CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204200Orig1s000
204200Orig2s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204-200 and 204-640
Priority or Standard	Standard
Submit Date(s)	March 7, 2012
Received Date(s)	March 7, 2012
PDUFA Goal Date	January 7, 2013
Division / Office	DPARP/OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	October 29, 2012
Established Name	Epinephrine injection, USP, 1mg/mL
(Proposed) Trade Name	Adrenalin®
Therapeutic Class	Catecholamine
Applicant	JHP Pharmaceuticals, LLC
Formulation(s)	Solution for injection
Proposed Dosing Regimen	Hypersensitivity reactions: IM or SC injection (b) (4) [Ophthalmic use: Topical irrigation or intraocular bolus injection]
Proposed Indication(s)	Hypersensitivity reactions: severe acute anaphylactic reactions, (b) (4) [Ophthalmic use: induction and maintenance of mydriasis during cataract surgery]
Intended Population(s)	Hypersensitivity reactions: No age restrictions [Ophthalmic use: No age restrictions]

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
March 7, 2012	March 7, 2012	SD-1, eCTD-0000	New NDA submission
April 9, 2012	April 9, 2012	SD-2, eCTD-0001	PREA waiver request – Anaphylaxis
April 9, 2012	April 9, 2012	SD-3, eCTD-0002	PREA waiver request – Mydriasis
April 18, 2012	April 18, 2012	SD-4, eCTD-0003	Request for proprietary name review
Sept 5, 2012	Sept 6, 2012	SD-22, eCTD-0021	Draft Ophthalmic Labeling
Oct 22, 2012	Oct 22, 2012	SD-27, eCDT-0026	Certification that EpiPen is the reference for the 505(b)(2) application

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X **APPROVAL**

____ **COMPLETE RESPONSE**

OTHER ACTION: ____

Table of Contents

Table of Tables

Table of Figures

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 drug product, Adrenalin® (epinephrine injection, USP), 1mg/mL (1:1000), for: (1) the emergency treatment of severe allergic reactions (anaphylaxis) (b) (4)[1], and (2) ophthalmic use for induction and maintenance of mydriasis during cataract surgery. This review only addresses the indication of anaphylaxis and not the ophthalmic surgery indication.

Adrenalin is currently marketed in both 1 mL and 30 mL vials, the two presentations differing in inactive ingredients: both contain sodium metabisulfite as an antioxidant, (b) (4)

The risk/benefit of epinephrine for the treatment of anaphylaxis is overwhelmingly in favor of its use for treatment of anaphylaxis. Anaphylaxis affects both the respiratory and the cardiovascular systems leading to bronchospasm, mucous membrane congestion, angioedema, and severe hypotension. While the use of epinephrine precedes the era of controlled clinical trials, extensive experimental and clinical experience has demonstrated that epinephrine is a life-saving drug in this setting. Even for those patients who are at increased risk for adverse reactions with epinephrine use, there is no contraindication for the use of epinephrine in the treatment of anaphylaxis. Nor, in this setting, is there a contraindication for the sulfite found in this product, even in patients with sulfite allergies. All patients who have anaphylaxis should receive

1 Note: The applicant calls these severe allergic reactions 'hypersensitivity reactions'. However, the Agency prefers the term 'anaphylaxis', and that term will be used throughout this review

epinephrine as early as possible after the start of symptoms and by whichever route is most appropriate for that patient, along with other supportive medical treatments and observation, to ensure that life-threatening signs or symptoms are treated immediately and appropriately.

It is important to note that this 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 the medical professional in the 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, with weight-based dosing that extends both higher (up to 0.5 mg for patients 30 kg or more) and lower (0.1 mg/kg for all weights less than 30 kg) than provided for with the epinephrine auto-injectors. The proposed intramuscular (IM) / subcutaneous (SC) dosing into the lateral thigh area (into or above the vastus lateralis muscle) matches that recommended in published anaphylaxis practice parameters and anaphylaxis guidelines. Additionally, whereas when patients self-administer epinephrine by auto-injector, either the SC or IM route into the anterolateral thigh is acceptable, the IM route into the vastus lateralis muscle is preferred when epinephrine is administered in the medically supervised setting because absorption and onset of action by the IM route is rapid and not delayed by local vasoconstriction.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

1.5 Pediatric Issues

This application will trigger PREA for both requested indications.

The indication of mydriasis will trigger PREA because of the new indication, route of administration, and dosing regimen. Note that the mydriasis indication is not covered in this review. Please refer to Dr. Chambers' clinical review for details. However, my understanding is that the Division of Ophthalmology and Transplant Products (DTOP) considers all age ranges to be covered by the data submitted to the application.

The indication of anaphylaxis will trigger PREA because of the new route of administration and dosing regimen. Since only one clinical trial is available from the literature to support the anaphylaxis indication, the supports for all ages come from pharmacologic and physiologic experiments in animals and in humans, as well as over 110 years of clinical experience with the drug for a variety of indications in all age groups. The underlying disease process and the pharmacologic and physiologic effects of the drug are considered the same for all age groups. Although specific safety information is not available for the youngest age groups (e.g., 0-1 year of age, including neonates), the extensive clinical use in all age groups for treatment of anaphylaxis, as well as for the treatment of asthma [in all age groups] for which the IM/SC dose is the same, provides sufficient efficacy and safety information to consider that the pediatric assessment has been fulfilled for all age groups. Therefore, when approved, I recommend that the Agency consider the pediatric assessment for this drug to have been fulfilled for all age groups.

The application was discussed at the Pediatric Review Committee (PeRC) meeting on June 12, 2012. The PeRC agreed with both Divisions that the pediatric assessment for this drug will be considered to have been fulfilled in all age groups for both indications.

2 Introduction and Regulatory Background

2.1 Introduction

This NDA was submitted by JHP Pharmaceuticals for the use of the currently marketed and unapproved product, Adrenalin® (epinephrine injection, USP), 1mg/mL (1:1000). Adrenalin is currently marketed by JHP in both 1 mL and 30 mL vials. The two presentations differ in inactive ingredients. Both contain sodium metabisulfite as an antioxidant, although the concentrations differ, and the 30 mL formulation also contains chlorobutanol as a preservative. As a 505(b)(2) application, the applicant references

the literature as well as EpiPen® Auto-Injector (epinephrine injection, USP) (NDA19-430) to support both efficacy and safety of epinephrine [for anaphylaxis].[2]

Originally, the sponsor submitted a single NDA (NDA 204-200) (b) (4) for the following indications:

- (b) (4) the emergency treatment of severe allergic reactions (anaphylaxis) (b) (4)
- (b) (4) ophthalmic use for induction and maintenance of mydriasis during cataract surgery.

This review pertains to and addresses the anaphylaxis indication (b) (4) Ophthalmic use (b) (4) is being addressed by separate reviews in the Division of Transplant and Ophthalmology Products (DTOP) within the Office of Antimicrobial Products. Please see those reviews for further details.

(b) (4)

It should also be noted that the PDUFA goal dates for the two indications differ. A priority (6-month) review clock was assigned to the application in DTOP because there are no other treatments approved for the mydriasis indication. However, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) assigned a standard review clock (10 months) for the anaphylaxis indication because there are other drugs approved for this indication.

Late in the 6-month review clock, JHP Pharmaceuticals submitted 9-month and 12-month stability updates for the three registration batches of drug product. Differences in the new stability data were not consistent with the proposed drug product specifications, resulting in the recommendation from the Office of New Drug Quality Assurance (ONDQA) to consider the submission a major amendment to the application and extend the PDUFA goal date for the mydriasis indication in order for further evaluate these differences. As a result, DTOP's goal date was extended by 3 months from September 7, 2012 to December 7, 2012, although the DPARP goal date remains the same: January 7, 2013.

2 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.

2.2 Regulatory Background

Adrenalin® is a marketed unapproved drug product that was originally marketed by Parke Davis & Co. starting in 1901 (see Section 2.6 for further details). In 1998, ownership was transferred to Parkedale Pharmaceuticals, Inc. (a wholly owned subsidiary of King Pharmaceuticals, Inc.), and in 2007, ownership was transferred to JHP.

Since the product has been marketed since 1901, its marketing predates the original Federal Food and Drugs Act of June 30, 1906, which prohibited the sale of adulterated or misbranded drugs, and the Federal Food, Drug, and Cosmetic Act (the FD&C Act) of 1938, which required that new drugs be approved for safety. In 1962, Congress amended the Act (Kefauver-Harris amendment) to require that a new drug must be shown to effective as well as safe in order to obtain approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that had been approved by the Agency as safe between 1938 and 1962. The Agency's administrative implementation of the effectiveness evaluations was called the Drug Efficacy Study Implementation (DESI) process. To make the determinations, the Agency contracted with the National Academy of Science/National Research Council to review the available efficacy data and provide recommendations to the Agency, which were then reviewed by the Agency. The Agency's final determinations were then published in the Federal Register.

Because it was a pre-1938 drug, Adrenalin was not subject to DESI review[3]. However, this product falls under the Prescription Drug Wrap-Up designation within section 440.100 of the Compliance Policy Guide (CPG) for Marketed Unapproved Drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf). The two main thrusts of the CPG are to ensure adequate compliance with good manufacturing procedures and adequate labeling to ensure safe use.

The CPG describes two grandfather clauses and one additional clause in the FD&C Act that potentially affect this application, although all have been construed very narrowly by the courts. For convenience, the discussion from the CPG is reproduced below:

> "Under the 1938 grandfather clause (see 21 U.S.C. 321(p)(1)), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that act was not considered a new drug and therefore was exempt from the requirement of having an approved new drug application. See Public Law 87-781, section 107 (reprinted following 21 U.S.C.A. 321); see also *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

3 Note: Although Adrenalin predates the DESI authority, a post-1938 drug, Sus-Phrine Suspension, which was an aqueous suspension of epinephrine manufactured by Cooper Laboratories, Wayne, N.J (NDA 7-942), was found under DESI 366 to be 'effective' for bronchial asthma, on the basis of clinical studies that provided substantial evidence of effectiveness. [42FR38647, July 29, 1977]

> Under the 1962 grandfather clause, the FD&C Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the FD&C Act at that time, and (c) not covered by an effective application. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion. See 21 CFR 314.200(e)(5); see also *United States v. An Article of Drug (Bentex Ulcerine)*, 469 F.2d 875, 878 (5th Cir. 1972); *United States v. Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir 1984).
>
> Finally, a product would not be considered a new drug if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time. See 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been construed very narrowly by the courts. See, e.g., Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); United States v. 50 Boxes More or Less Etc., 909 F.2d 24, 27-28 (1st Cir. 1990); United States v. 225 Cartons...Fiorinal, 871 F.2d 409 (3rd Cir. 1989). See also Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, FDA, to Gary D. Dolch, Melvin Spigelman, and Jeffrey A. Staffa, Knoll Pharmaceutical Co. (April 26, 2001) (on file in FDA Docket No. 97N-0314/CP2) (finding that Synthroid, a levothyroxine sodium product, was not GRAS/GRAE)."

Based on this, grandfathering for a drug product requires that there cannot have been any change in the drug or its labeling since 1938 or 1962, including changes in formulation, dosage form, potency, route of administration, indication, or intended treatment patient population. It is a firm's burden to prove that assertion. Additionally, to be recognized as GRASE requires that a product be the subject of adequate and well controlled clinical investigations that establish its safety and efficacy, that those investigations be published in the scientific literature and be available to qualified experts, and that the experts generally agree that the studies demonstrate that the product is safe and effective for its intended uses. This standard is exceptionally high, as it requires the same quantity and quality of data as would be necessary to support FDA approval for marketing. Although theoretically possible, the CPG goes on to state that at this time "the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*."

A pre-IND teleconference was held with the company on July 5, 2011, to discuss the filing of a new drug application (NDA) for their epinephrine product(s). The teleconference was prompted by a Notice of FDA Action sent by the Office of Compliance and received by JHP on July 23, 2009, regarding shipment of the active pharmaceutical ingredient (API), epinephrine, pending release from US Customs. JHP was requested to provide documentation of the grandfather status of their Adrenalin drug products, i.e., to clarify the linage of the Adrenalin drug product currently marketed by JHP with respect to the Adrenalin drug product initially marketed by Parke-Davis prior to June 25, 1938. JHP provided the requested information and the API was released from Customs on October 9, 2009, after which the Office of Compliance urged

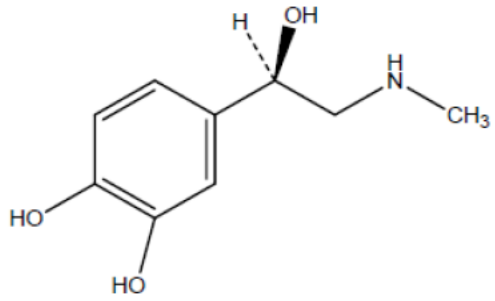
JHP to contact the Center for Drug Evaluation, Office of New Drugs to discuss the filing of an NDA for the product(s) [in order to comply with the CPG].

2.3 Product Information

The active ingredient, epinephrine, is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. It is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation.

The chemical formula of epinephrine is $C_9H_{13}NO_3$, and its chemical structure is shown below. The chemical structure consists of benzene ring and an ethylamine side chain.

There are two optical isomers (enantiomers): substitution of an hydroxyl group at the beta carbon atom on the ethylamine side chain yields *l*- and *d*- isomers [also described as L- or (-) and as D- or (+)]. Levorotatory rotation (*l*- form or *l*-epinephrine) confers at least 10-15 times higher systemic potency than the *d*-isomer (Patil 1975; Westfall 2011), with *l*-epinephrine being the natural form produced by the adrenal medulla. The drug substance is manufactured [redacted] (b) (4)



In the United States, the term epinephrine is the preferred name for this chemical, and the United States Approved Name (USAN) and International Nonproprietary Name (INN) is epinephrine. However, the British Approved Name (BAN) and European Pharmacopoeia (EP) term is adrenaline [with an e]. Pharmaceuticals that mimic the effects of epinephrine are termed 'adrenergics', and their receptors are called 'adrenergic receptors'. As a result, both epinephrine and adrenaline are terms used in the literature, although Adrenalin® [without an e] is the registered trade name for this product in the United States (see Section 2.6 for details on the history of epinephrine).

The proposed drug product, Adrenalin®, contains epinephrine injection, USP in a sterile solution at a concentration of 1 mg/mL (which is typically called 1:1000). It is packaged as 1 mL of solution in a [redacted] (b) (4) vial (NDA 42023-101-25, 25-pack) [redacted] (b) (4) contain sodium metabisulfite as an antioxidant [redacted] (b) (4)

(b) (4)

The currently marketed 1 mL and 30 mL vials are shown below in Figure 1.

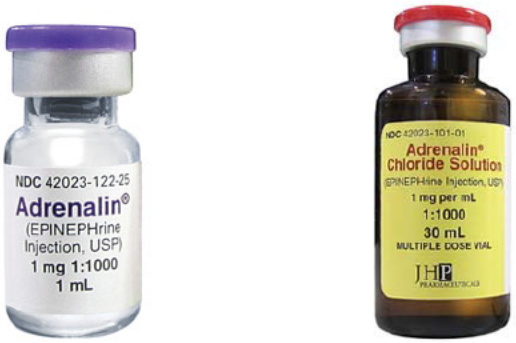


Figure 1. Currently marketed JHP Adrenalin for Injection, 1 mL and 30 mL vials

Source: http://www.jhppharma.com/products/brands/adrenalin.php, accessed 9/4/2012

Adrenalin® is currently marketed for the following indications:

1. Severe acute anaphylactic reactions, urticaria, angioedema
2. Prolongation of local anesthetic action
3. Hemostasis (including topical application), nosebleeds
4. Acute asthma exacerbations, severe bronchospasm in chronic bronchitis, emphysema and other obstructive pulmonary disease
5. Advanced cardiovascular life support (ACLS) during cardiopulmonary resuscitation (CPR)
6. Nasal decongestion and nasal preparation prior to flexible laryngoscopy or sinus surgery.

Only one of these indications is sought with these applications, treatment of anaphylaxis. In addition, JHP is requesting a new indication of maintenance of mydriasis during cataract surgery with the application (b) (4) (NDA 204-200). The proposed dosing instructions for ocular use during cataract surgery are irrigation (adults and pediatrics) with 1 to 10 µg/mL, or an intracameral bolus injection of a 0.1 mL volume of a 2.5 to 10 µg/mL solution. The mydriasis indication is otherwise not discussed in this review. Please refer to the DTOP reviews for further details.

It should be noted that, whereas the proposed product references EpiPen® Auto-Injector as a listed drug, EpiPen is drug-device combination that is approved for emergency

treatment of allergic reactions including anaphylaxis[4], and is not approved for ophthalmic use. Clinical support for mydriasis during cataract surgery must be stand-alone and cannot be provided by referring the Agency's previous findings of safety and efficacy for other indications.

While both Adrenalin and EpiPen would share the emergency treatment of anaphylaxis indication, the products and their intended use, dosing, and routes of administration for this indication differ. EpiPen® and EpiPen® Jr Auto-Injectors, as well as the other approved epinephrine auto-injector products (Twinject, Adrenaclick, and Auvi-Q[5]), are disposable, prefilled automatic injection devices intended for self-administration for treatment of life-threatening allergic reactions, including anaphylaxis, in people who are at risk for or have a history of serious allergic reactions. These drug-device combinations contain a single dose of epinephrine (or two doses, in the case of Twinject). Because the epinephrine auto-injectors are intended for immediate patient self (or caregiver) administration, they contain fixed doses of epinephrine standardized for weight ranges: 0.3 mg of epinephrine for patients who weigh 30 kg (66 lbs) or more, and 0.15 mg of epinephrine for patients who weigh 15-30 kg (33-66 lbs). No products are currently available for patients below 15 kg (33 lbs). These products are intended to be administered by either the intramuscular (IM) or the subcutaneous (SC) route. Patients/caregivers are instructed to use the product by injecting into the outer thigh at the first sign of an allergic emergency. They may repeat a dose if needed, but are instructed to seek emergency medical care after use because they may need more medicine. In summary, the intent of these products is for immediate non-medically supervised use at the first sign of an anaphylaxis episode by patients who are at risk for or have a history of serious allergic reactions.

However, the proposed drug product is intended for use under an entirely different set of circumstances: it is intended for use by the medical professional in the medically supervised setting. It therefore does not contain a device or a fixed dose of epinephrine. Additionally, the proposed dosing instructions for anaphylaxis include the potential to give multiple doses by the IM or SC routes (IM preferred) (b) (4) Finally, the doses extend above and below the dosing range for the auto-injector devices, i.e., the upper bound of dosing is intentionally higher because the patient is able to be monitored by a medical professional, and there is no lower age or weight bound for pediatric use.

4 The Indication statement for the EpiPen® and EpiPen® Jr Auto-Injectors [the other epinephrine auto-injectors have similar indication statements] reads as follows: "EpiPen® and EpiPen® Jr Auto-Injectors are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions."

5 The NDA for Auvi-Q was approved on August 10, 2012.

The proposed dosing for anaphylaxis is shown below:

(b) (4)

2.4 Tables of Currently Available Treatments for Proposed Indications

There are no products currently approved for the indication of mydriasis in cataract surgery.

Epinephrine is **the** primary treatment for anaphylaxis, with other treatments for this condition being adjunctive or supportive. Whereas there are a number of approved epinephrine-containing drug-device combination products available to the treatment of anaphylaxis, all differ from the proposed drug product in that they are disposable, prefilled automatic injection devices intended 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 approved epinephrine products for anaphylaxis are shown in Table 1.

Note that the different products use two different methodologies to achieve a smaller dose of epinephrine for patients with weights between 33 to 66 lb (15 to 30 kg) than for patients with weights above 66 lb (30 kg). To achieve the lower dose, the EpiPen Jr contains a more diluted concentration of epinephrine for injection (1:2000), but maintains the same dispensed volume. However, Twinject, Adrenaclick and its

authorized generic, and Auvi-Q dispense a smaller volume of the same 1:1000 concentration to achieve the lower dose.

Also of note, of the above products, only the Auvi-Q labeling is currently in Physician Labeling Rule (PLR) format; the other products are not in this format. Twinject and Adrenaclick are due to be converted to PLR format, but EpiPen is exempt from this requirement (EpiPen having been marketed prior to the date when applications are subject to the PLR format requirements, and therefore, PLR labeling is optional).

Table 1. Approved Epinephrine Products for Treatment of Anaphylaxis

Product	NDA	Packaging and Dose	Strength* and Dispensed Volume
EpiPen® EpiPen® Jr	19-430	Single dose of 0.3mg Single dose of 0.15 mg	1:1000 0.3 mL 1:2,000 0.3 mL
Twinject®	20-800	2 doses per injector, each contains 0.3 mg or 0.15 mg	 1:1000 0.3 mL 1:1000 0.15 mL
Adrenaclick™ and authorized generic	20-800	Single-dose version of Twinject, each containing 0.3 mg or 0.15 mg	Same as Twinject
Auvi-Q™	201-739	Single dose of 0.3mg Single dose of 0.15 mg	1:1000 0.3 mL 1:1000 0.15 mL
*Strength of Epinephrine Injection, USP: 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

It is important to note that JHP also markets a 30 mL vial of Adrenalin Chloride Nasal Solution (NDC 42023-103-01), as shown below in Figure 2. This is not a sterile product, and it was not submitted for approval as part of this NDA. (b) (4)

Figure 2. Currently marketed JHP Adrenalin Chloride Nasal Solution, 30 mL vial

Source: http://www.jhppharma.com/products/brands/adrenalin.php, accessed 9/4/2012

Several racemic mixtures of *l*- and *d*-epinephrine are or were marketed as nebulization solutions (2.25%, e.g., Vaponephrine, S2) for the treatment of symptoms of asthma, emphysema, and other breathing conditions. None were FDA approved products. In particular, they are often used for the treatment of bronchiolitis and croup in pediatric patients (http://www.drugstore.com/s2/plastic-container-2-25-neb-solution/qxn00487590199. accessed April 25, 2012).

