both epinephrine spiked with (b) (4) and epinephrine alone. Please see the Pharm/Tox review for details of the results.

4.4 Clinical Pharmacology

4.4.1 Requirement for *in vivo* bioequivalence

JHP did not perform or submit any clinical pharmacology studies to support this application. They have requested a waiver of *in vivo* bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is administered as an injection solution [REDACTED] (b) (4)

[REDACTED] (b) (4)

However, another epinephrine product, Twinject / Adrenaclick, contains the inactive ingredient chlorobutanol, and the Agency has extensive experience with this ingredient in concentrations similar to the one in this product. Additionally, the clinical experience with epinephrine is extensive and sufficient to determine that the presence of chlorobutanol in this product will not affect the efficacy, safety, dose, drug interactions, or use in special populations of the product. Therefore, the Division agrees with the applicant's proposal, and considers that *in vivo* bioequivalence bridging is not required.

Further, it should be noted that there are critical differences between the proposed product and the referenced product. The proposed product is intended for use in the medical setting by medically trained personnel, whereas the referenced product (EpiPen) is a drug-device combination, i.e., an auto-injector, intended for emergency self-use in non-medically supervised settings. Because of these differences, the dosing, weight, and age ranges for this product will extend beyond those for the referenced drug-device combination, resulting in different labeling for this product than EpiPen. Because this product is not a drug-device combination, is intended for different setting of use, and will have different dosing and administration instructions, there is no need to ensure bioequivalence to any of the currently marketed auto-injector products. Therefore, granting of a waiver of bioequivalence studies is both acceptable and appropriate.

I recommend that no clinical pharmacology studies be required, either for approval or as a post-marketing commitment.

4.4.2 Pharmacology of Epinephrine

There is an extensive literature base to support the pharmacology of epinephrine and discussions may be found in many pharmacology textbooks [as well as summarized in my review of NDA 204-200. Epinephrine is a naturally-occurring hormone that is secreted by the adrenal medulla in response to stress. It acts on both alpha and beta-adrenergic receptors as a non-selective agonist. Due to its non-selective activity, the

pharmacodynamic actions of epinephrine are complex. They include vasoconstriction leading to increased vascular resistance, increased blood pressure, and decreased airway mucosal edema mediated by α_1 receptors; inhibition of insulin secretion mediated by α_2 receptors; increased myocardial contractility, increased heart rate, and coronary vasodilation mediated by β_1 receptors; and decreased mast cell mediator release, bronchodilation, and release of glucose from the liver mediated by β_2 receptors. Many of these effects are beneficial in anaphylaxis [REDACTED] (b) (4).

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

Pharmacokinetics is linear across a wide range of weights, and therefore supports the proposed weight-based dosing up to the maximum proposed dose of 0.5 mg.

5 Sources of Clinical Data

NA

5.1 Tables of Studies/Clinical Trials

None

5.2 Review Strategy

See Sections 6 and 7 below.

5.3 Discussion of Individual Studies/Clinical Trials

No clinical trials were performed to support this application.

6 Review of Efficacy

This application relies on the Agency's previous findings of efficacy and safety for EpiPen for the treatment of anaphylaxis, and also links this product to the approved 1 mL Adrenalin product, which was approved in December 2012. The efficacy and safety of epinephrine for the treatment of anaphylaxis has already been established. Please see my review of NDA 204-200, for which I conducted a thorough review of the literature, and wrote a detailed review regarding the efficacy and safety of epinephrine for the treatment of anaphylaxis.

This product differs from both EpiPen and the 1 mL single-use presentation of Adrenalin in that it also contains chlorobutanol as an antimicrobial preservative. The presence of

chlorobutanol in the 30 mL vial presentation makes the risk/benefit for this presentation unacceptable for the mydriasis indication. Therefore, the applicant has only asked for approval of the severe allergic reactions / anaphylaxis indication for the 30 mL vial presentation, and this is appropriate and acceptable.