Several manufacturers sold epinephrine bitartrate metered dose inhalers for the treatment of asthma (MediHaler-Epi, NDA 10-374, 3M; Bronitin Mist and Primatene Mist, NDA 16-126, Wyeth Cons.; Bronkaid Mist, NDA 16-803, Sterling). Over-the-counter (OTC) use for the treatment of asthma was approved under the OTC monograph process, a process similar to the DESI process for Rx drugs with the exception that once monographed, a drug product may be marketed OTC without a new drug application as long as the manufacturer adheres to good manufacturing practices (GMP). However, all of the inhalers used chlorofluorocarbons (CFCs) as the solvent/propellant, and with the discontinuation of production of CFCs all of the CFC-containing products have been discontinued.

Finally, multiple companies and generic manufacturers sell (or sold) combinations of epinephrine with lidocaine, articaine, bupivacaine, and/or etidocaine as FDA-approved injectable anesthetic combinations to prolong local or regional anesthesia (RLDs for lidocaine with epinephrine: Xylocaine with Epinephrine, NDA 06-488, originally marketed November 19, 1948 by Astra, now manufactured by App Pharm; Xylocaine with Epinephrine, NDA 10-418, AstraZeneca, approved November 28, 1972). This use was approved under the DESI process. Lidocaine HCl and Epinephrine was/is also approved for topical use in iontophoresis systems (NDA 20-530, Iomed; NDA 21-486,

Empi) and as a patch to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions (NDA 21-504, Vyteris).

2.6 Important Safety Issues With Consideration to Related Drugs

Epinephrine is the primary treatment for anaphylaxis. Safety issues with epinephrine products intended for administration by the SC or IM routes are well known and characterized, and are reflected in the labeling of the auto-injector products, although the labeling for these products is directed to the fact that the product will be administered by the patient (or a surrogate), and not by a medical professional, in the non- medically supervised setting in the event of an anaphylactic emergency.

The auto-injector products intended for self-administration in an anaphylactic emergency include the following safety information:

CONTRAINDICATIONS:

None

WARNINGS AND PRECAUTIONS:

Do not inject into the buttock, digits, hands, or feet. The presence of sulfite in the product should not deter use. Administer with caution in patients with heart disease. May aggravate angina pectoris or produce ventricular arrhythmias.

ADVERSE REACTIONS:

Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

DRUG INTERACTIONS:

- Cardiac glycosides or diuretics: observe for development of cardiac arrhythmias.
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine.
- Beta-adrenergic blocking drugs: antagonize cardiostimulating and bronchodilating effects of epinephrine.
- Alpha-adrenergic blocking drugs: antagonize vasoconstricting and hypertensive effects of epinephrine.
- Ergot alkaloids: may reverse the pressor effects of epinephrine.

USE IN SPECIFIC POPULATIONS:

- Elderly patients may be at greater risk of developing adverse reactions

Pregnancy Category C: Teratogenic in rats, mice and hamsters.

The current labeling for Adrenalin for injection includes the following safety information:

CONTRAINDICATIONS:

Contraindicated for use in patients with "narrow angle (congestive) glaucoma, shock, during general anesthesia with halogenated hydrocarbons or cyclopropane and in individuals with organic brain damage. Epinephrine is also contraindicated with local anesthesia of certain areas, e.g., fingers, toes, because of the danger of vasoconstriction producing sloughing of tissue; in labor because it may delay the second stage; in cardiac dilatation and coronary insufficiency."

WARNINGS:

A caution for use in elderly people; those with cardiovascular disease, hypertension, diabetes, or hyperthyroidism; in psychoneurotic individuals; and in pregnancy; and patients with long-standing bronchial asthma and emphysema who have developed degenerative heart disease.

Cerebrovascular hemorrhage with overdosage or with inadvertent intravenous injection of epinephrine resulting from the sharp rise in blood pressure.

Fatalities from pulmonary edema because of the peripheral constriction and cardiac stimulation.

PRECAUTIONS:

Protect the product from exposure to light, alkalies, and oxidizing agents, including oxygen, chlorine, bromine, iodine, permanganates, chromates, nitrites, and salts of easily reducible metals, especially iron.

Drug Interactions with excessive doses of digitalis, mercurial diuretics, or other drugs that sensitize the heart to arrhythmias.

Anginal pain in patients with coronary insufficiency.

Potentiating of effects with tricyclic antidepressants, certain antihistamines (e.g., diphenhydramine, tripelennamine, d-chlorpheniramine), and sodium l-thyroxine.

Pregnancy Category C: Teratogenic in rats when given in doses about 25 times the human dose, with no adequate and well-controlled studies in pregnant women.

Not present in the current labeling for this product, but well documented in the literature and present as a WARNING/PRECAUTION in the auto-injector and the proposed labeling, is the safety issue of injection into the buttocks being related to increased incidence of gas gangrene infections.

2.7 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND teleconference was held with the company on July 5, 2011, at which time the Agency expressed the position that clinical trials would not be required for the proposed

indications, and that submission of relevant literature reviews would be acceptable. Additionally, the Agency recommended that JHP request a waiver of *in vivo* bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is an injection solution (b) (4)

[*Note*: In keeping with the Agency's recommendations, the applicant has requested a waiver of the requirement for bioequivalence studies. Please see Section 4.4 for further details regarding the reasons for granting a waiver for this product.]

2.8 Other Relevant Background Information

This section contains some historical background on the isolation of the hormone, epinephrine, and the terminology of 'epinephrine' and 'adrenaline,' with side notes about various related topics of interest.

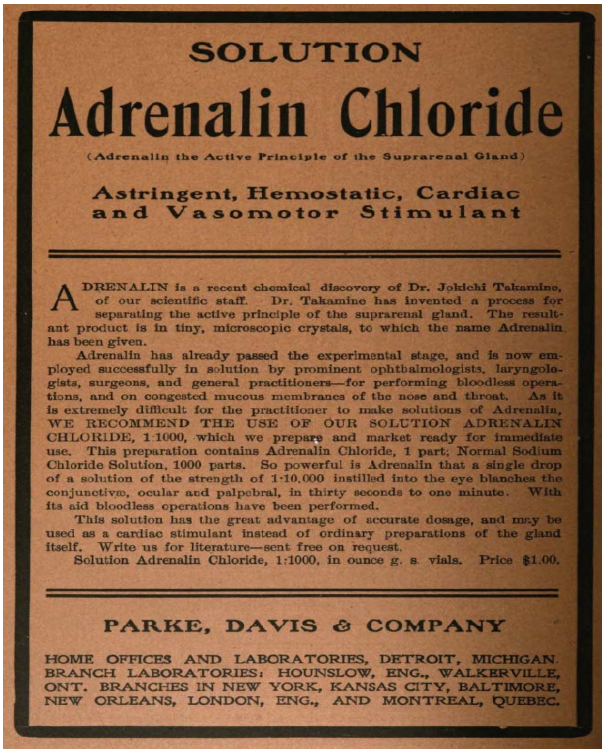
Depending upon the author, the discovery of epinephrine may be attributed to one of several individuals who were working in the field of endocrine physiology in the late 1800s. William Bates reported the discovery of a substance produced by the adrenal gland in the New York Medical Journal in May 1886. In 1894, George Oliver found that the adrenal glands contained a substance with dramatic pharmacological effects. (Oliver and Schafer 1895) In 1895, Polish physiologist Napoleon Cybulski found that adrenal extracts contain biologically active substances that elevate blood pressure. (Pawlik, Konturek et al. 2006)

John Jacob Abel, the first Professor of Pharmacology at Johns Hopkins, coined the term 'epinephrin' in 1897 when he prepared crude extracts of the adrenal glands. (Abel and Crawford 1897) However, his extracts did not behave physiologically like epinephrine (Aronson 2000) and were later found to be the benzoylated derivative. (Davenport 1982) By Abel's calculations, the substance he isolated had the chemical formula of $C_{17}H_{15}NO_4$. At around the same time Otto von Furth in Strasbourg prepared a small amount of an isolate (0.4 g) from the adrenal glands of pigs, which had the chemical formula of $C_5H_9NO_2$ or $C_5H_7NO_2$. He called his isolate 'suprarenin'. Neither of these, however, had the chemical formula of epinephrine ($C_9H_{13}NO_3$) and neither produced the same pharmacologic effect as the crude extracts themselves. (Jowett 1904; Dakin 1905; Davenport 1982; Yamashima 2003) Of course, it took almost a decade before it was discovered that the adrenal medulla produces a combination of epinephrine and norepinephrine so the pharmacologic effects of the crude extracts would never match that of epinephrine alone, and another decade before the concept of neurotrasmitters was more fully understood. And it was not until the mid-20th century and beyond that alpha and beta sympathetic receptors were described, allowing a more complete understanding of how these hormonal neurotransmitters actually exert their effects. (Pearce 2009)

In the summer of 1900, Keizo Uenaka, working in the laboratory of the Japanese chemist Jokichi Takamine in New York, developed the methodology to prepare a purified extract of the "active principle" from the adrenal glands of sheep and oxen.

(Takamine 1901; Takamine 1901; Yamashima 2003) As it turns out, Takamine had visited Abel's laboratory and observed Abel's process, but whether he had visited Abel's laboratory prior to his lab completing the isolation steps is uncertain and the subject of some debate. Takamine called his isolate, a diluted drop of which had the physiological property of blanching the white of the eye, 'adrenalin'. T.B. Aldrich, working in the Parke, Davis & Co laboratory, calculated the chemical formula of Takamine's extract to be $C_9H_{13}NO_3$, which was later confirmed to be the actual formula for epinephrine. Aldrich himself had already isolated a small amount of an extract from the adrenal gland, but never completed his work because Takamine presented his findings at a professional meeting in January of 1901. (Jowett 1904; Davenport 1982)

Dr. Takamine already had a previous business relationship with Parke, Davis & Co to market Taka-Diastase, a form of amylase derived from Aspergillis oryzae and used in the distillation process and as a digestive aid, and it was Parke Davis that funded his independent laboratory in New York. Takamine had also studied patent law in Washington, DC. (Yamashima 2003; Bennett and Yamomoto 2004) Takamine applied for a patent on November 5, 1900, trademarked the name Adrenalin® in the United States in 1901[6], and shortly thereafter Parke, Davis & Co began marketing of the product under the trade name Adrenalin, after which 'epinephrine' gradually became the generic name used in the United States, although the term 'adrenaline' continued to be used in Britain and elsewhere. (Bennett and Yamomoto 2004)



SOLUTION

Adrenalin Chloride

(Adrenalin the Active Principle of the Suprarenal Gland)

Astringent, Hemostatic, Cardiac and Vasomotor Stimulant

ADRENALIN is a recent chemical discovery of Dr. Jokichi Takamine, of our scientific staff. Dr. Takamine has invented a process for separating the active principle of the suprarenal gland. The resultant product is in tiny, microscopic crystals, to which the name Adrenalin has been given.

Adrenalin has already passed the experimental stage, and is now employed successfully in solution by prominent ophthalmologists, laryngologists, surgeons, and general practitioners—for performing bloodless operations, and on congested mucous membranes of the nose and throat. As it is extremely difficult for the practitioner to make solutions of Adrenalin, WE RECOMMEND THE USE OF OUR SOLUTION ADRENALIN CHLORIDE, 1:1000, which we prepare and market ready for immediate use. This preparation contains Adrenalin Chloride, 1 part; Normal Sodium Chloride Solution, 1000 parts. So powerful is Adrenalin that a single drop of a solution of the strength of 1-10,000 instilled into the eye blanches the conjunctivæ, ocular and palpebral, in thirty seconds to one minute. With its aid bloodless operations have been performed.

This solution has the great advantage of accurate dosage, and may be used as a cardiac stimulant instead of ordinary preparations of the gland itself. Write us for literature—sent free on request.

Solution Adrenalin Chloride, 1:1000, in ounce g. s. vials. Price $1.00.

PARKE, DAVIS & COMPANY

HOME OFFICES AND LABORATORIES, DETROIT, MICHIGAN. BRANCH LABORATORIES: HOUNSLOW, ENG., WALKERVILLE, ONT. BRANCHES IN NEW YORK, KANSAS CITY, BALTIMORE, NEW ORLEANS, LONDON, ENG., AND MONTREAL, QUEBEC.

6 Davenport (1982) reports that Takamine received a United States Trade Mark (86,269) on April 16, 1901. However, my search revealed that Adrenalin has active U.S. Trademark 53,934, dating from June 12, 1906. http://www.uspto.gov/trademarks/index.jsp, Searched May 7, 2012.

Of interest, it took three years for Dr. Takamine to receive his patents[7]. Although he submitted the patent application in 1900, the application was repeatedly denied by a senior patent examiner between 1900 and 1903, because the examiner believed that this product was merely an isolated hormonal product of nature, and therefore was unpatentable. This view was based on principles articulated in an 1889 case in which a patent on a pine-needle core used for making textiles was denied because the core was an isolated product of nature (Ex parte: Latimer). Takamine succeeded in obtaining patents by accepting the Latimer precedent but arguing that his product was different and not just a purified product of nature, because it was now "a stable, efficient, pure, concentrated, and reliable product, uniform and permanent in its action and free from injurious and decomposing ingredients." (Takamine 1903; Harkness 2011)

The molecule was synthesized independently in two laboratories in 1904, by Friedrich Stolz and by Henry Drysdale Dakin. (Stolz 1904; Dakin 1905; Bennett 1999) Takamine developed several processes for the isolation of epinephrine, which he also patented.[5] Which of these was used by Parke-Davis for the production of Adrenalin is unclear. Parke-Davis eventually changed the manufacturing process from one of isolation to chemical synthesis, but the exact date when this change took place is unknown.

Takamine's patents were the subject of a famous lawsuit that is considered crucial to modern patent law and now serves as the basis of most biotechnology patents. By 1904, multiple companies had begun to produce products similar to Adrenalin. In 1911, Parke, Davis brought a lawsuit against the most successful of these, H.K. Mulford, on the grounds that their product, 'Adrin' infringed in the patent for Adrenalin. After a protracted court battle, Judge Learned Hand ruled in favor of Parke-Davis and Mulford was ordered to cease infringing on the patent. By ruling in favor of Parke-Davis, Judge Hand cleared the path for subsequent biotechnology patents, including patents on genes. (Bennett and Yamomoto 2004; Harkness 2011) Although his opinion made no mention of the Pure Food and Drug Act of 1906[8], which provided the first legal definition of a drug[9], it was nevertheless the first instance in which a legal distinction was made between a natural product and a drug product:

> "…even if it were an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it available for any use

7 The application (35,546) was divided (35,546, 37,729, 37,730, 42,550, 155,747, and 156,746) and re-filed on seven occasions. Dr Takamine eventually received at least six United States Patents, including four process patents (730,175; 730,196; 730,198; 753,198) and a product patent for the isolate (730,176) issued on June 2, 1903, and a second product patent for the solution (753,177) issued on February 23, 1904. He also applied for an English Patent (1467), which he received on June 22, 1901. (Davenport 1982; Harkness 2011; Opinion of Judge Learned Hand 1911)

8 Judge Hand's opinion would not have referred to the Act because this was a patent dispute, whereas the Act was concerned with ensuring that foods and drugs were not adulterated, misbranded, or poisonous.

9 Section 6 of the Act states "That the term "drug," as used in this Act, shall include all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances *intended to be used for the cure, mitigation, or prevention of disease of either man or other animals*." [my emphasis added]

> by removing it from the other gland tissue with which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent." (Opinion of Judge Learned Hand 1911)

As a side note, it was Takamine who funded several gifts of cherry trees from the Mayor of Tokyo to the City of Washington. The trees are planted at the tidal basin in downtown Washington, DC. (Bennett and Yamomoto 2004)

In Great Britain, where Adrenalin was not marketed, the term 'adrenaline' was adopted as the generic name after much debate, primarily because Henry Dale, a pharmacologist working at the Wellcome Physiological Research Laboratories, insisted upon using that term in his publications. [In part, Dale insisted on using the term adrenaline because editors insisted that he do so in order to publish his articles.] Other authors used yet additional names; however, these two names stuck. (Aronson 2000) The term epinephrine (derived from the Greek) became the preferred name in the United States, the United States Approved Name (USAN), and International Nonproprietary Name (INN). However, adrenaline [with an e] (derived from the Latin) became the British Approved Name (BAN) and European Pharmacopoeia (EP) term.

Although descriptions of anaphylaxis may be found dating to the early Greek and Chinese medical literature, an understanding of the phenomenon roughly paralleled the isolation of epinephrine, early work on neurohumoral transmission and on immunizations, pharmacologic evaluations of the effect of epinephrine in animals, and the testing of epinephrine for the treatment of various allergic conditions. Nobel prize winner Charles Richet coined the term 'anaphylaxis' in 1902 in contra-distinction to the term 'prophylaxis', after trying to immunize dogs with a toxin purified from the tentacles of sea anemone and discovering an opposite effect, i.e., that far smaller doses would cause intense repeated reactions in dogs that had survived the first dose. (Editorial 1921; Ring 2004) Use of epinephrine for asthma is documented as early as 1904, with use of epinephrine for anaphylaxis as early as 1906. (Kaplin and Bullowe 1904; Doig 1905; 1906)

And the rest, as they say, is history.

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 epinephrine injection, USP, 1 mg/mL (1:1000), packaged in (b) (4) vials. The drug substance is manufactured by (b) (4), and the drug product is manufactured by JHP in Rochester, MN. The vials are filled (b) (4)

JHP originally proposed (b) (4) 1 mg/mL of epinephrin (b) (4) contain sodium metabisulfite as an antioxidant, (b) (4)

Epinephrine has two optical isomers (enantiomers), the naturally occurring endogenous form being the *l*- form (*l*-epinephrine). The drug substance is manufactured (b) (4)

(b) (4)

(b) (4)

Potency of the product is an important safety issue for the anaphylaxis indication, whereas it is not for the ophthalmic indication. A less potent product is not of specific concern for the ophthalmic indication because the product needs to be significantly diluted prior to use, and also, because *d*-epinephrine has been found to exhibit equipotent activity as *l*-epinephrine in the eye (mydriasis). However, a less potent product is of particular concern for the anaphylaxis indication because administration of a dose that is perhaps (b) (4) as potent systemically as expected could result in serious adverse outcomes, such as intubation and death, even in a closely monitored setting. Because the course of anaphylaxis is variable from patient to patient and patients may deteriorate rapidly, the medical practitioner would have no way of determining if the patient's clinical course and rapid deterioration was due to lack of expected potency of the product or due to worsening disease.

JHP is requesting (b) (4) expiration dating for the drug product when stored at the recommended label storage conditions of 20° to 25° C (68° to 77° F). To support the proposed expiry dating, JHP initially submitted stability data from 6 months storage under longer term (25° C / 60% RH) and accelerated conditions (40° C / 75% RH) in the container closure system proposed for marketing. The initial specifications proposed (b) (4)

Concerns (b) (4)

were communicated to the sponsor in the 74-day filing letter dated May 4, 2012, in a teleconference on June 21, 2012, and in a written information request dated June 13, 2012. In their review dated August 14, 2012, CMC reviewers Ying Wang, PhD and Xiaobin Shen, PhD recommended a complete response for this application due to high levels of impurities and inadequate analytical methods to measure these impurities.

JHP submitted 9-month and 12-month stability updates for the three registration batches in August 2012. The submission was considered a major amendment to the application, and prompted a 3-month extension of the review clock for the ophthalmic application because differences in the new stability data were not consistent with the proposed drug product specifications. The specifications for the product, including the levels of impurities and analytical methods to measure these impurities, are still being evaluated at the time of completion of this review. As a result, at this time, a final determination on approvability from a CMC perspective has not been made.

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) 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

No clinical pharmacology studies were conducted for this application. JHP has requested a waiver of *in vivo* bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is an injection solution (b) (4)

Biopharmacology is recommending to not waive this requirement.

The Clinical Team / Division disagrees with the Biopharmacology recommendations, and considers that bridging between the proposed and the reference products is not required. From a clinical perspective, the two products are not and need not be pharmaceutically equivalent. The proposed product is a drug intended for use in the medical setting by medically trained personnel, whereas the referenced product is a drug-device combination, i.e., an auto-injector, that is intended for emergency self use in the non-medically supervised setting. Because of these differences, the dosing, weight, and age ranges for this product will extend beyond those for the referenced drug-device combination, which will result in different labeling for this product than any of the currently marketed epinephrine auto-injector products. Because this product is not a drug-device combination and is intended for different setting of use with different dosing and administration instructions, there is no need to ensure bioequivalence to any of the currently marketed auto-injector products, and granting of a waiver of bioequivalence studies is both acceptable and appropriate.

4.4.2 Pharmacology of Epinephrine

Epinephrine belongs to a family of endogenous compounds called catecholamines, which include epinephrine, norepinephrine, and dopamine. The biosynthetic pathway

for epinephrine is from the precursor tyrosine, through DOPA, dopamine, and norepinephrine, as shown in Figure 3.

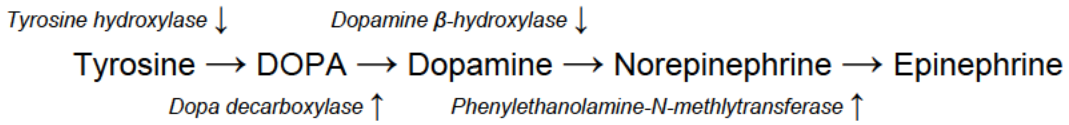


Figure 3. Biosynthetic Pathway for Epinephrine

As noted in Section 4.1, epinephrine has two optical isomers (enantiomers), the naturally occurring form being the *l*- form (*l*-epinephrine). When measured by its systemic effects (BP, etc), *l*-epinephrine has approximately 10-15 times more systemic activity than the *d*- form, *d*-epinephrine. (Patil 1975; Westfall 2011) (b) (4)

Epinephrine (i.e., *l*-epinephrine) is secreted by the adrenal medulla primarily in response to physical or mental stress. The adrenal medulla also makes secretes the precursor to epinephrine, norepinephrine, although in far smaller quantities than epinephrine (estimates are about 4-20%).

The pharmacologic and physiologic effects of epinephrine are well characterized, including stimulation of the sympathetic nervous system to increase heart rate and the force of heart contractions, increase blood pressure, and increase the breakdown of glycogen into glucose resulting in increased blood glucose levels. In short, epinephrine prepares the body for action in perceived emergency situations, boosting the supply of oxygen and energy, while at the same time suppressing some non-vital bodily processes. Other effects that make it suitable for treatment of anaphylaxis are further discussed below.

Sympathomimetics are classified by their interaction, including their specificity, with the various receptor types. Epinephrine is a non-selective adrenergic agonist that interacts with α_1, α_2, β_1, β_2, [and perhaps β_3] receptors. Its effects on target organs are, therefore, complex, as shown in Table 3. For additional and more detailed explanations than need be presented herein, the reader is referred to basic texts, such as Goodman & Gilman's The Pharmacological Basis of Therapeutics, Basic & Clinical Pharmacology, or Greenspan's Basic & Clinical Endocrinology. (Westfall 2011; Biaggioni 2012; Fitzgerald 2011)

Epinephrine only has a brief duration of action because it is rapidly removed from the circulation and metabolized. Organic cation transporters, which are expressed in many tissues, including the liver, rapidly remove epinephrine from the circulation where it is oxidized by monoamine oxidase (MAO) and then methylated by catechol-*0*-methyl transferase (COMT), and eventually converted to vanillyl mandelic acid (VMA), which is excreted by the kidneys. In the adrenal medulla and in extraneuronal sites, epinephrine may be acted on first by COMT and then by MAO to VMA. MAO, which is located on the outer surface of mitochondria; it is widely distributed, although it is particularly

abundant in adrenergic nerve endings. COMT is also widely distributed, and is found in the liver, kidneys, and smooth muscle. As a result of these processes, epinephrine exhibits high first-pass metabolism, especially when administered by the oral route. (AHFS 2011; Fitzgerald 2011; Westfall 2011)

The second of the two stress hormones released by the adrenal medulla is norepinephrine, which was discovered by Swedish Nobel-prize winning physiologist and pharmacologist Ulf von Euler[10] in the mid-1940s. Norepinephrine differs from epinephrine in that norepinephrine has a hydrogen atom attached to its nitrogen, whereas epinephrine has a methyl group. Norepinephrine is also a non-selective adrenergic agonist. However, it interacts with α_1, α_2, and β_1 receptors, and not with β_2 receptors. (Westfall and Westfall 2011), and its actions are both as a hormone and as a neurotransmitter. As a hormone (and, when injected into the body), it acts to increase blood pressure by increasing peripheral vascular tone (α-adrenergic) and as an inotropic stimulator of the heart and dilator of coronary arteries (β-adrenergic). However, ~80% of norepinephrine release is via the sympathetic nervous system rather than via the adrenal medulla, whereas the reverse is true for epinephrine. Norepinephrine release by sympathetic nerves in the heart acts to increase the heart rate and dilate the coronary arteries, and in the brain acts to stimulate the nucleus in the brainstem called the locus cereleus to trigger the sympathetic pathways [in the brain] that extend into the cerebral cortex, limbic system, and the spinal cord. Activation of this pathway increases attention and prepares the body for the fight-or-flight stress reaction. Norepinephrine also acts as a neurotransmitter within the central nervous system, acting on both alpha and beta adrenoreceptors to relay, amplify, and modulate the electrical signals in the brain. As such, it is implicated in a number of conditions including attention deficit / hyperactivity disorder, depression, and schizophrenia.

Whereas both epinephrine and norepinephrine have similar α and β_1 effects, norepinephrine differs from epinephrine in that it exhibits little effect on β_2 receptors, resulting predominantly in α receptor-mediated (peripheral vasoconstriction) and cardiac effects. The added β_2 effects of epinephrine, which include relaxation of bronchial smooth muscles resulting in an increase in bronchial airflow, dilation of blood vessels in skeletal muscles and the liver, release of glucose into the circulation, and inhibition of release of mediators from stimulated eosinophils, mast cells, and basophils (Winslow

10 Ulf von Euler (1905-1983) was born in Stockholm, the son of Dr. Hans von Euler-Chelpin, a Nobel Prize winner (1929) and Professor of Chemistry, and Dr. Astrid Cleve, a Professor of Botany and Geology. His maternal grandfather, Per Teodor Cleve, was a Professor of Chemistry at the Uppsala University and the discoverer of the chemical elements thulium and holmium. von Euler studied medicine at the Karolinska Institute, and worked in Sir Henry Dale's laboratory as a postdoctoral student, where he co-discovered substance P with John H. Gaddum in 1931. After returning to Stockholm, von Euler discovered four other important endogenous substances, prostaglandin, vesiglandin (1935), piperidine (1942), and norepinephrine (1946). From 1946 on, von Euler devoted most of his research work to the distribution and fate of norepinephrine, and made the key discovery that norepinephrine was produced and stored in intracellular vesicles at synaptic terminals. In 1970, he was awarded the Nobel Prize for his work jointly with Sir Bernard Katz and Julius Axelrod.
Abstracted from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1970/euler-bio.html and http://en.wikipedia.org/wiki/Ulf_von_Euler, April 20, 2012.

and Austen 1982), explain why epinephrine is ideally suited for the treatment of anaphylaxis, whereas the lack of β_2 receptor stimulation makes norepinephrine a good drug to support blood pressure in shock but less than ideal for the treatment of anaphylaxis.[11]

Table 3. Main pharmacologic effects of epinephrine

Receptor	Pharmacologic effect
α_1	Increased vasoconstriction and vascular resistance Increased blood pressure Decreased mucosal edema in the airways
α_2	Inhibition of insulin secretion
β_1	Increased myocardial contractility force (inotropic) Increased heart rate (chronotropic) Coronary vasodilation
β_2	Decreased mast cell mediator release Bronchial smooth muscle relaxation, increased bronchodilation Increased skeletal muscle vasodilation[1] Increased glycogenolysis and release of glucose from liver

1 Skeletal muscles contain both α and β_2 receptors. Skeletal muscle β_2 receptors are more sensitive to epinephrine stimulation than α receptors, resulting in mixed responses and only small changes in blood pressure (BP) with lower administered doses, but significant increases in BP with higher doses.

Sources: Kemp 2008; Simons 2011; Westfall 2011

5 Sources of Clinical Data

JHP has not performed any clinical trials to support the application. Instead, JHP submitted a relevant literature search (in Module 5) and relevant overview documents (in Module 2). This is in conformance with discussion held at a pre-NDA meeting on August 4, 2011, at which time the Agency expressed the position that clinical trials would not be required for the proposed indications, and that submission of relevant literature reviews would be acceptable.

11 Because of its intravascular effects, the bitrartrate salt of norepinephrine is approved (Levophed, NDA 7513, Hospira, approved July 13, 1950; and generics) for control of blood pressure in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions), and as an adjunct in the treatment of cardiac arrest and profound hypotension.

5.1 Tables of Studies/Clinical Trials

None

5.2 Review Strategy

The review strategy was to review 1) the submitted literature references, 2) additional non-submitted published literature found by various literature searches [including PubMed searches], and 3) the Agency's previous findings of efficacy and safety of epinephrine products.

5.3 Discussion of Individual Studies/Clinical Trials

NA

6 Review of Efficacy

Efficacy Summary

Anaphylaxis is "a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance." (Sampson 2006) Although no clinical trials have been performed, the efficacy and safety of epinephrine use is supported by a vast literature published over a span of over 110 years of clinical use, and such use is supported by the pharmacology of the drug and is accepted by all medical authorities.

This review finds support for the proposed dosing schema. Most patients respond to a dose of 0.01 mg/kg of a 1:1000 dilution, with the maximum dose being 0.5 mg for adults and 0.3 mg for children. The IM route is the preferred route in the medically supervised setting. Repeated dosing is based on continued [or recurrent, as in the case of biphasic reactions] clinical signs and symptoms (b) (4)

6.1 Indication(s)

6.1.1 Treatment of Anaphylaxis

6.1.1.1 Introduction and Discussion

Anaphylaxis is “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.” (Sampson 2006) Although there is no universal agreement on the definition or the criteria for diagnosis, significant strides have been made in the last decade in this respect, with multiple publications from panels of scientific experts that help to standardize the criteria for diagnosis as well as treatment. (Sampson 2006; Lieberman 2010; Simons WAO 2011) Anaphylaxis has thereby been defined via one of three clinical scenarios, [often referred to as the Sampson criteria] as shown in Table 4.

Previously, the term “anaphylactoid reaction” was used for episodes that were clinically similar to anaphylaxis, but were not IgE-mediated. However, the World Allergy Organization (WAO) has suggested that this term be eliminated, and that all episodes clinically similar to IgE-mediated reactions be called anaphylaxis. Anaphylaxis may then be divided into immunologic and non-immunologic reactions. Likewise, immunologic reactions may be divided into those mediated by IgE mast cell/basophil mediator release and those occurring through other immunologic mechanisms (e.g., certain transfusion reactions). (Johansson WAO 2004) This is a reasonable approach from a clinical perspective, since the available evidence suggests that treatment is the same regardless of etiology.

During an anaphylactic reaction, vasoactive mediators are released from tissue mast cells and circulating basophils, including histamine, eosinophilic chemotactic factor of anaphylaxis (ECF-A), slow-reacting substance of anaphylaxis (SRS-A), platelet activating factor (PAF), kinins, and prostaglandins. Mediator release is independent of the trigger, i.e., it is not dependent upon whether the trigger is IgE mediated (so-called ‘anaphylactic reaction’) or directly mediated (so-called ‘anaphylactoid reaction’); therefore anaphylaxis includes both types of reactions. Histamine, one of the mediators of the initial or acute manifestations, causes decreased systemic vascular resistance through effects on vascular smooth muscle, increased vascular permeability, and coronary vasoconstriction. These effects are mediated by both H_1 and H_2 receptors, although evidence suggests that H_1 and H_2 antihistamines are not effective in treating anaphylaxis once these mediators have been released.

Table 4. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
PEF, Peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 [2 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson 2006, Table 1.

From a regulatory viewpoint, there are several supports for accepting the use of epinephrine for the indication of anaphylaxis, which are discussed in turn below.

The first support is the most obvious, i.e., the Agency's prior regulatory decision with regard to efficacy and safety of epinephrine for this indication. In addition to the literature (discussed further below), this application references the auto-injectable form of epinephrine, EpiPen, which the Agency has approved for emergency self-administration for the [initial] treatment of anaphylaxis. By referencing EpiPen, the application gains support from the Agency's prior regulatory decision with regard to efficacy and safety of epinephrine for this indication. However, it should be noted that the approval of EpiPen in December 1987, was itself based entirely on literature support and no clinical trials, and the same is true for subsequent NDA applications for other epinephrine auto-injector products.

The difference for this product compared to the currently approved auto-injector products is that they are drug-device combinations that are intended for self- or caregiver-administration in the medically unsupervised setting, and are therefore approved at specified dose levels of 0.3 for patients 30 kg and over and 0.15 mg for patients 15-30 kg via IM or SC administration in the anterolateral thigh. In contrast, this drug product is intended for use by healthcare professional in the medically supervised setting. Therefore all weight and age groups are included, and there are additional dosing recommendations that extend above and below those approved for the auto-injector (b) (4) The extended doses and additional route of administration reflect the change in focus for this drug product from intended medically unsupervised self-

administration at the first sign of symptoms (i.e., EpiPen and other epinephrine auto-injectors) to intended administration by a medical professional for the treatment of the signs and symptoms of anaphylaxis (b) (4) (i.e., this application for Adrenalin) in the medically supervised setting.

The basis for approval of EpiPen was briefly summarized by Richard Nicklas, MD[12], the Medical Officer who reviewed the original EpiPen application, after which he cited all of the references that served to support the indication [Medical Officer Review of NDA 19-430, dated February 18, 1985]:

> "The onset of anaphylaxis is usually sudden and unexpected. Reactions are characterized by rapid progression with involvement of the cutaneous, respiratory, and/or circulatory systems. The most common manifestations of anaphylaxis are urticaria, flushing, or angioedema. Major life-threatening manifestations are those involving the circulatory and respiratory systems. Reactions occurring immediately tend to be more severe. Control of mild symptoms can prevent more severe reactions (Patterson and Valentine, 1982). The clinical course is extremely variable and can be fatal.
>
> Epinephrine is the drug of choice in the initial treatment of anaphylaxis. The pharmacologic actions of epinephrine inhibit further release of mediators and reverse end-organ responses. Its use is indicated in all major or severe reactions and acutely in apparent minor reactions to abort a potential severe reaction (Fath and Cerra, 1984).
>
> Due to the rapid clinical course and potentially life-threatening nature of anaphylaxis, prompt therapy is essential. Because prevention by avoidance is not always possible, emergency self-treatment is widely advocated. In fact, increasing the availability of emergency treatment for insect sting allergy was the subject of a NIH Consensus Development Conference in 1978.
>
> The EpiPen Auto-Injector is designed for easy use by the lay person. It is a reliable means for injecting epinephrine in a predetermined therapeutic dose, quickly, safely, and conveniently. The EpiPen Auto-Injector is especially useful in emergency circumstances where rapid administration is critical. The simplicity of use of the auto-injector allows wider availability of earlier treatment, an important therapeutic objective in that the incidence of severe and fatal reactions may be reduced."

The second regulatory support is weaker but nevertheless notable. Epinephrine [and specifically Adrenalin®] predates the DESI process (see Section 2.1), which mandated an examination of efficacy for those drugs marketed between 1938 and 1962 that had only been required to be safe in order to receive marketing approval. However, the DESI process indirectly supports use of epinephrine for the treatment of anaphylaxis because a number of first generation antihistamines were examined and found by the

12 Note: Dr. Nicklas is currently a Clinical Professor of Medicine at The George Washington University School of Medicine. He has served on multiple expert panels, including those for anaphylaxis. As such, he is listed a co-author of some of the expert opinion presented in the applicant's references.

DESI panels, and subsequently by the Agency, to be "effective" as adjunctive treatments to epinephrine for the treatment of anaphylaxis [DESI 6290, 42 FR 44275, 1977], thereby *de facto* implying that epinephrine is effective for this indication. Additionally, cortisone products were found to be "probably effective" for anaphylaxis, and "effective" for treatment of acute noninfectious laryngeal edema with a notation that epinephrine is the drug of first choice [DESI 7110, 37 FR 3775, 1972], again with the same implication.

The third and primary support for this application comes from the literature. The sponsor has submitted multiple literature references that support the scientific rationale for the use of epinephrine for the treatment of anaphylaxis, including updated literature citations since the approval of EpiPen. Please see Section 6.1.1.4 for brief summaries of all of the literature submitted in support of this application, and section 6.1.1.5 for brief summaries of other pertinent literature that was not submitted but nevertheless supports the indication.

Use of epinephrine for the treatment of anaphylaxis makes sense from a pharmacological and physiological perspective. Historically, the use of epinephrine for anaphylaxis is supported by pharmacologic and physiologic experiments in multiple animal models dating to the early to mid 20th century, thereby providing a substantial and reasoned body of evidence to support the pharmacologic basis for carrying this treatment into humans. Additional knowledge of specific α and β receptor subtypes and functions, which were not fully worked out until into the 1970s and 1980s, further supports this use. The efficacy of epinephrine for anaphylaxis is based on its mixed α and β adrenergic receptor effects, including α_1, α_2, β_1, and β_2 effects. Alpha$_1$-receptor activation reduces mucosal edema and membrane leakage and increases vasoconstriction and vascular resistance, resulting in increased blood pressure to treat hypotension. Beta$_1$-receptor activation stimulates the myocardium to increase contraction force and heart rate, resulting in increased cardiac output. Beta$_2$-receptor activation produces bronchodilation, decreases mediator release, and relaxes coronary blood vessels. And mixed α and β effects stimulate glycogenolysis and redirect blood flow to vital end-organs. This combination is ideal from a pharmacologic and physiologic perspective, as it prevents and treats all of the signs and symptoms of anaphylaxis, including upper airway edema, urticaria, bronchospasm, hypotension, and shock. (Simons 2010; Westfall 2011; Simons WAO 2011)

Since its introduction over 110 years ago, there has been extensive anecdotal clinical experience with the use of epinephrine at the doses proposed and used for treatment of anaphylaxis. This experience comes from use to treat anaphylaxis, asthma, and shock, the doses being similar for all three indications except that the doses used during cardio-respiratory arrest (codes) can extend to much higher levels. Although no prospective, <u>controlled</u> clinical trials have been performed to substantiate the use of epinephrine for treatment of anaphylaxis (Sheikh 2011), one prospective, <u>uncontrolled</u> trial (Brown 2004) does provide significant support and is further discussed below. The lack of prospective, controlled clinical trials for the treatment of anaphylaxis in humans is not surprising, and has its basis in the fact that anaphylaxis is a true life-threatening medical emergency and there is no other first-line therapy. Therefore, withholding of

available treatment, even for short periods of time, would not allow for equipoise in a clinical trial. On the basis of this vast clinical experience, and as noted in Dr. Nicklas' review, epinephrine has been adopted as the standard-of-care, first-line treatment of anaphylaxis. This treatment is accepted by all medical authorities and all allergy and anaphylaxis experts in the United States and abroad. (Lieberman 2010; Samson 2006; Simons WAO 2011; Soar 2008)

All other treatments of anaphylaxis are often critical, but they are either supportive or second-line, and therefore adjunctive in nature. They include: discontinuation of any suspected allergen, recumbent positioning; establishment of an adequate airway and administration of oxygen; rapid administration of IV fluids to expand blood volume (crystalloids) for patients in shock; H_1 antihistamines such as diphenhydramine or chlorpheniramine; H_2 antagonists such as cimetidine or ranitidine; inhaled beta-agonists such as albuterol, glucocorticoids; and sedatives and vasodepressing agents. Additional treatment may include blood pressure support with intravenous norepinephrine or other pressors until adequate volume expansion has been achieved and glucagon for patients taking beta-blockers who have refractory hypotension. (Lieberman 2010; Simons WAO 2011)

One prospective, uncontrolled trial supports the use of epinephrine for the treatment of anaphylaxis. (Brown 2004) This study prospectively evaluated a protocol for the treatment of sting anaphylaxis using an infusion of IV epinephrine (1:100,000), oxygen, and volume resuscitation (if needed) in adults who had systemic allergic reactions to a diagnostic sting challenge following either venom or placebo immunotherapy. All 19 patients who experienced a reaction to insect venom received epinephrine treatment and recovered fully. Additionally, 5 patients required volume resuscitation and 2 patients also required atropine to treat bradycardia. Importantly, physical signs of anaphylaxis recurred in 9 of the cases after epinephrine was initially stopped, but resolved after restarting the infusion, suggesting that these patients fulfill Koch's postulates. The conclusion from this study was that carefully titrated intravenous epinephrine combined with volume resuscitation is an effective strategy for treating anaphylaxis due to stings.

Use of epinephrine is also indirectly supported by outcome studies that have looked, for example, at deaths due to anaphylaxis. These studies note the appalling lack of use, or late use, of epinephrine in these patients. However, many of these patients did not have immediate access to epinephrine, as would be expected in the case of first-time anaphylaxis episodes, in large part explaining why the numbers are not better. Additionally, in those unfortunate fatal cases in which the patient had been identified as needing a kit and had one available, only a few used it or used it correctly, suggesting that had it been available and used in a timely fashion many of these lives could have been saved. It is clear from these publications that much work remains in identifying patients at risk, and ensuring that they are adequately trained and prepared to deal with an allergic emergency and carry their medication with them at all times. (Pumphrey 2000; Pumphrey 2007; Sampson 1992)

In sum, the efficacy [and safety] of epinephrine for the treatment of anaphylaxis by this vast array of data and is unquestionable.

6.1.1.2 Pediatric Use

Several pharmacokinetic and pharmacodynamic studies have been conducted evaluating dosing, PK, and PD effects of epinephrine in children. (Fischer 1993; Simons 1998; Simons 2002) The pharmacokinetic evaluations in children show linear clearance in all age ranges, and pharmacodynamic evaluations in children demonstrate similar pharmacologic response, including effects on BP, HR, etc. as seen in adults. Similarly, the underlying disease process is considered the same regardless of age, lending support for use in all pediatric age groups.

6.1.1.3 Dosing and Administration

The sponsor has proposed (b) (4) IM or SC injection (b) (4) based on the literature and long-standing clinical experience. (b) (4) .

(b) (4) For IM and SC dosing, no dilution of the product is necessary.