Another epinephrine product, Twinject / Adrenaclick, contains chlorobutanol, and the Agency has extensive experience with this ingredient in concentrations similar to the one in this product. Additionally, the clinical experience with epinephrine for the treatment of anaphylaxis is extensive and sufficient to determine that the presence of chlorobutanol in this product will not affect the efficacy, safety, dose, drug interactions, or use in special populations of the product for this indication. Therefore, the presence of this preservative in the multiple-dose vial presentation is acceptable, and the Agency's previous finding of efficacy and safety for the referenced product for the treatment of anaphylaxis is sufficient to support the efficacy and safety of this product.

7 Review of Safety

This application relies on the Agency's previous findings of efficacy and safety for EpiPen for the treatment of anaphylaxis, and also links this product to the approved 1 mL Adrenalin product, which was approved in December 2012. The efficacy and safety of epinephrine for the treatment of anaphylaxis has already been established. Please see my review of NDA 204-200, for which I conducted a thorough review of the literature, and wrote a detailed review regarding the efficacy and safety of epinephrine for the treatment of anaphylaxis.

This product differs from both EpiPen and the 1 mL single-use presentation of Adrenalin in that it also contains chlorobutanol as an antimicrobial preservative. The presence of chlorobutanol in the 30 mL vial presentation makes the risk/benefit for this presentation unacceptable for the mydriasis indication. Therefore, the applicant has only asked for approval of the severe allergic reactions / anaphylaxis indication for the 30 mL vial presentation, and this is appropriate and acceptable.

Another epinephrine product, Twinject / Adrenaclick, contains chlorobutanol, and the Agency has extensive experience with this ingredient in concentrations similar to the one in this product. Additionally, the clinical experience with epinephrine for the treatment of anaphylaxis is extensive and sufficient to determine that the presence of chlorobutanol in this product will not affect the efficacy, safety, dose, drug interactions, or use in special populations of the product for this indication. Therefore, the presence of this preservative in the multiple-dose vial presentation is acceptable, and the Agency's previous finding of efficacy and safety for the referenced product for the treatment of anaphylaxis is sufficient to support the efficacy and safety of this product.

8 Postmarket Experience

NA

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

NA

9.2 Labeling Recommendations

Labeling has not been finalized as of the time of completion of this review. Labeling recommendations will be similar to those for the currently approved Adrenalin 1 mL vial presentation. JHP wishes to have combined labeling for both presentations, and this is acceptable. The 30 mL presentation will be limited to the indication of anaphylaxis because the multiple-dose vial cannot be used for the indication of induction and maintenance of mydriasis during intraocular surgery. Therefore, the new labeling will require statements limiting use of 30 mL vial to the anaphylaxis indications. The only other proposed differences in the labeling relate to the CMC sections to describe the new presentation.

During the review period, a labeling consult was performed by the Division of Medication Error Prevention and Analysis (DMEPA), and an Information Request will be sent with their labeling comments after completion of this review. As is standard practice at this time, the Study Endpoints and Labeling Development (SEALD) team will also be reviewing the labeling prior to finalization.

9.3 Advisory Committee Meeting

No advisory committee was convened to discuss this application.

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/s/

PETER R STARKE
11/25/2013

JANET W MAYNARD
11/25/2013

CLINICAL FILING CHECKLIST FOR NDA 204-640

NDA: 204-640
Applicant: JHP Pharmaceuticals, LLC
Drug Name: Adrenalin® (epinephrine injection, USP)
NDA Type: 505(b)(2)
Stamp Date: August 2, 2013
Reviewer: Peter Starke, MD
Team Leader: Janet Maynard, MD
Date of Review: September 11, 2013

Introduction and Background

This is a 505(b)(2) application submitted by JHP Pharmaceuticals, LLC (JHP) for the use of the currently marketed but unapproved, multiple-use 30 mL vial presentation of Adrenalin® (epinephrine injection, USP), 1mg/mL (1:1000), 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 in inactive ingredients: both contain sodium metabisulfite as an antioxidant, although the concentrations differ, and the 30 mL presentation also contains chlorobutanol as a preservative.