(b) (4)

6.1.1.3.1 Intramuscular and subcutaneous administration

The proposed IM/SC dosing regimen is supported by pharmacodynamic data in animals, PK data in adult and children, and a vast amount of clinical experience in all age groups. It is in keeping with the literature and is consistent the latest anaphylaxis dosing and treatment recommendations from the Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology). (Lieberman 2010)

Because of the linear kinetics, dosing of epinephrine is appropriately and necessarily weight based. As a result, a dose of 0.01 mg/kg of 1:1000 dilution (which is what is contained in this product) is accepted, and appears to be adequate for most individuals to control anaphylaxis symptoms and maintain blood pressure. The recommended upper bound of 0.5 mg for adults and 0.3 mg for children (age not defined) is primarily based on the side effects and adverse reactions (particularly cardiac and nervous system), which become more difficult to tolerate and/or potentially more serious at higher doses. Given the short half-life, the instruction for repeated dosing every 5-10 minutes as needed is appropriate. Whereas for the epinephrine auto-injector products only two doses are recommended to be administered in the medically unsupervised setting, this is not the case in the medically supervised setting. Repeated dosing is based on the clinical response, i.e., the presence of continued or recurrent [as in the case of biphasic reactions] signs and symptoms. As a result, there is no maximum, i.e., total, dose for epinephrine, with the need for repeated dosing based entirely on clinical status. This dosing appears to be effective for the majority of patients. Although some patients do not respond, for many the failure to respond may be due to a variety of other issues, such as a delay in recognition of the diagnosis, delay before administration or not administering the dose for any of a number of other reasons (including failure to recognize the severity of a reaction, and failure to have a dose immediately available). (Bock 2001; Bock 2007; Garvey 2011; Pumphrey 2000; Pumphrey 2007; Sampson 1992; Simons 2011)

Currently, the dosing recommendations include both intramuscular (IM) or subcutaneous (SC), administration, and there are reasons to that both routes are acceptable depending upon the clinical setting. The IM route, which is associated with shorter time to maximum concentration, is definitely the preferred route in the medically supervised setting because it reaches the central circulation promptly, whereas the SC route leads to vasoconstriction and slower absorption. (Samson 2006; Lieberman 2010; Simons 2010) This recommendation is sensible in the medically supervised setting, where speed of onset is the overriding concern, repeated doses are available, and monitoring is also available. However, in the self-administered, medically unsupervised setting the dosing recommendation and rationale may reasonably differ. In this setting, either route is acceptable, and an argument may be made that the slightly slower absorption associated with SC injection may aid in prolonging the effects of initial self-therapy while awaiting additional emergency medical care, especially in situations where additional doses may not be available. (Pijak 2006) Further, the needle length of the approved self-administered auto-injectors cannot guarantee IM administration into the vastus lateralis muscle because of variability in the overlying fat layer of the thigh, and this is also acceptable for self-administered use. (Simons 2001; Chowdhury 2002; Simons 2010)

It is also of note that the anterolateral thigh (vastus lateralis muscle) is the most appropriate location/muscle for SC/IM administration because of its location, size, and available blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended because of differences in PK associated with this use. (Simons 2001) Injection into the buttock is not recommended because there have been reports of gas gangrene infections after dosing into this area. (Harvey 1968) Clostridial infection

secondary to injections may occur when spores are transmitted by the needle from the skin into an area where the spores can germinate and create an infection. *Clostridium perfringens* [formerly known as *C. welchii*], the bacteria associated with gas gangrene, is found in soil and in stool. Since *C. perfringens* is a preferential anaerobe, it has been suggested that the vasoconstriction associated with epinephrine use may increase the likelihood of infection with this organism. (Harvey 1968) Clostridial infection after injection of epinephrine into the buttock, then, was postulated as secondary to stool contamination. It is also of note that alcohol does kill Clostridium spores; therefore, wiping with alcohol may not prevent this rare occurrence. (Harvey 1968; APIC *C diff Elimination Guide* 2008) As a result, the recommendation/warning to avoid the buttock for epinephrine injections appears to be supported by a reasonable scientific rationale.

It should also be noted that there have also been isolated reports of gas gangrene after epinephrine injection into the anterolateral thigh. Most of these reports have either been in association with injection of a long-acting epinephrine [either an epinephrine in oil suspension or a different form of long-acting epinephrine called 'Hyperduric adrenaline'[13] into [the buttock or] the thigh, or in association with use of needles that had been sterilized and reused [in the days prior to the introduction and routine use of disposable needles and syringes]. In more modern times, these reports are extremely rare, with only one such case reported after EpiPen use (Stuart Hannah 2011)

(b) (4)

13 Hyperduric adrenaline, also known as adrenaline mucate, consisted of adrenaline 0.1 %, mucic acid 0.2%, NaCl 0.9%, phenyl mercuric nitrate 0.002%, sodium metabisulphite 0.15 % and aqua pro inject. ad 100%. It had a prolonged action due to hydrolysis of adrenaline mucate within the tissues to release pharmacologically active adrenaline, such activity could be detected in 30 minutes and continued up to 8 to 12 hours. (Harvey 1968)

All of the reports of the use of this term that this reviewer has found appear in British medical journals along with use the term 'adrenaline', suggesting that these products were marketed in Europe. This reviewer has not come across any information suggesting that they were marketed in the United States.

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

6.1.2 Other Indications

The reader should note that this section contains information about the use of epinephrine for other indications. Inclusion of this information is for completeness only, and should not imply that these indications are supported by this review, nor were these indications proposed by the applicant.

6.1.2.1 Treatment of Asthma

Epinephrine has been widely used for the treatment of asthma, and was the standard of care for many years until the introduction of inhaled non-selective, and later, selective short-acting β_2-agonists, such as albuterol and other products. Such use was an approved DESI indication for Sus-Phrine [NDA 7-942], an aqueous suspension of epinephrine for injection, which was found to be "effective" for the symptomatic treatment of bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema under DESI [DESI 366, 42 FR 38647, 1977]. Use for this indication is also supported by multiple published clinical trials conducted in adults and in children. Several epinephrine bitartrate metered dose inhalers (MediHaler-Epi, NDA 10-374, 3M; Bronitin Mist and Primatene Mist, NDA 16-126, Wyeth Cons.; Bronkaid Mist, NDA 16-803, Sterling) were also approved for the over-the-counter (OTC) treatment of asthma under the OTC monograph process. However, all of the inhalers used chlorofluorocarbons (CFCs) as the solvent/propellant, and with the discontinuation of production of CFCs all of the CFC-containing products have been discontinued.

Over the last 15 years, the guidelines for asthma management have changed. It was recognized that epinephrine has the potential to cause excessive cardiac stimulation,

especially with repeated doses. This unwanted side effect can lead to cardiac stress and heart attacks, especially in older individuals or those with heart disease. Safety concerns regarding increased morbidity and mortality with routine use of epinephrine as well as another non-selective beta-agonist, fenoterol, lead to the recommendation that selective β_2-agonists be used as the first line treatment of bronchospasm [associated with asthma as well as other conditions]. Additionally, advances in the understanding of pathophysiology of asthma (i.e., that asthma includes an inflammatory component) have led to the recommendation that selective β_2-agonist use be restricted to as-needed 'rescue' use and that anti-inflammatory agents be added to asthma management if beta-agonists are needed on a regular basis. (AFHS 2011; GINA 2011; NAEPP 2007) With these changes in the management of asthma, Sus-Phrine use diminished, and the manufacturer of Sus-Phrine withdrew the product from the market in 2006 [72 FR 62858, 2007]. As a result, the risk/benefit balance for epinephrine use for treatment of asthma (bronchospasm) has changed, and epinephrine (and other nonspecific beta-agonist) use is now specifically discouraged except under specific circumstances, e.g., when the bronchospasm is associated with and part of anaphylaxis or in severe emergent situations where a selective β_2-agonist is not available [14,15].

Nevertheless, the asthma literature in children provides a reasonable amount of safety information throughout the pediatric age range that supports the dosing of epinephrine for treatment of anaphylaxis (same dose used for both conditions). See Section 6.1.1.2, Pediatric Use, for details.

6.1.2.2 As an Adjunct to Anesthetics for Prolongation of Anesthesia

Use of epinephrine for this indication was the subject of DESI review in combination with multiple local and regional anesthetics, such as lidocaine, articaine, bupivacaine, and/or etidocaine (RLDs for lidocaine with epinephrine: Xylocaine with Epinephrine, NDA 06-488, originally marketed November 19, 1948 by Astra, now manufactured by App Pharm; Xylocaine with Epinephrine, NDA 10-418, AstraZeneca, approved November 28, 1972), and this use was approved under the DESI process. Lidocaine HCl and Epinephrine was/is also approved for topical use in iontophoresis systems (NDA 20-530, Iomed; NDA 21-486, Empi) and as a patch to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions (NDA 21-504, Vyteris).

---

14 While the current NAEPP guideline still includes dosing for epinephrine (0.01 mg/kg up to 0.3-0.5 mg and 0.3-0.5 mg administered SC every 20 minutes for 3 doses, in children and adults, respectively), it specifically states that non-selective beta-agonists, including epinephrine, "are not recommended due to their potential for excessive cardiac stimulation, especially in high doses." However, in the setting of when EMS providers do not have an albuterol nebulizer or inhaler available, the guideline states that "subcutaneous epinephrine [or terbutaline] should be given for severe exacerbations." (NAEPP 2007).

15 The GINA guideline states that "A subcutaneous or intramuscular injection of epinephrine (adrenaline) may be indicated for acute treatment of anaphylaxis and angioedema, but it is not routinely indicated during asthma exacerbations", but goes on to state that "If there is a possibility that anaphylaxis is involved in an asthma attack, epinephrine should be the drug of choice." (GINA 2011)

6.1.2.3 Nasal Decongestion

Adrenalin has also been marketed in non-sterile 30 mL rubber-stoppered vials for use as a nasal decongestant. This use dates back to the earliest physiologic and pharmacologic experiments with extracts of the adrenal medulla in the late 1800s, and the effects of epinephrine in this regard are well documented. Such use is supported pharmacologically because α-adrenergic receptors, which are expressed in the blood vessels of the nasal mucosa, cause vasoconstriction when stimulated by sympathomimetics like epinephrine. (Biaggioni and Robertson 2012) However, the applicant has not requested and has not submitted literature to support this indication. Further, there are reports of medical errors resulting from confusion of the 30 mL sterile vials for injection and the 30 mL vials intended for use as a topical decongestant. (ISMP 2009). Therefore, at this point in time this indication is not being considered.

(b) (4)

7 Review of Safety

Safety Summary

The safety assessment for this application is considered adequate. No clinical trials were conducted to support the indication of anaphylaxis. The safety information comes from the literature, including many pharmacological studies in animals, pharmacokinetic, pharmacodynamic, and epidemiologic studies in humans, one clinical trial in patients with anaphylaxis, adverse event reports, and over 110 years of clinical experience. This

drug has been used in all age ranges, and the target population is any individual of any age who has an anaphylactic reaction. Given the serious nature of anaphylaxis, there are no absolute contraindications for such use.

Additional safety information to support pediatric use also comes from randomized, active-controlled clinical trials in over 360 pediatric asthma patients using the same dose of epinephrine as is recommended for anaphylaxis administered subcutaneously. Overall, the data provide a sufficient understanding of safety to adequate label this drug for safe use in all populations.

Epinephrine has a narrow therapeutic window, with overlap between life-saving pharmacologic effects that are associated with therapeutic clinical efficacy and other pharmacologic effects that are seen as common adverse reactions. As a result, the higher the dose, the more likely that there will be side effects that potentially may be significant. Typical reactions include restlessness, pallor, tremor, anxiety, palpitations, dizziness, and headache; their presence indicates that the administered dose is having a pharmacologic effect. The most serious reactions include transient hypertension with attendant risks of cerebral bleeding, and cardiac toxicity including myocardial ischemia, infraction, and cardiac arrhythmias. Serious reactions are rare with IM and SC use at recommended doses. (b) (4)

7.1 Methods

The literature was reviewed, including both the submitted literature and other literature found through PubMed searches, including searches regarding the history, pharmacology, toxicology, pharmacokinetic, safety, efficacy, clinical trials, reviews, and case reports of/for epinephrine. Please see Appendix 9.1 for the submitted literature (including reviews) and other literature that was not submitted but was reviewed as part of this application.

7.2 Adequacy of Safety Assessments

The safety assessment is considered adequate. The applicant did not conduct clinical trials to support the indication of anaphylaxis, and no controlled clinical trials are published in the literature in patients with anaphylaxis. The safety information comes from the literature, including many pharmacological studies in animals as well as pharmacodynamic and epidemiologic studies in humans, PK data, safety reports and reviews, and over 110 years of clinical use. The data provide a sufficient understanding of safety to adequate label this drug for safe use.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

This drug has been used in all age ranges. The target population is any individual of any age who has an anaphylactic reaction.

7.2.2 Explorations for Dose Response

The safety for use of epinephrine for treatment of anaphylaxis comes from over 100 years of clinical use, PK and PD studies, as well as clinical trials in the setting of asthma, which have demonstrated linear kinetics and clearly outlined the adverse reactions that may be expected with this drug.

Epinephrine is well known to have a narrow therapeutic window (Simons 2006; Kemp 2008), with overlap between life-saving pharmacologic effects that are associated with therapeutic clinical efficacy and other pharmacologic effects that are seen as common adverse reactions. In fact, restlessness, pallor, tremor, anxiety, palpitations, dizziness, headache are typical reactions to epinephrine treatment, and their presence indicates that the administered dose is having a pharmacologic effect. (Kemp 2008; Simons 2011; Westfall 2006). While texts usually recommend treatment with rest, recumbent positioning, and reassurance, adverse effects from epinephrine wear off quickly without additional treatment, and these treatments are just as likely to aid in treatment of the underlying condition, anaphylaxis.

Serious adverse reactions are rare. Most serious reactions are associated with medication errors and overdose, or IV use (Mclean-Tooke 2003; Simons 2010; Simons 2011; Sheikh 2011) rather than being associated with the doses routinely administered IM or SC, although there are rare case reports at these dosage levels as well.

PK data in adults and children show a reasonably linear relationship between dose and weight, supporting weight based dosing as proposed for this product (Clutter 1980; Ensinger 1992; Fisher 1993; Simons 1998; Simons 2001; Simons 2002; Abboud 2009). These findings have also been demonstrated in animals (Gu 1999).

Higher doses are more frequently associated with cardiac toxicity, including transient hypertension, chest pain, palpitations, ST elevation, ventricular tachycardia, ventricular arrhythmias, cardiomyopathy, vasospasm-induced acute coronary syndromes (angina, myocardial infarction, arrhythmias), pulmonary edema, and cardiac arrest. Such toxicity is of more concern in patients with underlying organic heart disease, including patients with cardiac arrhythmias, coronary artery disease, or hypertension, in patients who are on drugs that may sensitize the heart to arrhythmias, in elderly patients with cardiovascular disease, and in patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women.

Since the heart is itself a potential target organ in anaphylaxis, it should be noted that acute coronary symptoms may be associated anaphylaxis itself rather than epinephrine treatment, regardless of whether the patient has known or coronary artery disease, i.e., these symptoms may occur in patients in whom subclinical coronary artery disease is

unmasked as well as in patients who have no coronary artery disease, for whom the symptoms are the result of transient vasospasm. (Barach 1984; Brown 1998; Hema 2008; Kanwar 2010; Kounis 2006; Shaver 2006; Simons 2011; Sheikh 2011; Triggiani 2008)

(b) (4)

[redacted]

7.2.3 Data from Animals

Epinephrine has physiologic and pharmacologic effects that are well known and well characterized. A large number of studies have been performed in animals and *in vitro* to evaluate the pharmacologic and physiologic effects of epinephrine. Many of these studies, dating to the 1890's, predate identification of the specific receptors that allow a detailed understanding of how the drug effects each organ system within the body, a process that took much of the 20th century and produced multiple Nobel Prize winners. That understanding is sufficiently understood that it is published in basic textbooks of pharmacology and medicine, a brief summary of which may be found in Section 4.4 of this review, and will not be discussed here.

Epinephrine is cardiotoxic in animals. These effects have also been demonstrated in humans, and this clinical information is reflected in the labeling.

Although epinephrine is an endogenous compound, *in vitro* data shows that epinephrine is genotoxic (see next paragraph). However, because there are no long-term clinical uses for epinephrine, long-term carcinogenicity studies have not been conducted in animals, and carcinogenicity has not been evaluated in humans.

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. However, this should not deter the use of epinephrine for any of the indications being considered in this application.

The potential for epinephrine to impair reproductive performance has not been evaluated, but epinephrine has been shown to decrease implantation in female rabbits.

7.2.4 Routine Clinical Testing

NA

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor did not conduct any metabolic, clearance, or drug interaction studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

NA.

7.3 Major Safety Results

7.3.1 Deaths

Anaphylaxis may result in death, and there are a number of publications included in this submission that discuss that eventuality (see Appendix 9.1). Appropriate treatment with epinephrine (and other measures) can be life-saving. Epinephrine, however, can be cardiotoxic, especially in high doses and in patients with underlying heart disease. See other sections of this review for details.

7.3.2 Nonfatal Serious Adverse Events

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation, i.e., for the treatment of anaphylaxis. Patients for whom there is a greater risk for developing adverse reactions include:

- Patients with heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias including fatal ventricular fibrillation.
- Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease.
- Patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

The safety issue of injection into the digits has been reported with use of the epinephrine auto-injector products. This usually occurs when the user mistakes the live end for the top and mistakenly holds the thumb or another finger over the top (which is not part of the instructions). Because epinephrine causes vasoconstriction, lack of blood flow to the digit can potentially be associated with anoxic tissue loss. Epinephrine products used in conjunction with local anesthetics also carry a warning not to inject into a digit. That warning is carried into the proposed labeling for this product. While a general warning is appropriate, detailed warnings are not necessary, as this safety issue is of more specific concern to the epinephrine auto-injector products that are intended for self-use rather than for epinephrine vials intended for use by the medical professional.

Gas gangrene has been associated with injections of epinephrine into the buttocks. Therefore, injection into the vastus lateralis muscle of the thigh is the most appropriate location for administration when injected IM or SC. See section 6.1.1.3.1 for further details.

7.3.3 Dropouts and/or Discontinuations

NA

7.3.4 Significant Adverse Events

NA

7.3.5 Submission Specific Primary Safety Concerns

NA

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events with epinephrine use are well described and include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

7.4.2 Laboratory Findings

Epinephrine causes transient decreases in potassium levels due to stimulation of potassium uptake into cells, particularly skeletal muscle (β_2) and decreased renal potassium excretion. (Westfall 2006)

7.4.3 Vital Signs

Epinephrine use can cause a rapid rise in blood pressure. See Section 7.3.2.

7.4.4 Electrocardiograms (ECGs)

Epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias including fatal ventricular fibrillation. See Section 7.3.2.

7.4.5 Special Safety Studies/Clinical Trials

NA

7.4.6 Immunogenicity

NA

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See other sections of this review that discuss dose dependency with regard to the pharmacodynamic as well as potentially toxic effects.

7.5.2 Time Dependency for Adverse Events

Epinephrine is short-acting, lasting only a few minutes before it is removed from the circulation and metabolized (see Section 4.4.2). Most side effects, including effects on blood pressure and the CNS resolve rapidly as the drug is metabolized.

7.5.3 Drug-Demographic Interactions

NA

7.5.4 Drug-Disease Interactions

Populations that are particularly vulnerable to the effects of epinephrine include individuals at the extremes of age, those with hypertension, peripheral vascular disease, coronary artery or ischemic heart disease, organic heart disease, patients with long-standing or significant emphysema who may also have degenerative heart disease, cerebrovascular disease, diabetes, untreated hyperthyroidism, and pheochromocytoma.

In patients with diabetes, epinephrine may transiently increase blood glucose levels. Uncontrolled hyperthyroidism makes the myocardium more sensitive to the β-adrenergic effects of epinephrine due to an increased number of β-adrenergic receptors in the vasculature of these individuals. (Goldenberg 1950; Kemp 2008; Mclean-Tooke 2003) Patients with Parkinson's disease may experience psychomotor agitation or notice a temporary worsening of symptoms.

7.5.5 Drug-Drug Interactions

Because the pharmacology of epinephrine is well characterized and there is vast clinical experience with this drug, drug-drug interactions are also well known. Some medications increase the risk of adverse reactions from epinephrine due to a drug-drug interaction. Others may decrease the effectiveness of epinephrine treatment. Nevertheless, the use of any of these drugs by a patient does not constitute an absolute contraindication the use of epinephrine to treat anaphylaxis. (Kemp 2008; Mclean-Tooke 2003)

Alpha-blockers, and Alpha- and Beta-adrenergics

Not surprisingly α-blocking agents can block the α-pharmacologic effects of epinephrine, and α- and β-adrenergic agents can potentiate the α- and β-pharmacologic effects of epinephrine, respectively.

Beta-blockers

The evidence suggests that anaphylaxis may be made worse by the presence of β-blockers such as propranolol. (Lang 1995) Furthermore, and perhaps not surprisingly, patients on β-blockers do not respond well to epinephrine treatment. (Barach 1984) While higher doses of epinephrine are required to overcome the lack of a β-adrenergic response, the unopposed α-adrenergic stimulation may increase the risk for use of even standard doses, leading to bradycardia, hypertension, coronary artery constriction, and bronchoconstriction. (Mclean-Tooke 2003) This finding has been noted even with use of eye drops containing a β-blocker. (Moneret Vautrin 1993) As a result, the general recommendation is to withdraw use of β-blockers in patients who are considered at risk of anaphylaxis, and substitute alternative treatments. (Mclean-Tooke 2003)

Treatment guidelines for patients on β-blockers who develop anaphylaxis have not been published. However, because of the sensitivity to unopposed α-adrenergic stimulation, use of drugs with pure β-adrenergic effects, such as glucagon, along with fluid resuscitation, is recommended. (Lieberman 2010)

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOI)

Tricyclic antidepressants and monoamine oxidase inhibitors are known to potentiate the effects of epinephrine and increase the risk of cardiac arrhythmias. Although at least one publication suggests halving the dose of epinephrine in these patients (Mclean-Tooke 2003), others suggest that the inter-individual variability in response is sufficiently large that the usual dose should be administered and the patient observed for a clinical response and side effects, with further dosing titrated accordingly (Soar 2008).

Other Drug Interactions

Ergot alkaloids may reverse the pressor effects of epinephrine. Coadministration with halogenated hydrocarbon anesthetics, such as halothane, or with cardiac glycosides, digitalis, diuretics, quinidine, and other antiarrhythmics, may result in cardiac arrhythmias. Cocaine and amphetamines sensitize the myocardium to the effects of epinephrine, increasing the risk of toxicity. (Kemp 2008) Epinephrine should not be used systemically to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Although epinephrine is an endogenous compound, *in vitro* data shows that epinephrine is genotoxic. However, because there are no long-term clinical uses for epinephrine, long-term carcinogenicity studies have not been conducted in animals, and carcinogenicity has not been evaluated in humans.

7.6.2 Human Reproduction and Pregnancy Data

Epinephrine is Pregnancy Category C. There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women. Epinephrine has been shown to teratogenic in rabbits, mice, and hamsters. As a result, the labels for the approved products carry the standard warning for this pregnancy category, i.e., that epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both). However, it should be noted that anaphylaxis is just such a use. The treatment of anaphylaxis with epinephrine involves short-term use, and the treatment is life-saving. Therefore, although the labels carry this concern, the benefits for use far outweigh the risks.

7.6.3 Pediatrics and Assessment of Effects on Growth

Epinephrine is an endogenous compound. As is the case in adults, the doses of epinephrine for use in children are empiric, having been used for much of the last 100 years in the clinical setting. The pharmacologic response to epinephrine, as well as the underlying disease process, are considered the same regardless of age, lending support for use in all pediatric age groups. There has been no assessment of the effects of epinephrine on growth, but given the way this drug is used there is no expectation that such an assessment would be beneficial.

With regard to labeling for use in children, the sponsor proposes making the following statement in subsection 8.4, the Pediatric Use section:

(b) (4)

Although the available PK and PD data do support the statement regarding weight-based dosing (see section 6.1.1.2), my review did not uncover any evidence to support the statement (b) (4)

Although no controlled clinical trials have been conducted to evaluate the safety and efficacy of epinephrine in children with anaphylaxis, adverse reactions are available from a range of controlled clinical trials conducted in pediatric patients with asthma [see Sections 9.1.1.7 and 9.1.2.2]. (Becker 1983; Ben-Zvi 1982; Lin 1996; Simons 1981; Turpeinen 1984) All of the pediatric asthma trials compared epinephrine with a beta agonist. While asthma is a different disease and a different indication, the studies provide safety data with the use of epinephrine, since the dosing recommendations for asthma (0.01 mg/kg of a 1:1000 dilution administered SC) and anaphylaxis are similar. [*Note*: Although similar, dosing for the two indications are not identical, as the dosing recommendations for asthma include repeated doses every 20-30 minutes, whereas the dosing recommendations for anaphylaxis are more frequent. Additionally, for asthma the SC route is preferred, whereas for anaphylaxis both routes are acceptable although the IM route is preferred in the medically supervised setting.] The asthma trials nevertheless demonstrate that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults. An additional study performed in wheezing children under 2 years of age demonstrated similar findings, supporting use of epinephrine in all pediatric age groups. (Lowell 1987)

In fact, with certain exceptions, adults, and in particular older adults, are more likely to be at risk from epinephrine use. Cardiac adverse effects from epinephrine are associated with higher doses and are more of a concern in patients with underlying heart disease. Children are less likely than adults to have underlying organic heart disease, coronary artery disease, be on a medication, or have some underlying disease such as hyperthyroidism or Parkinson's disease that would predispose them to arrhythmias or potentiate the adverse reactions associated with epinephrine administration. However, children are perhaps more likely to have an underlying acquired or congenital condition, such as congenital heart disease or other abnormality, that may place them at higher risk and predispose them to arrhythmias, perfusion problems, or other adverse effects secondary to epinephrine administration. For many children, their underlying condition is known and the risks identified. However, and unfortunately for some, these conditions have not been diagnosed prior to a significant event. For example, fatal arrhythmias are sporadically reported in children who are strenuously exercising, primarily in adolescents and older children for whom an underlying diagnosis was never made, and epinephrine can mimic those exercise effects. However, this risk cannot be generalized to all children.

The issue of whether neonates and young children less than one year of age are more sensitive to the effects of epinephrine is an open one, as little data are available. However, the frequency of use in this age range is significantly less than for older children because anaphylaxis is rare in this age range.

(b) (4)

In contrast, subsection 8.5, Geriatric Use, appropriately states that older patients may be particularly sensitive and be at increased risk, with consideration to be given to lower initial doses to take into account potential concomitant disease or other drug therapy.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Because of the pharmacologic side effects, this drug is not likely to be abused.

7.7 Additional Submissions / Safety Issues

NA

8 Postmarket Experience

Since this drug has been marketed since 1901, all of the experience with the drug is postmarket. However, that clinical experience is substantial. See other sections of this review for details.

9 Appendices

9.1 Literature Review/References

9.1.1 Submitted Literature

The following references were submitted by the applicant in support of the indication of anaphylaxis. It should be noted that one reference was submitted but not included in the applicant's listing of citations within the clinical summary (Brown 1998). All are included in the listing below. References submitted to support the indication of maintenance of mydriasis during cataract surgery are not included herein. Following each reference is a brief discussion of what this material adds to the supports for epinephrine for treatment of anaphylaxis. The references are divided by topic, including Pharmacologic/Physiologic Experiments; Drug Information Materials and Textbooks; Pharmacokinetic, Pharmacodynamic, and Safety Studies; Case Reports; Epidemiologic/Disease Studies; Reviews, Consensus Management Conferences, and Guidelines; and Clinical Studies. Additional literature that was not submitted also supports the indication of treatment of anaphylaxis. The additional non-submitted literature follows in the next section (Section 9.1.2).

9.1.1.1 Listing of Submitted Literature References for Anaphylaxis

Abboud I, Lerolle N, et al., 2009. Pharmacokinetics of epinephrine in patients with septic shock: modelization and interaction with endogenous neurohormonal status. Crit Care. 13(4): R120.

AHFS, 2011. Epinephrine. In *AHFS drug information 2011*. Bethesda, Maryland, American Society of Health-System Pharmacists, Section 12.12.12: 1379-1385.

Allwood MJ, Cobbold AF, et al., 1963. Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. Br Med Bull. 19: 132-136.

Becker AB, Nelson NA, et al., 1983. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. J Pediatr. 102(3): 465-469.

Bock SA, Muñoz-Furlong A, et al., 2001. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 107(1): 191-193.

Bock SA, Muñoz-Furlong A, et al., 2007. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol. 119(4): 1016-1018.

Brown AFT, 1998. Therapeutic controversies in the management of acute anaphylaxis. J Accid Emerg Med. 15(2): 89-95.

Brown SG, 2005. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. Curr Opin Allergy Clin Immunol. 5(4): 359-364.

Brown SG, Blackman KE, et al., 2004. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. Emerg Med J. 21(2): 149-154.

Brown SG, Mullins RJ, et al., 2006. Anaphylaxis: diagnosis and management. Med J Aust. 185(5): 283-289.

Chaudhuri K, Gonzales J, et al., 2008. Anaphylactic shock in pregnancy: a case study and review of the literature. Int J Obstet Anesth. 17(4): 350-357.

Cheng A, 2011. Emergency treatment of anaphylaxis in infants and children. Paediatr Child Health. 16(1): 35-40.

Chowdhury BA and Meyer RJ, 2002. Intramuscular versus subcutaneous injection of epinephrine in the treatment of anaphylaxis. J Allergy Clin Immunol. 109(4): 720; author reply 720-721.

Clutter WE, Bier DM, et al., 1980. Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest. 66(1): 94-101.

Ellis AK and Day JH, 2007. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. Ann Allergy Asthma Immunol. 98(1): 64-69.

Ensinger H, Lindner KH, et al., 1992. Adrenaline: relationship between infusion rate, plasma concentration, metabolic and haemodynamic effects in volunteers. Eur J Anaesthesiol. 9(6): 435-446.

Fisher DG, Schwartz PH, et al., 1993. Pharmacokinetics of exogenous epinephrine in critically ill children. Crit Care Med. 21(1): 111-117.

Frew AJ, 2011. What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? Allergy. 66(1): 15-24.

Garvey LH, Belhage B, et al., 2011. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. Anesthesiology. 115(1): 111-116.

Goldenberg M, Aranow H, Jr., et al., 1950. Pheochromocytoma and essential hypertensive vascular disease. AMA Arch Intern Med. 86(6): 823-836.

Gu X, Simons FER, et al., 1999. Epinephrine absorption after different routes of administration in an animal model. Biopharm Drug Dispos. 20(8): 401-405.

Hema HA, Kulkarni A, et al., 2008. Ventricular Tachycardia due to Intranasal Adrenaline in Nasal Surgery- a Case Report. Indian Journal of Anaesthesia. 52(2): 199-201.

ISMP, 2009 "ALERT: Fatal Outcome after Inadvertent Injection of Epinephrine Intended for Topical Use." ISMP Canada Safety Bulletin 9.

Kanwar M, Irvin CB, et al., 2010. Confusion about epinephrine dosing leading to iatrogenic overdose: a life-threatening problem with a potential solution. Ann Emerg Med. 55(4): 341-344.

Kemp SF, Lockey RF, et al., 2008. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 63(8): 1061-1070.

Kounis NG, 2006. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol. 110(1): 7-14.

Lieberman P, Nicklas RA, et al., 2010. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 126(3): 477-480 e471-442.

Manivannan V, Campbell RL, et al., 2009. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. Ann Allergy Asthma Immunol. 103(5): 395-400.

McLean-Tooke AP, Bethune CA, et al., 2003. Adrenaline in the treatment of anaphylaxis: what is the evidence? BMJ. 327(7427): 1332-1335.

Mertes PM, Malinovsky JM, et al., 2011. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol. 21(6): 442-453.

Mink SN, Simons FE, et al., 2004. Constant infusion of epinephrine, but not bolus treatment, improves haemodynamic recovery in anaphylactic shock in dogs. Clin Exp Allergy. 34(11): 1776-1783.

Pumphrey RSH, 2000. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy. 30(8): 1144-1150.

Pumphrey RSH and Gowland MH, 2007. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol. 119(4): 1018-1019.

Rudders SA, Banerji A, et al., 2010. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. Pediatrics. 125(4): e711-718.

Sampson HA, Mendelson L, et al., 1992. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 327(6): 380-384.

Sampson HA, Muñoz-Furlong A, et al., 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 117(2): 391-397.

Shaver KJ, Adams C, et al., 2006. Acute myocardial infarction after administration of low-dose intravenous epinephrine for anaphylaxis. CJEM. 8(4): 289-294.

Sheikh A, Shehata YA, et al., 2009. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock (Review). The Cochrane Library, The Cochrane Collaboration. 2011, Issue 2.

Simons FER, 2004. First-aid treatment of anaphylaxis to food: focus on epinephrine. J Allergy Clin Immunol. 113(5): 837-844.

Simons FER, Ardusso LR, et al., 2011. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. WAO Journal. 2011(February): 13-37.

Simons FER, Gu X, et al., 2002. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. J Allergy Clin Immunol. 109(1): 171-175.

Simons FER, Gu X, et al., 2001. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol. 108(5): 871-873.

Simons FER, Gu X, et al., 2002. Reply to letter. J Allergy Clin Immunol. 108:720-721.

Simons FER, Roberts JR, et al., 1998. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 101(1 Pt 1): 33-37.

Simons KJ and Simons FER, 2010. Epinephrine and its use in anaphylaxis: current issues. Curr Opin Allergy Clin Immunol. 10(4): 354-361.

Soar J, Pumphrey R, et al. Working group of the resuscitation council (UK), 2008. Emergency treatment of anaphylactic reactions--Guidelines for healthcare providers. Resuscitation. 77(2): 157-169.

Song TT, Nelson MR, et al., 2005. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy Asthma Immunol. 94(5): 539-542.

Stecher D, Bulloch B, et al., 2009. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? Pediatrics. 124(1): 65-70.

Tran TP and Muelleman RL, 2010. Allergy, Hypersensitivity, and Anaphylaxis. In *Rosen's Emergency Medicine*. 7th ed, Chapter 117: 1511-1528.

Triggiani M, Patella V, et al., 2008. Allergy and the cardiovascular system. Clin Exp Immunol. 153 Suppl 1: 7-11.

Westfall TC and Westfall DP, 2006. Adrenergic Agonists and Antagonists. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York, McGraw-Hill. 11th ed, Chapter 12: 257-295.

World Health Organization, March 2011. WHO Model List of Essential Medicines. 17th list. http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

World Health Organization, March 2011. WHO Model List of Essential Medicines for Children. 3rd list. http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

9.1.1.2 Pharmacologic/Physiologic Experiments

Allwood MJ, Cobbold AF, et al., 1963. Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. Br Med Bull. 19: 132-136.

This article is a review of the peripheral vascular effects of norepinephrine, isopropylnorepinephrine and dopamine when administered by IV infusion [in humans].

However, it also contains information regarding the effects of epinephrine infusion on blood pressure [in humans]. This review is referred by pharmacology texts such as Goodman and Gillman's Textbook of Pharmacology, which presents a modified version of Figure 1 from this review paper to illustrate the differences between the pharmacologic effects of epinephrine and norepinephrine infusion on systolic and diastolic blood pressure.

Gu X, Simons FER, et al., 1999. Epinephrine absorption after different routes of administration in an animal model. Biopharm Drug Dispos. 20(8): 401-405.

This article reports on a prospective, randomized, five-way crossover study in rabbits to determine the relationship between the route of epinephrine administration and the rate and extent of epinephrine absorption. Plasma epinephrine concentrations were measured before and at intervals up to 180 min after by IM, SC, and inhalation administration; IV epinephrine and IM saline were used as positive and negative controls, respectively. Absorption of epinephrine was significantly faster after IM than SC injection, although the extent of absorption was satisfactory after both. Maximum plasma epinephrine concentrations were higher, and occurred more rapidly, after IM than SC injection. The elimination half-life [t(1/2)] after IV administration was 11.0+/-2.5 min. Neither the rate nor the extent of absorption was satisfactory after administration by inhalation.

Mink SN, Simons FE, et al., 2004. Constant infusion of epinephrine, but not bolus treatment, improves haemodynamic recovery in anaphylactic shock in dogs. Clin Exp Allergy. 34(11): 1776-1783.

Because treatment guidelines are based on anecdotally derived data, the authors conducted randomized, controlled, crossover studies to examine the time course of hemodynamic recovery in a canine model of anaphylactic shock when epinephrine was administered at the initiation of allergen challenge before fully developed shock had occurred. The studies were performed approximately 3-5 weeks apart in ragweed-sensitized dogs while the animals were ventilated and anesthetized. Epinephrine was administered by IV, SC, or IM bolus (0.01 mg/kg) and by continuous IV infusion (dose titrated to maintain mean arterial pressure at 70% of preshock levels), and compared no treatment. With continuous infusion, cardiac output, mean arterial pressure, and stroke volume were significantly higher and the amount of epinephrine infused was significantly less than over approximately the first hour after a bolus. The conclusion was that, in a canine model, bolus treatment by SC, IM or even the IV route causes limited hemodynamic improvement whereas constant infusion at a lower total dose produced significant hemodynamic improvement. These findings support the conclusion that continuous infusion is the preferred route in the treatment of anaphylaxis when shock is part of the clinical picture, and tie in very well with the prospective human study of an intravenous epinephrine infusion protocol. (Brown 2004)

9.1.1.3 Drug Information Materials and Textbooks

AHFS, 2011. Epinephrine. In *AHFS drug information 2011*. Bethesda, Maryland, American Society of Health-System Pharmacists, Section 12.12.12: 1379-1385.

AHFS Drug Information states that it is a drug information database that provides an evidence-based foundation to assist pharmacists and health professionals re safe and effective drug therapy (http://www.ahfsdruginformation.com/, Accessed 5/16/2012). The summary includes sections on the uses, dosing and administration, cautions, drug interactions, toxicity, pharmacology, pharmacokinetics, and chemistry/stability of epinephrine. Unfortunately, references to the sources of the information in this publication are not provided, and therefore, while the information may be accurate, it cannot be used as a source document.

Westfall TC and Westfall DP, 2006. Adrenergic Agonists and Antagonists. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York, McGraw-Hill. 11th ed, Chapter 12: 257-295.

This is a basic textbook of pharmacology that summarizes the basis for epinephrine use for various treatments. This textbook is widely used by medical schools across the United States (and presumably elsewhere as well) as a textbook of pharmacology. It includes references to pertinent source documents, including information on adrenergic receptors and pharmacologic experimental data.

Tran TP and Muelleman RL, 2010. Allergy, Hypersensitivity, and Anaphylaxis. In *Rosen's Emergency Medicine*. 7th ed, Chapter 117: 1511-1528.

This chapter in a basic textbook of emergency medicine outlines the pathophysiology, clinical features, diagnostic strategies, differential considerations, and management of anaphylaxis. The doses of epinephrine recommended are consistent with other recommendations:

1. Intramuscular (subcutaneous route acceptable) 1: 1000
   a) Adult: 0.3-0.5 mL every 5 min as necessary, titrated to effects
   b) Pediatric: 0.01 mL/kg, every 5 min as necessary, titrated to effects
   c) Alternatively, epinephrine (EpiPen) (0.3 mL) or EpiPen Jr (0.15 mL) can be administered into anterolateral thigh. Removal of clothing is unnecessary.
2. Intravenous 1:100,000 (0.1 mL of 1:1000 in 10 mL of NS)
   a) Continuous hemodynamic monitoring required
   b) 10 mL of 1 : 100,000 over 10 min, titrated to effects, repeat as necessary

World Health Organization, March 2011. WHO Model List of Essential Medicines. 17th list. http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

Epinephrine is included in this is listing of medications that have been determined to be essential medicines by the World health Organization.

World Health Organization, March 2011. WHO Model List of Essential Medicines for Children. 3rd list.
http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

This is a similar listing to that above, but for children. Epinephrine is likewise included as an essential medicine for children.

9.1.1.4 Pharmacokinetic, Pharmacodynamic, and Safety Studies

Abboud I, Lerolle N, et al., 2009. Pharmacokinetics of epinephrine in patients with septic shock: modelization and interaction with endogenous neurohormonal status. Crit Care. 13(4): R120.

This article reports on the results of a study designed to investigate the pharmacokinetics of epinephrine and its determinants in patients with septic shock. Thirty-eight adult patients with septic shock were prospectively recruited immediately before epinephrine infusion. After a baseline blood sample a second blood sample was taken to assess epinephrine and norepinephrine concentrations under steady-state infusion at a fixed cumulative epinephrine dose adjusted to body weight. Using nonlinear mixed effect modeling, it was determined that epinephrine pharmacokinetics are linear in septic shock patients without any saturation at high doses, and that basal neurohormonal status does not influence epinephrine pharmacokinetics.

Chowdhury BA and Meyer RJ, 2002. Intramuscular versus subcutaneous injection of epinephrine in the treatment of anaphylaxis. J Allergy Clin Immunol. 109(4): 720; author reply 720-721.

This correspondence is from authors at the Division of Pulmonary and Allergy Drug Products (now the Division of Pulmonary, Allergy, and Rheumatology Products) at the FDA. It points out that a study by Simons (Simons 2001) evaluated epinephrine levels after IM injection in the anterolateral thigh (vastus lateralis muscle) vs SC injection in the deltoid, but it did not evaluate epinephrine levels after IM injection in the anterolateral thigh. Lack of this information hinders deciding whether IM dosing is superior than SC dosing [in the thigh]. Further, it notes that in the clinical setting auto-injectors such as EpiPen may wind up being administered either by IM or SC route depending upon various factors such as the patient's sex [which affects fat thickness under the skin and above the muscle layer], body habitus, amount of clothing, etc. Further, it notes that there are no reports suggesting that those who may be more likely to receive the auto-injection as a SC injection are at higher risk. Therefore, additional studies are needed to determine whether SC injection in the anterolateral thigh makes a difference with regard to either epinephrine levels or clinical outcomes.

The response by Simons, et al. notes that they did not test a SC injection into the vastus lateralis because that site is not recommended for SC epinephrine injections in clinical practice because patients may have to undress in order to administer the injection. (Hogan 2000) This response points out a problem with some current textbooks, which may recommend an inappropriate site for injection of epinephrine. [See Gas Gangrene references]

Clutter WE, Bier DM, et al., 1980. Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest. 66(1): 94-101.

This article summarizes the results of evaluations of plasma epinephrine thresholds for its metabolic and hemodynamic actions and plasma epinephrine metabolic clearance rates in normal human subjects. For this determination, intravenous epinephrine was infused at nominal rates of 0.1, 0.5, 1.0, 2.5, and 5.0 microgram/min for 60 minutes in six volunteers. The article concludes that: "(a) the plasma epinephrine thresholds for its hemodynamic and metabolic actions lie within the physiologic range, (b) epinephrine and norepinephrine accelerate their own metabolic clearance, and (c) epinephrine is 10 times more potent than norepinephrine."

Ensinger H, Lindner KH, et al., 1992. Adrenaline: relationship between infusion rate, plasma concentration, metabolic and haemodynamic effects in volunteers. Eur J Anaesthesiol. 9(6): 435-446.

The present study investigated the relationship between supra-physiological plasma concentrations of epinephrine and the resulting hemodynamic and metabolic effects in eight adult males (22-27 years). At infusion rates between 0.01 and 0.2 mcg/kg/min), a linear correlation was noted between infusion rate and epinephrine concentrations. Typical hemodynamic responses were seen, along with increases in plasma concentrations of glucose, lactate, and non-esterified fatty acids. The article warns that if similar metabolic effects occur in patients during epinephrine treatment, they may further increase breakdown of energy stores in a situation of increased catabolism, and impair utilization of parenteral nutrition. The article does not discuss, however, this would only become a clinical concern with continuous treatment over a prolonged period of time.