Originally, the sponsor submitted a single 505(b)(2) NDA application for both the 1mL and 30mL presentations under NDA 204-200. The application was requested by the Agency as part of an initiative to obtain new drug applications submitted for marketed unapproved products, as set forth in the Compliance Policy Guide (CPG) for Marketed Unapproved Products, issued in 2006. The Sponsor sought two indications: anaphylaxis and mydriasis during cataract surgery. The application referenced the literature [for both indications] as well as the Agency's previous findings of safety and efficacy of EpiPen® Auto-Injector (epinephrine injection, USP) (NDA19-430) [for anaphylaxis]¹ to support the following presentations and indications:

For the 1 mL and 30 mL presentations: the emergency treatment of severe allergic reactions (anaphylaxis), (b) (4).

For the 1 mL presentation only: ophthalmic use for induction and maintenance of mydriasis during cataract surgery.

Because of the presence of chlorobutanol as a preservative (which is not appropriate for ophthalmic use) and the volume of liquid (which can lead to medication errors when diluting for ophthalmic use), the 30 mL vial presentation cannot be used for the intraocular indication. Hence, the two presentations differ with respect to their indications. As a result, during the review of NDA 204-200, the 30 mL multiple-use vial presentation was transferred to a separate NDA (NDA 204-640). However, the second application invoked a second user fee,

¹ EpiPen® and EpiPen® Jr. Auto-Injectors are manufactured by Meridian Medical Technologies™, Inc. (MMT) of Columbia, Maryland, for Dey Pharma, L.P. of Napa, California, and marketed by MMT. MMT is a wholly owned subsidiary of King Pharmaceuticals®, Inc., which was acquired by Pfizer in March 2011. EpiPen® and EpiPen® Jr are registered trademarks of Mylan, Inc. licensed exclusively to its wholly-owned affiliate, Dey Pharma, L.P.

which the applicant did not pay. Therefore, NDA 204-640 was not accepted by the Agency, and a refuse to file letter was issued on September 20, 2012. NDA 204-200 for the 1 mL presentation was approved for both indications on December 12, 2012, to be marketed under the [previous] Trade Name, Adrenalin.

The applicant has now decided to pay the user fee and reopen the application for NDA 204-640, for review of the 30 mL vial presentation of Adrenalin. The applicant has submitted only CMC data, and no clinical data to this application, referencing their other NDA (204-200) for any additional information. This is acceptable; the Agency has already made the decision that the risk/benefit of the 1 mL vial of Adrenalin is favorable for the treatment of anaphylaxis [and mydriasis]. The reader is referred to the reviews of NDA 204-200 for clinical support for the NDA and for other background information. While the listed drug is still EpiPen, this application appropriately cross-references NDA 204-200 for the Adrenalin 1 mL single-use presentation.

It should also be noted that JHP has requested a shortened review timeline and PDUFA goal date for this application, stating that they are temporarily discontinuing manufacture of the 30 mL vial during the review period and have contacted drug shortages regarding their plans.

Clinical Filing Checklist

An initial overview of the NDA/BLA application was performed for filing purposes, and the results are shown below.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	No clinical sections submitted to this NDA, only sections M1 and M3. Form 356h references NDA 19-430 for EpiPen, and cross-references NDA 204-200 for the 1 mL vials.
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	See 2 above.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?			X	See 2 above.
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			

Clinical Filing Checklist • NDA 204-640

	Content Parameter	Yes	No	NA	Comment
	studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			See 2 above.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ²) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			See 2 above.
23.	Has the applicant submitted the coding dictionary ³ used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			See 2 above.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Literature references. See 2 above.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Previously submitted to NDA 204-200.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses			X	

² For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

³ The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
	available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

Filing Recommendations

The application is fileable from a clinical perspective. I recommend a standard review timeline for this application.

Potential Review Issues and Clinical 74-Day Comments

None

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/s/

PETER R STARKE
09/11/2013

JANET W MAYNARD
09/11/2013