Fisher DG, Schwartz PH, et al., 1993. Pharmacokinetics of exogenous epinephrine in critically ill children. Crit Care Med. 21(1): 111-117.

This study was designed to determine the steady-state plasma concentrations and clearance rates of epinephrine in critically ill children, to examine if epinephrine pharmacokinetics conform to a linear model, and to compare epinephrine clearance rates with clearance rates of dopamine and dobutamine. This was a prospective study performed in the pediatric ICUs of two tertiary care teaching hospitals in patients who were hemodynamically stable while requiring continuous epinephrine infusions. Epinephrine levels during steady-state infusions of 0.03 to 0.2 mcg/kg/min suggested linear pharmacokinetics, with a mean of 4360 +/- 3090 pg/mL (23,810 +/- 16,870 pmol/L) and a range from 670 to 9430 pg/mL (3660 to 51,490 pmol/L). Epinephrine clearance rates ranged from 15.6 to 79.2 mL/kg/min (mean 29.3 +/- 16.1) and were not dependent on steady-state plasma concentrations. The clearance rates noted in critically ill children appear to be lower than those reported in healthy adults. Also of note, the clearance rates of dopamine and dobutamine were significantly correlated with the clearance rate of epinephrine.

Garvey LH, Belhage B, et al., 2011. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. Anesthesiology. 115(1): 111-116.

This was a retrospective study conducted at the Danish Anaesthesia Allergy Centre in patients referred due to suspected anaphylaxis during anesthesia. The objective was to investigate how often epinephrine is used in the treatment of suspected anaphylaxis during anesthesia in Denmark and whether timing of treatment is important. Reactions had been graded by severity: C1, mild reactions; C2, moderate reactions; C3, anaphylactic shock with circulatory instability; C4, cardiac arrest. Use of epinephrine, dosage, route of administration, and time between onset of circulatory instability and epinephrine administration were noted. A total of 122 (45.2%) of 270 referred patients had C3 or C4 reactions, i.e., reactions associated with cardiovascular instability; of those, only 101 (82.8%) received epinephrine, suggesting a reluctance on the part of anesthetists to administer epinephrine, instead choosing to administer antihistamines and steroids before epinephrine in 16.8% and not administering epinephrine at all in 17.2%. Route of administration was intravenous in 95 (94%) patients. The study also suggests that anaphylaxis may be difficult to diagnose during anesthesia and as a consequence, treatment with epinephrine can be delayed. The median time from onset of reported hypotension to treatment with epinephrine was 10 min (range, 1–70 min). Defining epinephrine treatment ≤10 min after onset of hypotension as early, and >10 min as late, infusion was needed in 12 of 60 patients (20%) treated early versus 12 of 35 patients (34%) treated late (odds ratio, 2.09) (95% confidence interval, 0.81–5.35). The authors recommend that anaphylaxis should be considered and treated in patients with circulatory instability during anesthesia of no apparent cause who do not respond to the usual treatments.

Goldenberg M, Aranow H, Jr., et al., 1950. Pheochromocytoma and essential hypertensive vascular disease. AMA Arch Intern Med. 86(6): 823-836.

This is an article that evaluated the underlying causes of persistent or intermittent hypertension associated with pheochromocytoma. Contrary to previous publications, tumors were shown to contain either both epinephrine and 'arterenol' (norepinephrine), with amounts varying from patient to patient and tumor to tumor, such that patients with predominantly epinephrine containing tumors had more persistent hypertension, tachycardia, hyperhidrosis, hypermetabolism and frequently, hyperglycemia, with positive piperoxan HCl reactions, whereas patients with norepinephrine-only containing tumors had a syndrome mimicking essential hypertension vascular disease.

Simons FER, Gu X, et al., 2002. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. J Allergy Clin Immunol. 109(1): 171-175.

This was a randomized, double-blind study that investigated the rate and extent of epinephrine absorption after self-injected use of either EpiPen Jr or EpiPen auto-injector in children 4-8 years of age who weighed 15 to 30 kg and were at risk for anaphylaxis. The study was conducted at the Health Science Center Children's Hospital in Winnipeg, Manitoba, Canada. Plasma epinephrine concentrations, blood glucose, blood pressure,

heart rate, and adverse effects were monitored before and for 180 minutes after the injection. Children (n=5, mean weight 18.0 ±0.6 [SEM] kg, mean age 5.4 ±0.4 [SEM] years) who received an EpiPen Jr (0.15 mg) injection achieved a maximum plasma concentration of 2,037 ±541 pg/mL at 16 ±3 minutes. Children (n=5, mean weight 25.4 ±1.5 kg, mean age 6.6 ±0.5 years) who received an EpiPen (0.3 mg) injection achieved a maximum plasma concentration of 2,289 ±405 pg/mL at 15 ±3 minutes. Mean systolic blood pressure 30 minutes after injection was significantly higher with the EpiPen than with the EpiPen Jr. After injection with the EpiPen Jr, every child experienced transient pallor; some also experienced tremor and anxiety. After injection with the EpiPen, every child developed transient pallor, tremor, anxiety, and palpitations or other cardiovascular effects; some also developed headache and nausea. These results suggest that the therapeutic window of epinephrine is so narrow that "the beneficial pharmacologic effects and the adverse pharmacologic effects … cannot be dissociated." The authors recommend that the availability of additional premeasured, fixed doses of epinephrine would facilitate more precise dosing in young children. However, they provide no rationale for why fixed doses [for self or caregiver administration via an auto-injector] that are lower, between, or higher than the approved fixed doses would be necessary other than the ability to titrate the dose between the recommended dose of 0.01 mg/kg to the patient's actual weight.

Simons FER, Gu X, et al., 2001. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol. 108(5): 871-873.

This PK study serves as one basis for the recommendation of administering epinephrine via an IM injection into the anterolateral thigh rather than via SC injection. For a letter to the editor about the article and a discussion of potential issues with the study, please see Chowdhury 2002 and the author's reply in the next reference below (Simons 2002).

This was randomized blinded, placebo-controlled, 6-way crossover study evaluated the systemic exposure of epinephrine after either an intramuscular or subcutaneous injection. The study was performed at the University of Manitoba, Canada, in 13 healthy allergic men 18-35 years of age. Each subject received 4 injections of 0.3 mg epinephrine 1:1000 (0.3 mL) and 2 injections of isotonic saline (0.3 mL). These included: EpiPen IM in the anterolateral thigh, epinephrine IM in the anterolateral thigh, epinephrine IM in the deltoid, epinephrine SC in the deltoid, and saline IM or SC in the deltoid. Mean peak plasma epinephrine concentrations were significantly higher ($p < 0.01$) after epinephrine was injected IM into the thigh (Cmax for EpiPen 12,222 pg/mL, Cmax for epinephrine 9,722 pg/mL) than after epinephrine was injected IM (mean Cmax 1,821 pg/mL) or SC (Cmax 2,877 pg/mL) into the upper arm (Cmax after saline 1,458 pg/mL). On the basis of the results, the authors recommend that IM injection of epinephrine into the thigh be the preferred route and site for the initial treatment of anaphylaxis.

Simons FER, Gu X, et al., 2002. Reply to letter. J Allergy Clin Immunol. 108(5) :720-721.

This is the author's reply to the letter to the editor from Drs. Chowdhury and Meyer (Chowdhury 2002), which refers to the article (Simons 2001) above.

Simons FER, Roberts JR, et al., 1998. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 101(1 Pt 1): 33-37.

This was a randomized, single-blind study that investigated the rate and extent of epinephrine absorption after either 0.01 mg/kg of epinephrine solution administered by SC injection or 0.3 mg of epinephrine administered IM via an EpiPen auto-injector in 17 children 4-12 years of age who were at risk for anaphylaxis. The study was conducted at the Health Science Center Children's Hospital in Winnipeg, Manitoba, Canada. Plasma epinephrine concentrations, heart rate, blood pressure, and adverse effects were monitored before and for 180 minutes after the injection. Mean plasma epinephrine concentrations were 1,802 ±214 pg/mL (n=9) at 34 ±14 minutes (range, 5 to 120 minutes) and 2,136 ±351 pg/mL (n=8) at 8 ±2 minutes for the SC and IM injections, respectively. Mean time to maximum plasma concentrations was significantly faster after IM injection ($p < 0.05$), with 6/8 children achieving maximum plasma concentrations by 5 minutes after IM injection compared to 2/9 after SC injection. After SC injection, absorption was so variable that it was not possible to calculate reliable terminal elimination half-life values, clearance rates, or volumes of distribution. After IM injection, the terminal elimination half-life was 43 ±15 minutes. No serious adverse effects were noted in any child. The author's conclusion was that SC injection may be associated with a delay that could have important clinical implications during an episode of systemic anaphylaxis. Therefore, they conclude that the intramuscular route of injection is preferable.

Song TT, Nelson MR, et al., 2005. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy Asthma Immunol. 94(5): 539-542.

The study evaluated whether the needle length of the EpiPen auto-injector (1.43 cm) is sufficient for IM delivery of epinephrine in men and women. The study found that the skin-to-muscle distance in the anterolateral aspect of the thigh is greater in women than men, suggesting that EpiPen may not deliver epinephrine to the intramuscular tissue in many women. Skin-to-muscle distance of the anterolateral thigh was measured in 50 men and 50 women who underwent computed tomography of the area for other medical reasons. The mean [±SD] distance from skin to muscle was 0.66 ±0.47 cm for men and 1.48 ±0.72 cm for women ($p < 0.001$). One obese man (BMI 42.2) and 21 women (11 characterized as obese with a mean BMI of 35.2, 6 characterized as overweight with a mean BMI of 30.1, and 4 characterized as normal with a mean BMI of 24.5) had a greater skin to muscle distance than the EpiPen needle length of 1.43 cm.

Stecher D, Bulloch B, et al., 2009. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? Pediatrics. 124(1): 65-70.

This study evaluated whether the needle length on EpiPen auto-injectors is adequate to deliver epinephrine intramuscularly in children. Investigators at Phoenix Children's Hospital, Phoenix, Arizona, enrolled 256 patients 1-12 years of age who presented to either the ED or the radiology department for an ultrasound evaluation. An ultrasound was performed to assess the skin-to-muscle depth over the vastus lateralis muscle, and the patient's body mass index was recorded. The study assessed the auto-injector

doses based on the needle length for the EpiPen products, which is stated to be 5/8" for EpiPen and ½"for EpiPen Jr. It did not assess the length in comparison with Twinject, which has an extended length of ½" (length available for first dose) for both of the 0.15 and the 0.3 mg doses and a nominal needle length of 5/8" (length available for second manual dose). Ultrasound was performed on 128 (50%) girls, and 128 (50%) boys. Nineteen of 158 children who weighed <30 kg (12%) had a skin-to-muscle distance of >½", suggesting that they might not receive an injection IM from any of the current auto-injectors. Twenty nine of 98 children who weighted ≥30 kg (30%) had a skin-to-muscle distance of >5/8", suggesting that they might not receive epinephrine from EpiPen IM. [Note: no information given with respect to the ½ inch dimension for the Twinject first dose.] The study concluded that the needle on epinephrine auto-injectors is not long enough to reach the muscle in a significant number of children, and that increasing the needle length on the auto-injectors would increase the likelihood that more children receive epinephrine by the "recommended" IM route.

Aside from the issue of whether it is more appropriate to self-inject epinephrine by the SC or the IM in the ambulatory first aid setting, a significant deficiency with this study report was that the paper did not provide plots of the skin-to-muscle depth by weight or weight group, although plots were provided comparing skin-to-muscle depth vs BMI,. Lack of this information prevents others from using the results to assess what the appropriate needle length should be if one wants to administer an injection intramuscularly. Further the study design was deficient in that it did not assess skin-to-bone depth. This information is critical if one wants to assess whether use of longer needle lengths, as recommended by the authors, presents any danger of hitting bone. A second deficiency in the study was that, although reference was made to a study conducted in adults that evaluated how much subcutaneous fat is displaced under pressures akin to those needed to trigger an auto-injector, this study did not attempt to find out similar information in children. These missing data are critical to allowing a full assessment of the effect of any changes to needle length of auto-injectors, as recommended by the authors.

Triggiani M, Patella V, et al., 2008. Allergy and the cardiovascular system. Clin Exp Immunol. 153 Suppl 1: 7-11.

This article discusses that "the heart is both a source of and a target for the chemical mediators released during allergic reactions. Mast cells are abundant in the human heart, where they are located predominantly around the adventitia of large coronary arteries and in close contact with the small intramural vessels. Cardiac mast cells can be activated by a variety of stimuli including allergens, complement factors, general anesthetics and muscle relaxants. Mediators released from immunologically activated human heart mast cells strongly influence ventricular function, cardiac rhythm and coronary artery tone. Histamine, cysteinyl leukotrienes and platelet-activating factor (PAF) exert negative inotropic effects and induce myocardial depression that contribute significantly to the pathogenesis of anaphylactic shock. Moreover, cardiac mast cells release chymase and renin that activates the angiotensin system locally, which further induces arteriolar vasoconstriction. The number and density of cardiac mast cells is increased in patients with ischaemic heart disease and dilated cardiomyopathies. This

observation may help explain why these conditions are major risk factors for fatal anaphylaxis. A better understanding of the mechanisms involved in cardiac mast cell activation may lead to an improvement in prevention and treatment of systemic anaphylaxis."

9.1.1.5 Case Reports

Hema HA, Kulkarni A, et al., 2008. Ventricular Tachycardia due to Intranasal Adrenaline in Nasal Surgery- a Case Report. Indian Journal of Anaesthesia. 52(2): 199-201.

It is not clear why this case report from India was submitted, as it relates to the use of local anesthetics with epinephrine, and not to epinephrine for treatment of anaphylaxis. However, it does point out that ventricular tachycardia may occur after epinephrine use. This case involves 32 year old female patient who developed ventricular tachycardia after intranasal administration of epinephrine (via a packing of 4% lidocaine with adrenaline (6mg), with infiltration of an additional 2% lidocaine with adrenaline 1:1000) in the nose in preparation for functional endoscopic sinus surgery (FESS). The report also notes that others have reported permanent visual field defects after administration of a local anesthetic with epinephrine into the nasal cavity.

ISMP, 2009 "ALERT: Fatal Outcome after Inadvertent Injection of Epinephrine Intended for Topical Use." ISMP Canada Safety Bulletin 9.

This is a Canadian Safety Bulletin alert. However, the title alert is less than clear, and in fact is misstated. This is a case of a medical error resulting in a fatal outcome after the inadvertent injection of epinephrine injection (1:1000) that had been substituted in the operating room for epinephrine for topical use. After being drawn up by syringe, the syringe was not labeled. It was then inadvertently substituted for a local anesthetic with epinephrine (1:100,000) for injection for an ENT procedure. After the local injection, the patient immediately experienced an arrhythmia leading to cardiac arrest.

Additionally, the bulletin makes note that the packaging of epinephrine for topical use may be similar to packaging used for vials containing epinephrine for injection, with use of a rubber stopper and metal ferrule, as shown in the picture below. This has led some practitioners to withdraw the epinephrine for topical use with a needle and syringe instead of removing the top to pour into an open container, thereby introducing the potential for medication substitution errors. Note that the product shown in the picture below is Canadian product made by a different manufacturer. [See Section 2.2 for the Adrenalin products currently marketed by JHP in the United States.]

Shaver KJ, Adams C, et al., 2006. Acute myocardial infarction after administration of low-dose intravenous epinephrine for anaphylaxis. CJEM. 8(4): 289-294.

This is a case report of vasospasm-induced myocardial injury following intravenous epinephrine administration, illustrating a potential danger of the use of epinephrine at therapeutic doses. The authors also identified 2 case reports of myocardial infarction after a therapeutic dose of epinephrine (2 after SC injection and 1 after self-administration of epinephrine from an auto-injector). This syndrome is referred to as Kounis syndrome (see Kounis 2006). This case report is of a 29-year-old woman who presented to the ED with an acute severe anaphylactic reaction to penicillin. In addition to other medications, she received 0.1 mg (1 mL) of 1:10,000 epinephrine intravenously (from a pre-loaded 10-mL syringe), after which she immediately developed severe chest pain. Of note, the rapidity of administration was not stated in the report. Her ECG showed ST elevations consistent with an anterior myocardial infarction, and her serum troponin level was elevated. The patient was treated with ASA and a nitroglycerine drip and became pain-free with a return to normal ECG by 40 minutes after the initial ECG, although she had a recurrence of pain without abnormal ECG several hours later, treated with nitroglycerine and morphine. The patient's cardiac risk profile included occasional smoking and a positive family history of premature coronary artery disease. A CT angiogram showed no signs of coronary artery disease or abnormal anatomy. She was discharged in good health.

9.1.1.6 Epidemiologic/Disease Studies

Bock SA, Muñoz-Furlong A, et al., 2001. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 107(1): 191-193.

The objective of this article was to document and characterize fatal anaphylactic reactions to foods. The authors report on 32 fatal cases obtained from a national registry established by the American Academy of Allergy, Asthma, and Immunology, with the assistance of the Food Allergy and Anaphylaxis Network, for whom adequate data could be collected and analyzed. Cases could be divided into 2 groups: those in

whom there was sufficient data to identify peanut (14/32) or tree nuts in (7/32) as the responsible food, and those in whom fatalities were considered to be probably due to an allergen (peanut in 6/32, tree nuts in 3/32, and one case each of milk and fish). Thus, peanuts and tree nuts accounted for more than 90% of the fatalities. Most cases occurred in adolescents or young adults, with both sexes equally affected. All but one of the subjects were known to have food allergy before the event, yet most did not have epinephrine available at the time of their fatal reaction. The conclusion was that fatalities due to ingestion of allergenic foods in susceptible individuals remain a major health problem. The major lesson with regard to this review is that lack of epinephrine availability at the time of an anaphylactic reaction to foods may indeed be life-threatening.

Bock SA, Muñoz-Furlong A, et al., 2007. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol. 119(4): 1016-1018.

This is a letter to the editor expanding on the previous study (Bock 2001) and reporting on an additional 31 fatalities due to food anaphylaxis in patients 5-50 years of age. Peanut accounted for 17 deaths, tree nuts for 8, milk for 4, and shrimp for 2. Locations (when known) where the deaths occurred included: schools (3; including colleges), homes (12; including homes of friends), restaurants (8), work/office setting (4), and camp (2). Of those cases where the information was available, only 4 individuals appearing to have had epinephrine administered in a timely manner. One of the conclusions was that lack of readily accessible epinephrine continues to remain a substantial problem.

Brown SGA, 2005. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. Curr Opin Allergy Clin Immunol. 5(4): 359-364.

The purpose of this review was to examine studies that may aid in the management and diagnosis of anaphylaxis. Although most episodes of anaphylaxis respond to treatment with epinephrine, cardiovascular collapse associated with anaphylaxis can be resistant to treatment, creating difficulties with management as well as diagnostic uncertainty that may compromise follow-up care. The review found that “nausea, vomiting, incontinence, diaphoresis, dyspnoea, hypoxia, dizziness and collapse are associated with hypotension. Relative bradycardia (falling heart rate despite hypotension) is a consistent feature of hypotensive insect sting anaphylaxis and may represent a non-specific physiological response to severe hypovolaemia in conscious individuals. Upright posture has been found to be associated with death from anaphylaxis. Animal studies have found the intramuscular route for epinephrine is ineffective, intravenous boluses temporarily effective, but intravenous infusions of epinephrine are able to reverse anaphylactic shock. In one animal model, antihistamines were found to be harmful. A prospective human study provides evidence for the efficacy of treatment with intravenous epinephrine infusion and fluid (volume) resuscitation. (Brown 2004) Case reports support the use of the vasoconstrictors metaraminol, methoxamine and vasopressin if adrenaline is ineffective. (Heytman 2004) Repeated measurements of mast cell tryptase are more sensitive and specific than a single measurement for the diagnosis of anaphylaxis.”

The conclusions were that management should include placing the patient in a supine / Trendelenburg position, administration of epinephrine by intravenous infusion, aggressive volume resuscitation, and consideration for the use of atropine for severe bradycardia and other vasoconstrictors as needed. It also recommends that confirmation of the diagnosis may be aided by serial measurements of mast cell tryptase rather than relying upon a single measurement.

Chaudhuri K, Gonzales J, et al., 2008. Anaphylactic shock in pregnancy: a case study and review of the literature. Int J Obstet Anesth. 17(4): 350-357.

This review points out that anaphylaxis during pregnancy is a relatively rare but potentially life-threatening event. Several etiological agents may be responsible, with penicillin being the leading cause of anaphylaxis-related mortality. Therefore, immediate discontinuation of the suspected allergen is essential. The review notes that although epinephrine is the drug choice in the non-pregnant patient, during pregnancy it may pose a risk to the placental-fetal circulation because it can cause uterine vasoconstriction, although the increased systemic vascular resistance associated with its use also improves cardiac output and utero-placental perfusion. Therefore, use of epinephrine remains somewhat controversial, particularly when used by the IV route, and alternative treatments are discussed. Additionally, the timing and mode of delivery of the neonate in the face of anaphylactic shock remains controversial.

Ellis AK and Day JH, 2007. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. Ann Allergy Asthma Immunol. 98(1): 64-69.

This article describes the indicence and characteristics of biphasic anaphylaxis in a Canadian tertiary care center. Twenty of 103 patients (19.4%) experienced a biphasic response, with an average time to onset of 10 hours after the initial reaction. Those with biphasic reactions tended to have received less epinephrine and less corticosteroids.

Kounis NG, 2006. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol. 110(1): 7-14.

This paper summarizes the pathophysiology and clinical findings of Kounis syndrome, first described by the same author in 1991. Kounis syndrome is an acute coronary artery syndrome associated with acute allergic reactions. It is felt to be caused by inflammatory mediators released through mast cell activation during anaphylactic or anaphylactoid insults. The author postulates that drugs and natural molecules which stabilize mast cell membrane and monoclonal antibodies that protect mast cell surface could emerge as novel therapeutic modalities capable to prevent acute coronary and cerebrovascular events.

Manivannan V, Campbell RL, et al., 2009. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. Ann Allergy Asthma Immunol. 103(5): 395-400.

This article summarizes the factors associated with the need for repeated dosing of epinephrine during the treatment of anaphylaxis, based on the results of a population-

based study with medical record review of the charts of 208 patients (55.8% female), 104 (50.0%) of whom received epinephrine treatment. The objective was to help identify high-risk patients who may benefit from carrying more than 1 dose of epinephrine. The inciting agents were food (29.6%), insects (11.1%), medications (22.2%), others (7.4%), and unknown (29.6%). Twenty-seven [of the 208 patients] (13.0%) received repeated epinephrine doses (see Table 5). These patients were younger (median age 18.9 years vs 31.1 years (p = 0.06)) and were more likely to have wheezing (p = 0.03), cyanosis (p = 0.001), hypotension and shock (p = 0.03), stridor and laryngeal edema (p = 0.007), nausea and emesis (p = 0.04), arrhythmias (P <0.01), and cough (p = 0.04) and less likely to have urticaria (p = 0.049). They also were more likely to be admitted to the hospital than patients who did not receive repeated doses (48.2% vs 15.6%; p <0.001). However, a history of asthma did not predict the need for repeated doses (p = 0.17).

Table 5. Number of epinephrine doses and sites of administration during an anaphylactic event (Manivannan 2009)

Number of doses	Number of patients	Place administered
0	104	NA
1	77	Home 3 EMS 3 ED 71
2	25	Home and ED 2 EMS and ED 1 ED 22
3	2	Home (1 dose) and ED (2 doses) 1 EMS (2 doses) and ED (1 dose) 2

Source: Manivannan 2009, Table 1, p 397

Pumphrey RSH, 2000. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy. 30(8): 1144-1150.

The objective of this study was to investigate circumstances that may lead to fatal anaphylaxis. Results were based on a review of certified death certificates from Office of National Statistics register, along with details of the previous medical history, the reaction, and necropsy. A total of 164 fatalities were found between 1992-1998 that could be traced to anaphylaxis as a possible cause. Of the 125 identified cases, approximately a quarter each were due to food or insect venom, and the rest reflected a combination of causes such as anesthetic exposure, antibiotic use, and unknown causes. A key finding was that in 48 of cases the patient never received epinephrine, in an additional 60 cases epinephrine was only administered after arrest, leaving a total of 17 cases (14%) where epinephrine had been administered prior to arrest. Only 22% (8/37) of food-allergic and 18% of venom-allergic (6/32) fatalities had had a previous severe reaction, suggesting that most of those at risk would have an epinephrine auto-injector kit available at the time of the first (fatal) reaction. Nine patients out of the 14 (64%) with a previous severe reaction had been issued an epinephrine auto-injector. Of those, 5 did not use the kit at all, two are said to have used the kit but the data presented in the article suggest that the auto-injector was either used incorrectly or too

late to be of benefit, and two used 2 (n=1) or 3 (n=1) doses without benefit during the fatal reaction. The conclusion was that immediate recognition of anaphylaxis and early treatment is crucial for successful outcomes, although a few reactions will be fatal despite treatment. Therefore, optimal management should include avoidance of the cause whenever possible.

Pumphrey RSH and Gowland MH, 2007. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol. 119(4): 1018-1019.

The authors report on 48 additional deaths in the UK from 1999 to 2006. Epinephrine auto-injector pens had been provided to 19 (40%), including 11 of the 13 with previous severe reactions. Of concern in the report is the discussion of whether patients carried and used an epinephrine auto-injector, illustrating that auto-injectors may be an important part of early treatment but additional treatment is often warranted, and that epinephrine and other treatments cannot take the place of prudence and avoidance. "Epinephrine auto-injector pens had been provided to 19 (40%), including 11 of the 13 with previous severe reactions. Over half the deaths occurred in patients whose previous reactions had been so mild that it was unlikely that a doctor would have recommended they should carry a pen. Pens were (apparently) used correctly by 9 (but 2 had time-expired); 1 used 3 pens correctly but still died. For some, pens may have failed to deliver an intramuscular injection because of the depth of the subcutaneous adipose tissue, but this was not the case for at least 3. Pens not used correctly were used too late in the reaction (5), had not been carried on that occasion (4), or were misused (1). Recently, a 16-year-old girl with a nut allergy took the risk of eating a chocolate because she trusted her pen would save her. She used it immediately when she saw nuts in the chocolate but nonetheless died from her reaction."

Rudders SA, Banerji A, et al., 2010. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. Pediatrics. 125(4): e711-718.

This study evaluated the frequency of receiving more than one dose of epinephrine in children who present to the emergency department (ED) with food-related anaphylaxis. Medical chart review was performed of 605 children who presented to the ED at Boston hospitals for food-related acute allergic reactions between January 1, 2001, and December 31, 2006. Median age was 5.8 years (95% CI 5.3-6.3), 62% males. Approximately half (52%; 95% CI 48-57) of the children met diagnostic criteria for food-related anaphylaxis (peanuts 23%, tree nuts 18%, and milk 15%). Among these children, 12% (38) received a second dose of epinephrine. Risk factors for repeat epinephrine use included older age and transfer from an outside hospital. Results of the study were considered to support the recommendation that children at risk for food-related anaphylaxis carry 2 doses of epinephrine. It should be noted that among those patients who met the diagnostic criteria for anaphylaxis, only 14% (95% CI 10–17) had been assigned a discharge diagnosis that included the term "anaphylaxis," although 79% of those who met the diagnostic criteria and were hospitalized carried a discharge diagnosis that included the term, suggesting that there is still a learning curve for healthcare providers with regard to essentials of the diagnosis.

Sampson HA, Mendelson L, et al., 1992. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 327(6): 380-384.

This study reports on the medical record review of the 13 children and adolescents 2 to 17 years of age with fatal or near-fatal anaphylactic reactions to foods, six of whom died and seven of whom nearly died and required intubation. Twelve had asthma that was well controlled, and all had known food allergies but had unknowingly ingested a food containing the responsible allergen, including peanuts (4), nuts (6), eggs (1), and milk (2), such as candy, cookies, and pastry. The report notes that "six patients who died had symptoms within 3 to 30 minutes of the ingestion of the allergen, but only two received epinephrine in the first hour. All the patients who survived had symptoms within 5 minutes of allergen ingestion, and all but one received epinephrine within 30 minutes. The course of anaphylaxis was rapidly progressive and uniphasic in seven patients; biphasic, with a relatively symptom-free interval in three; and protracted in three, requiring intubation for 3 to 21 days." The conclusion was that failure to recognize the severity of reactions and to administer epinephrine promptly increases the risk of a fatal outcome.

9.1.1.7 Reviews, Consensus Management Conferences, and Guidelines

Brown AFT, 1998. Therapeutic controversies in the management of acute anaphylaxis. J Accid Emerg Med. 15(2): 89-95.

This review summarizes and evaluates previous recommendations, and provides specific recommendations, regarding the role, route of delivery, dose, concentration, and efficacy of various drugs used in anaphylaxis, including epinephrine. Although the paper does not address the dose or route of administration for self-administration, it concludes that doses of 0.3 to 0.5 mg (0.3 to 0.5 mL of 1:1000 epinephrine) administered IM are usually highly effective for early treatment and treatment of milder cases, as well as in cases when IV access is difficult or when the patient is unmonitored, and that the dose may be repeated every five to ten minutes if needed. The IM route is stated to be preferred because of the prolonged and variable absorption when epinephrine is administered by the SC route. It states that the IV route is preferred for serious cases and in cases involving hypovolemia, shock, or severe airway compromise, although the only reasoning given is that it affords rapid absorption. However, this reasoning is only partially correct, in that IV treatment also allows treatment of hypovolemia with IV fluids as well as IV access for other drugs as needed. The paper then reviews the dose of epinephrine when administered IV, which is confused by a wide variation in proposed doses ranging from 1 mcg/minute to a 2 mg bolus. Increased systolic and diastolic blood pressure, coronary artery syndrome, and arrhythmias including ventricular fibrillation have all been associated with IV dosing, particularly when epinephrine is administered rapidly or at high doses. The conclusion was that epinephrine should be diluted to a 1:100,000 dilution and administered at an initial rate of 1-2 ml (10-20 mcg) per minute for an initial dose of 0.75-1.5 mcg/kg, followed by an infusion if continued treatment is required. The paper also gives a recommendation for how to obtain the 1:100,000 dilution: "The 1:100,000 adrenaline is

prepared by drawing up 1 mg adrenaline (1 ml of 1:1000 adrenaline) in a 20 ml syringe, and 9 ml saline to give a total volume of 10 ml. All but 2 ml of this is discarded (leaving 200 mcg of adrenaline in the syringe). Saline is then drawn up to a total volume of 20 ml, giving a final concentration of 10 mcg per ml – that is, a 1:100,000 dilution. Alternatively, an infusion of adrenaline may be prepared by putting 1 mg of adrenaline in 100 ml normal saline and running at 60-120 ml/hour using an infusion device (that is, 10-20 mcg/min)." Finally, the paper notes that significant reactions can include a biphasic response which may require additional therapy hours later.

Brown SGA, Mullins RJ, et al., 2006. Anaphylaxis: diagnosis and management. Med J Aust. 185(5): 283-289.

This review of the pathophysiology, acute management, and follow-up care of anaphylaxis provides a reasonably concise guide for treatment that is intended for general practitioners and emergency medicine physicians. The one addition is that this paper provides is an assessment of the level for some of the evidence-based recommendations, based on the Australian National Health and Medical Research Council levels of evidence. (NHMRC CP69 2000) These include:

- Placement of the patient in a supine position and give adrenaline and intravenous volume resuscitation (Level IV). (Sampson 2006)
- Intramuscular injection into the lateral thigh (vastus lateralis) is preferred to injections into arm or deltoid muscles or subcutaneously, because of better absorption (Level III-1). (Simons 2001; Simons 1998)
- A controlled intravenous infusion of adrenaline is a safe and effective management for anaphylaxis (Level III-3). (Brown 2004)
- A reasonable length of observation after symptom resolution is 4–6 hours in most patients, with more prolonged observation recommended in patients with severe or refractory symptoms (Level IV). (Sampson 2006)
- Venom immunotherapy prevents anaphylaxis to insect stings and significantly improves quality of life compared with carrying injectable adrenaline (EpiPen) alone (Level II). (Brown 2003; Oude Elberink 2002)

Cheng A, 2011. Emergency treatment of anaphylaxis in infants and children. Position Statement AC 2011-01. Paediatr Child Health. 16(1): 35-40.

This is a position statement from the Canadian Paediatric Society, Acute Care Committee. It provides a basic guide to the management of anaphylaxis. References for IV use include: Brown 2005 and Mink 2004.

Frew AJ, 2011. What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? Allergy. 66(1): 15-24.

This review describes the different epinephrine auto-injectors currently available in the European Union and discusses potential barriers to the use of these drug-device combinations, with the goal of identifying the feature sets that the authors consider may help ensure ease of use, portability, and accurate delivery of epinephrine in the

emergency self-use setting. Two things are of note. First, because of the focus of this article, it does not provide any support for the current submission. Second, the article discusses a device called EpiCard, which is not a marketed device, thereby introducing the potential suggestion to the mind of the reader that devices that may or may not in the development stage may offer solutions to the authors' perceived barriers to use of these products.

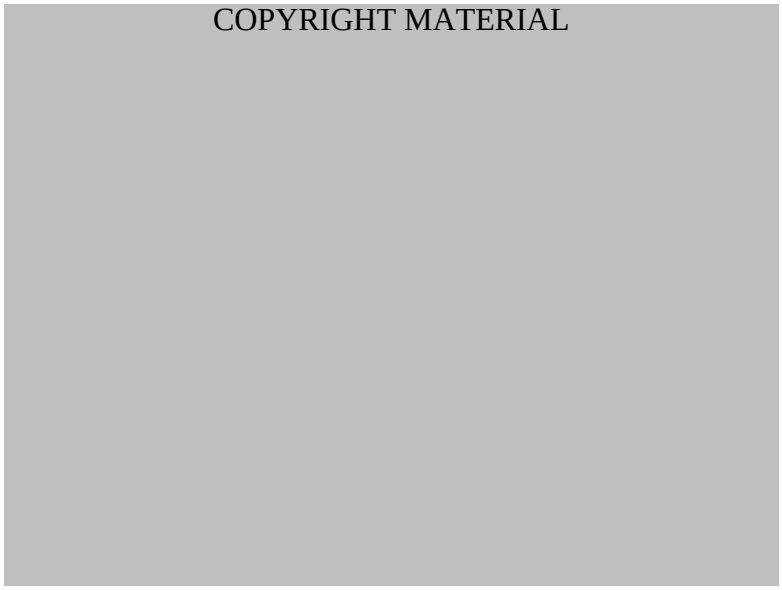
Kanwar M, Irvin CB, et al., 2010. Confusion about epinephrine dosing leading to iatrogenic overdose: a life-threatening problem with a potential solution. Ann Emerg Med. 55(4): 341-344.

This article tries to make the point that the dosing and route of administration of epinephrine when used for the treatment of anaphylaxis and cardiac arrest are different, potentially leading to medication errors and overdoses. They provide recommendations for dosing based on the 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Based on these recommendations, an IM dose of 0.3 to 0.5 mg (1:1000) of epinephrine is recommended for anaphylaxis, with 0.1 mg (1:10,000) of epinephrine injected by IV slowly during 5 minutes reserved for anaphylaxis symptoms refractory to IM doses or anaphylactic shock whereas the recommended first dose for cardiac arrest is 1 mg (1:10,000) by IV push. (AHA 2005)

***Reviewer's Note*: *IMPORTANT!* This article in itself serves as an example of the confusion between dosing recommendations for IV epinephrine based on the AHA guidelines for cardiopulmonary resuscitation and emergency cardiovascular care and the dosing recommendations for treatment of anaphylaxis from organizations such as the World Allergy Organization and the Joint Task Force on Practice Parameters, etc. The AHA guidelines recommend dilution to a 1:10,000 concentration as part of treatment of both anaphylaxis and acute cardiac life support, whereas the WAO and Joint Parameters recommend dilution to a 1:100,000 concentration for anaphylaxis. This represents a dosing difference of a concentration factor of 10. Only the 1:100,000 concentration has been shown to be effective in a clinical trial (Brown 2004), and the 10,000 concentration has been associated with multiple reports of cardiac-related adverse events.** (b) (4)

[redacted]

The authors state that, in the stocking and preparation of the crash carts at their institution, they have taken the approach to stocking crash carts with prefilled and labeled epinephrine syringes, one for IM use (EpiPen), and one for IV use (Epinephrine for injection (1:10,000)). [Note: The NDC number in the picture corresponds to the Epinephrine for Injection (1:10,000) product marketed by Amphastar. See Table 2]



The article also makes the point that the availability of epinephrine in differing concentrations (1:1000 and 1:10,000) in multidose vials can create another source of medication errors. However, this statement is not correct, as I am not aware of any manufacturers marketing a 1:10,000 epinephrine product other than the one pictured above in a pre-packaged 10 mL syringe.

2005a American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2005;112:1-211. 2.

2005b American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2005;112:IV-58-IV-66.

Kemp SF, Lockey RF, et al., 2008. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 63(8): 1061-1070.

This is an expert consensus document from the World Allergy Organization, providing and summarizing the basis for dosing recommendations for epinephrine for treatment of anaphylaxis [See Section 6.1.1.2 for further details].

The article references Simons 2006 for a figure showing the narrow therapeutic window for epinephrine, noting that the common pharmacologic effects that occur at recommended doses regardless of route of administration as well as the less common adverse reactions that may occur (myocardial ischemia or infarction, pulmonary edema, prolonged QTc interval, ventricular arrhythmias, accelerated hypertension, and intracranial hemorrhage), and that most often occur with overdosage or with overly rapid IV treatment.

It also notes those populations that are particularly vulnerable, including: “those individuals at the extremes of age and those with hypertension, peripheral vascular disease, ischemic heart disease, or untreated hyperthyroidism (increased number of b-adrenergic receptors in the vasculature of these individuals render the myocardium

more sensitive to b-adrenergic effects of epinephrine) (McClean-Tooke 2003). Certain medications might also increase the risk of adverse events from drug interactions (Lieberman 2005; Simons 2006; Lieberman 2003; McClean-Tooke 2003). Some medications decrease the effectiveness of endogenous catecholamine stores or exogenously administered epinephrine (b-adrenergic blockers), interfere with intrinsic compensatory responses to hypotension (angiotensin converting enzyme inhibitors and possibly angiotensin-II receptor blockers), or impede epinephrine metabolism and lead to increased plasma and tissue concentrations (tricyclic antidepressants and monoamine oxidase inhibitors). b-adrenergic antagonists and a-adrenergic antagonists also potentially can exaggerate pharmacologic effects of epinephrine by permitting unopposed adrenergic (vasoconstrictor) and b-adrenergic (vasodilator) effects, respectively. Cocaine and amphetamines sensitize the myocardium to effects of epinephrine, thus increasing the risk of toxicity. However, none of these circumstances poses an absolute contraindication to epinephrine administration for anaphylaxis (Lieberman 2005)."

Lieberman P, Nicklas RA, et al., 2010. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 126(3): 477-480 e471-442.

This is the third iteration of an expert consensus practice parameter document developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. The objective of this parameter is to improve the care of patients by providing the practicing physician with an evidence based approach to the diagnosis and management of anaphylactic reactions.

McLean-Tooke AP, Bethune CA, et al., 2003. Adrenaline in the treatment of anaphylaxis: what is the evidence? BMJ. 327(7427): 1332-1335.

This review discusses the safety and efficacy of epinephrine in the treatment of anaphylaxis in the light of available evidence [i.e., evidence available at the time the article was written].

Mertes PM, Malinovsky JM, et al., 2011. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol. 21(6): 442-453.

This is an updated expert consensus guideline document developed and implemented in France by the French Society for Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation [SFAR]) and the French Society of Allergology (Société Française d'Allergologie [SFA]). The members of the European Network for Drug Allergy (ENDA) approved the guidelines.

Sampson HA, Muñoz-Furlong A, et al., 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 117(2): 391-397.

This is an expert consensus document that is now referenced as providing a standard and universally accepted definition of anaphylaxis, including clinical criteria that allow accurate identification of cases with high precision. It represents the results of a second meeting convened by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network, including representatives from 16 different organizations or government bodies, from North America, Europe, and Australia. The report also reviews the evidence on the most appropriate management of anaphylaxis, and outlines the research needs in this area.

Sheikh A, Shehata YA, et al., 2009. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock (Review). The Cochrane Library, The Cochrane Collaboration. 2011, Issue 2.

This is a Cochrane review of the literature that assessed the benefits and harms of epinephrine (adrenaline) in the treatment of anaphylaxis. Searches of databases were performed, including: the Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 11), MEDLINE (1966 to November 2010), EMBASE (1966 to November 2010), CINAHL (1982 to November 2010), BIOSIS (to November 2010), ISIWeb of Knowledge (to November 2010 and LILACS (1982 to November 2010), looking for randomized and quasi-randomized controlled trials comparing epinephrine with no intervention, placebo or other adrenergic agonists were eligible for inclusion. They also searched websites listing ongoing trials and contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material. Not surprisingly, they found no studies that satisfied the inclusion criteria. Nevertheless, they recommend the following: “In the absence of appropriate trials, we recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular (i.m.) injection should still be regarded as first-line treatment for the management of anaphylaxis.”

Simons FER, 2004. First-aid treatment of anaphylaxis to food: focus on epinephrine. J Allergy Clin Immunol. 113(5): 837-844.

This review article summarizes the first-aid treatment of anaphylaxis due to food, focusing primarily on epinephrine, but noting that epinephrine is usually, but not always effective. The article cites all the potential reasons for a lack of reponse, including the evidence regarding epinephrine exposure (percent of labeled dose) with use of out of date auto-injectors as well as the lack of more than two fixed doses of auto-injectors to cover the wide range of patient ages and weights, lack of and timeliness of use, and dosing via alternative routes.

Simons FER, Ardusso LR, et al., 2011. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. WAO Journal. 2011(February): 13-37.

This is an expert consensus document presenting Guidelines from the World Allergy Organization for the treatment of anaphylaxis. These Guidelines represent the views of over 100 allergy/immunology specialists across 6 continents, and are stated to be based on the best evidence available through December 2010. Epinephrine is considered the first-line treatment, along with positioning, oxygen, management of

respiratory distress, and circulatory support (treatment of hypotension and shock). These Guidelines include information regarding dosing and route, as well as adverse effects of epinephrine.

Simons KJ and Simons FER, 2010. Epinephrine and its use in anaphylaxis: current issues. Curr Opin Allergy Clin Immunol. 10(4): 354-361.

This article reviews the practical pharmacology of epinephrine in the treatment of anaphylaxis, its intrinsic limitations, and the pros and cons of different routes of administration. The article describes the adverse effects as well as the evidence for use of epinephrine in the treatment of anaphylaxis, noting that there are no absolute contraindications for its use. The article lists the reasons why physicians fail to prescribe epinephrine auto-injectors for patients with anaphylaxis, and why patients fail to self-inject epinephrine during an episode. The main emphasis of the article is the primary role that epinephrine auto-injectors serve as the cornerstone of emergency treatment of anaphylaxis in the out-patient setting, including the need to identify those patients who should be given a prescription for an auto-injector device.

Soar J, Pumphrey R, et al. Working group of the resuscitation council (UK), 2008. Emergency treatment of anaphylactic reactions--Guidelines for healthcare providers. Resuscitation. 77(2): 157-169.

This Guideline is published by Working Group of the Resuscitation Council (UK) and is intended for healthcare providers in the UK. The guideline emphasizes that anaphylactic reactions are life-threatening. Despite the fact that there are no controlled trials, the guideline considers that "a wealth of clinical experience" supports a treatment algorithm using the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach, with early treatment with IM epinephrine being the treatment of choice. The recommended dose of epinephrine is:

- Adults and adolescents >12 years of age: 0.5 mg (0.5 mL) IM
- 6-12 years of age: 0.3 mg (0.3 mL) IM
- <6 years of age: 0.15 mg (0.15 mL) IM.

However, the guideline does not provide any references to suggest that these doses are preferable to the typical dosing recommendation of 0.01 mg/kg. The guideline recommends that IV epinephrine be used in "certain specialist settings and only by those skilled and experienced in its use." The guideline also recommends that individuals who are suspected of having had an anaphylactic reaction be referred for evaluation by an allergist; those at high risk should receive training and carry an epinephrine auto-injector.

9.1.1.8 Clinical Studies

Becker AB, Nelson NA, et al., 1983. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. J Pediatr. 102(3): 465-469.

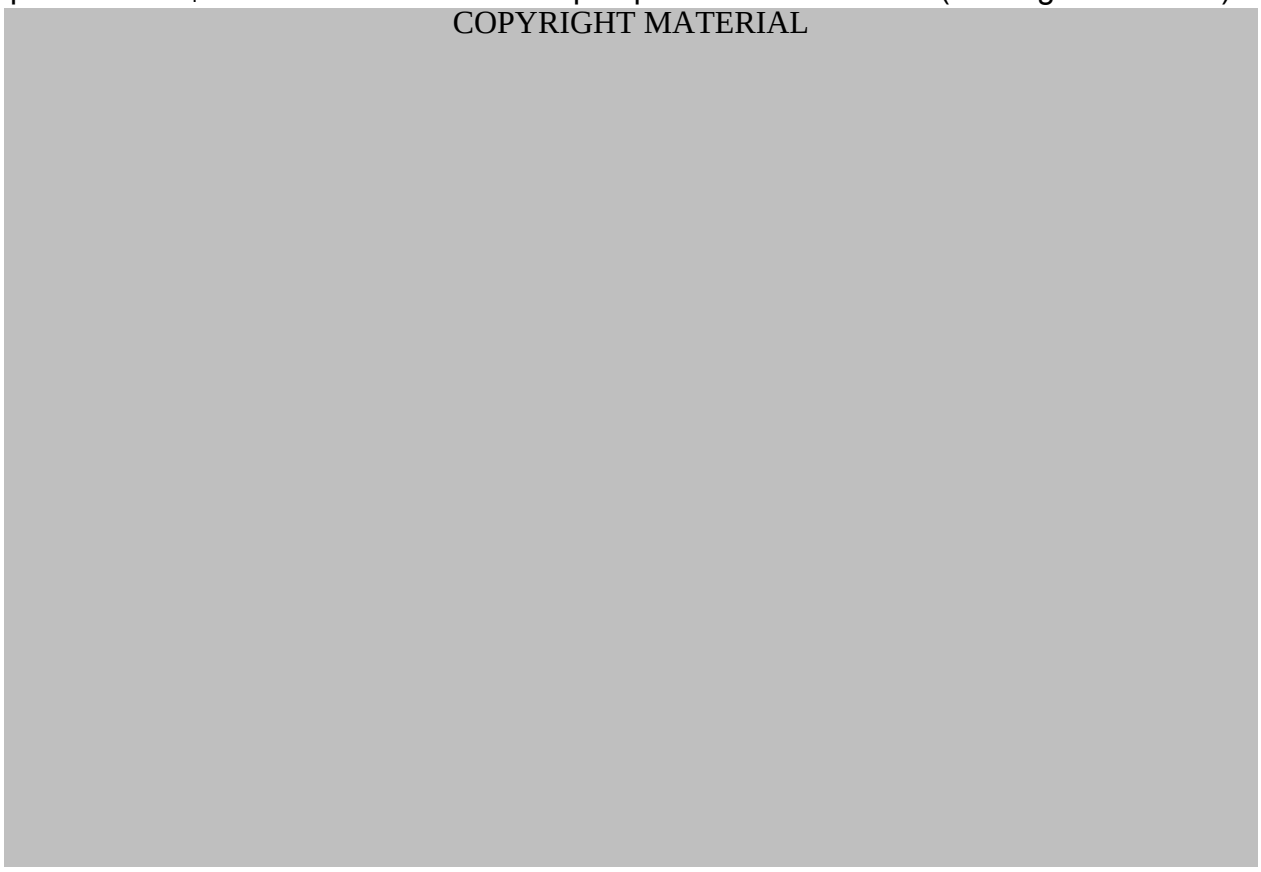
This was a randomized, double-blind, placebo-controlled, efficacy and safety trial that compared nebulized inhaled albuterol (0.5% solution, 0.02 mL/kg, maximum 1 mL, administered with oxygen by face mask) with subcutaneous epinephrine (1:1000, 0.01 mg/kg, maximum 0.4 mL) in 40 children 6-17 years of age with acute asthma. The article supports the safety of epinephrine administration, while also pointing out the associated adverse reactions associated with its use in children. The pharmacologic effects and adverse reactions reported are consistent with the known effects of and reactions to epinephrine in adults, and do not point to any safety differences between its use in adults and children.

The trial was conducted at the University of Manitoba Children's Hospital in the fall of 1981. The use of placebo control meant that all children received 100% oxygen by face mask and a SC injection. Evaluations included history and physical examinations; vital signs; a clinical score denoting asthma severity; the pulmonary index (derived from respiratory rate, wheezing, inspiratory-expiratory ratio, and use of accessory muscles); spirometry measurements (FVC, FEV_1, FEF_{25-75}) normalized for sex, age, and height; arterial blood gas sampling (30 minutes after treatment, after d/c of O2 for 10 minutes); and serum theophylline levels. VS, clinical assessments, and spirometry measures were repeated at 15 and 30 minutes post treatment, with repeated treatments at 30 minutes if clinically indicated, followed by continued assessments at 45 and 60 minutes.

Twenty children received each treatment. The children (12 M and 8 F) who received epinephrine treatment had a mean age of 10.4 ±0.7 years, and the children (13 M and 7 F) who received albuterol treatment had a mean age of 10.6 ±0.7 years. There were no significant differences (i.e., $p > 0.05$) between the two treatments for clinical score, respiratory rate, heart rate, blood pressure, repeat treatment, hospital admission, PaO_2, $PaCO_2$, FVC, FEV_1, FEV_1/FVC, or $FEF_{25-75\%}$. However, the two treatments had different effects on individual parameters, as shown in the figures reproduced from the article show. Whereas there were only minor changes in heart rate after epinephrine, there was a significant increase from baseline in heart rate at 15 and 30 minutes after albuterol administration (see Figure 1 below). Whereas there were only minor changes in respiratory rate after epinephrine, the change in respiratory rate after albuterol administration was also significant (see Figure 1 below).

After epinephrine administration, a decrease from baseline in diastolic BP and an increase in pulse pressure was noted ($p < 0.01$), whereas albuterol did not have this effect (see Figure 2 below).

In both groups, the improvement from baseline in percent predicted FEV_1, FVC, FEF25-75, and percent FEV_1/FVC were all statistically significant at all timepoints except for percent FEV_1/FVC at 30 minutes after epinephrine administration (see Figure 3 below).



Additionally, significantly more adverse effects of nausea, vomiting, tremor, palpitations, excitement and pallor were seen within the group given epinephrine than the group given albuterol (10/20 vs 0/20; $p<0.01$). The conclusion was that, although both treatments are effective, the noninvasive treatment and lack of adverse effects of inhaled salbutamol makes its use the recommended treatment of acute asthma in children.

Brown SGA, Blackman KE, et al., 2004. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. Emerg Med J. 21(2): 149-154.

This sub-study of a sting anaphylaxis immunotherapy study comes from Australia. The objective was to prospectively assess a protocol for the treatment of sting anaphylaxis using oxygen, IV epinephrine, and volume resuscitation (if needed) with normal saline in otherwise healthy adults who had systemic allergic reactions to a diagnostic sting challenge following either venom immunotherapy or placebo. Sixty-eight patients 17-65 years of age with systemic reactions to *M pilosula* were randomly allocated in a double-blind fashion to receive either immunotherapy with venom extract or placebo. Patients were excluded if they had heart disease, hypertension, poorly controlled lung disease, or were on ACE inhibitors or beta blockers. Patients who had a reaction were treated

with a standardized protocol, which included an IV infusion of epinephrine 1:100,000 at a starting rate of 30-100 mL/hour (5-15 mcg/minute), with titration up or down based on the clinical response and side effects. The infusion was stopped at 30 minutes after resolution of all symptoms, with continued observation for 2 hours post-infusion. Patients also received 1000 mL of normal saline infused rapidly over 1-3 minutes and repeated as necessary if hypotension was severe or did not respond promptly to epinephrine. For hypotension resistant to these measures, bolus of epinephrine, glucagon, and norepinephrine infusion with central venous access was to be used.

There were 21 systemic reactions in the placebo group, and none in the venom immunotherapy group. Of 19 patients who required intervention, all received epinephrine and 5 received volume resuscitation. Importantly, physical signs of anaphylaxis recurred in 9 of the cases after epinephrine was initially stopped, but resolved after restarting the infusion. The median total dose and infusion duration were 590 mg and 115 minutes respectively, but were significantly higher for eight patients who had hypotensive reactions (762 mg and 169 minutes respectively) compared to those without hypotension (520 mcg and 92 minutes). Hypotension was always accompanied by a relative bradycardia, which was severe and required atropine treatment in two patients. One patient with an otherwise mild reaction had widespread T wave inversion prior to starting epinephrine treatment. Two patients required additional therapy with atropine for bradycardia. All patients recovered fully, and all (except the one patient with ECG changes who was observed overnight) were able to be discharged on the same day. The conclusion was that carefully titrated intravenous epinephrine combined with volume resuscitation is an effective strategy for treating sting anaphylaxis, although additional treatment may be needed for patients with severe bradycardia.

9.1.2 Additional References

This section includes references for various sections and subsections of this review. In addition, this reviewer conducted multiple PubMed searches using terms such as epinephrine, clinical trials, etc, to explore whether additional literature that was not submitted by the applicant would nevertheless support the application. A number of references were found that were not submitted but have specific bearing to support either for use for the indication of anaphylaxis or use in specific populations, such as studies in children. .

9.1.2.1 History of Epinephrine and Adrenalin

1906. *Calcutta Medical Journal* 58.

Abel J and Crawford A, 1897. On the blood-pressure-raising constituent of the suprarenal capsule. *Bull Johns Hopkins Hosp* 8: 151-157.

Aronson JK, 2000. Where name and image meet: The argument for adrenaline. *British Medical Journal* 320: 506-509.

Bennett J and Yamomoto Y, 2004. Dr. Jokichi Takamine: Japanese father of American Biotechnology. Kennesaw, GA, Deerland Enzymes.

Bennett M, 1999. One hundred years of adrenaline: The discovery of autoreceptors. *Clin Auton Res* 9(3): 145-159.

Dakin HD, 1905. The synthesis of a substance allied to noradrenaline. *Proc Roy Soc Lond, Series B* LXXVI: 491-497.

Davenport HW, 1982. Epinephrin(e). *Physiologist* 25: 76-82.

Doig RL, 1905. Epinephrin. *Cal St J Med* 3: 54-55.

Editorial, 1921. The history of anapyhlaxis. *JAMA* 76(6): 380.

Opinion of Judge Learned Hand 1911. Parke-Davis & Co. v. H. K. Mulford Co., April 28, 1911. 189 F. 95, Circuit Court, S.D. New York. LEXIS 5245

Harkness J, 2011. Dicta on Adrenalin(e): Myriad Problems with Learned Hand's Product-of-Nature. *Journal of the Patent and Trademark Office Society* 93(4): 363-399.

Jowett HAD, 1904. The constitution of epinephrine. *J Chem Soc, Trans* 85: 192-197.

Kaplin DM and Bullowe JCM, 1904. *Progr Med* 3: 56.

Oliver G and Schafer EA, 1895. The physiological effects of extracts of the suprarenal capsules. *Journal of Physiology* 18: 230-276.

Pawlik WW, Konturek SJ, et al., 2006. Napoleon Cybulski--Polish pioneer in developing of the device for measuring blood flow velocity. *J Physiol Pharmacol* 57(Suppl 1): 107-118.

Pearce JMS, 2009. Links between nerves and glands: The story of adrenaline. *Advances in Clinical Neuroscience and Rehabilitation* 9(5): 22-28.

Ring J, Brockow K, et al., 2004. Anaphylaxis. *Novartis Foundation Symposium* 257: 6-24.

Stolz F, 1904. Uber Adrenalin und Alkylaminoacetobrenzcatechin. *Ber Dtsch Chem Ges* 37: 4149-4154.

Takamine J, 1901. Adrenalin the active principle of the suprarenal glands and its mode of preparation. *Am J Pharm* 73: 523-531.

Takamine J, 1901. The isolation of the active principle of the suprarenal gland. *Journal of Physiology* 27: xxix-xxx.

Takamine J, 1903. Patent No: 730,176. Glandular Extractive Product. June 2, 1903. U. S. P. T. Office

Yamashima T, 2003. Jokichi Takamine (1854-1922), the samurai chemist, and his work on adrenalin. *J Med Biogr* 11(2): 95-102.

9.1.2.2 Clinical Pharmacology

AHFS, 2011. Section 12.12.12. Epinephrine. *AHFS drug information 2011*. Bethesda, Maryland., American Society of Health-System Pharmacists**:** 1379-1385.

Barrett KE, Barman SM, et al., 2012. Chapter 7. Neurotransmitters & Neuromodulators. In: Barrett KE, Barman SM, Boitano S, Brooks HL, eds. *Ganong's Review of Medical Physiology*. 24th ed. New York, McGraw-Hill.

Bylund D, 2003. Norepinephrine. *Encyclopedia of the Neurological Sciences*. Amsterdam, Boston, Academic Press**:** 638-640.

Biaggioni I and Robertson D, 2012. Adrenoceptor Agonists & Sympathomimetic Drugs. *Basic & Clinical Pharmacology*. B. G. Katzung, S. B. Masters and A. J. Trevor. New York, McGraw-Hill.

Fitzgerald PA, 2011. Adrenal Medulla and Paraganglia. *Greenspan's Basic & Clinical Endocrinology*. D. G. Gardner and D. Shoback. New York, McGraw-Hill.

Patil PN, Miller DD, and Trendelenburg U, 1975. Molecular geometry and adrenergic drug activity. Pharmacological Reviews 26(4): 323-393.

Westfall TC and Westfall DP, 2011. Adrenergic Agonists and Antagonists. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. L. L. Brunton, B. A. Chabner and B. C. Knollmann. New York, McGraw-Hill**:** 257-295.

Winslow CM and Austen KF, 1982. Enzymatic regulation of mast cell activation and secretion by adenylate cyclase and cyclic AMP-dependent protein kinases. *Fed Proc* 41(22).

9.1.2.3 Guidelines for Management of Asthma

National Asthma Education and Prevention Program (NAEPP) 2007. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung and Blood Institute. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm (accessed 8/14/2012).

Global Initiative for Asthma (GINA) 2011. Global Strategy for Asthma Management and Prevention 2011 (Update). Available at http://www.ginasthma.org/ (accessed 8/14/2012).

9.1.2.4 Other References

Barach EM, Nowak RM et al., 1984. Epinephrine for the treatment of anaphylactic shock. JAMA 251(16): 2118-2122.

Brown SGA, Wiese MD, et al., 2003. Ant venom immunotherapy: a double-blind, placebo-controlled, crossover trial. Lancet 361(9362): 1001-1006.

Fisher MM 1986. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. Anaesth Intensive Care 14:17–21.

Heytman M, Rainbird A, 2004. Use of alpha-agonists for management of anaphylaxis occurring under anaesthesia: case studies and review. Anaesthesia 9:1210–1215.

This series of two cases is notable for the fact that excellent care including aggressive volume resuscitation and high-dose infusions of adrenaline was not successful, whereas the addition of metaraminol produced immediate responses in both cases.

Hogan MA, 2000. Health maintenance: medication management. In Fundamentals of Nursing. Caring and clinical judgment. H. Harkereader, ed. Philadelphia, W.B. Saunders. 563-574

Johansson SG, Bieber T, et al., 2004. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 113(5): 832-836.

Joint Task Force on Practice Parameters, 2005. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 115(3 Suppl 2): S483-523.

Lang DM 1995. Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers. Drug Safety 12(5):299-304.

Lieberman P, 2003. Use of epinephrine in the treatment of anaphylaxis. Curr Opin Allergy Clin Immunol. 3(4): 313-318.

Moneret Vautrin DA, Kanny G, et al., 1993. Severe anaphylactic shock with cardiac arrest caused by coffee and gum Arabic potentiated by beta-blocking eyedrops. Rev Med Interne 14(2):107-11.

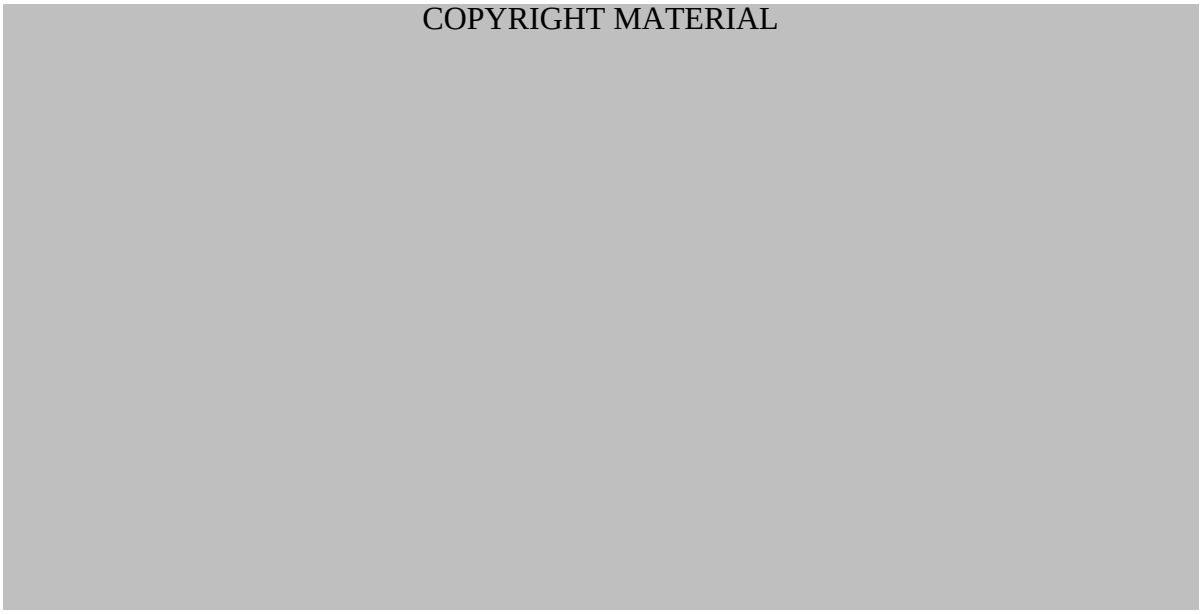
National Health and Medical Research Council, 2000. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC CP69. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp69.pdf (accessed May 17, 2012).

Oude Elberink JN, De Monchy JG, et al., 2002. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol. 110(1): 174-182.

Pijak MR and Gazdik F, 2006. Dilemmas regarding the proper route of adrenaline administration in anaphylaxis. Bratisl Lek Listy. 107(1-2): 26-30.

Simons FER, 2006. Anaphylaxis, killer allergy: long-term management in the community. J Allergy Clin Immunol. 117(2): 367-377.

This article contains a figure depicting the narrow therapeutic window of epinephrine, as shown below.



Simons FER, 2008. Emergency treatment of anaphylaxis. BMJ. 336(7654): 1141-1142.

Westfall TC and Westfall DP, 2011. Adrenergic Agonists and Antagonists. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York, McGraw-Hill. 12th ed, Chapter 12. http://www.accessmedicine.com/content.aspx?aID=16661344, Accessed June 19, 2012.

9.1.2.5 Clinical Studies - Pediatric Use

The following references were not submitted by the applicant, but nevertheless were reviewed to provide support for safety with pediatric use.

Ben-Zvi Z, Lam C, et al., 1982. An evaluation of the initial treatment of acute asthma. Pediatrics. 70(3): 348-353.

This was a randomized, single-blind trial that compared nebulized fenoterol (0.5 mL [2.5 mg] of 0.5% solution diluted with isotonic saline delivered by mask) with subcutaneous epinephrine (1:1000, 0.01 mg/kg, maximum 0.3 mg; followed in 25 minutes by Sus-Phrine, 0.025 mg/kg, maximum 0.75 mg) in 50 patients 12 and 20 years of age with acute asthma. The trial was conducted in the emergency room setting at Mount Sinai Hospital, New York, under a grant from Boehringer-Ingelheim, Ltd, Ridgefield, CT. VS and clinical assessments, and PEF were performed over a two-hour period at 10, 20, 60, 90, and 120 minutes after initial treatment. The asthma clinical score was the sum of the wheezing and retraction scores on a 0-4 scale, where 0 = none and 4 = no aeration. Spirometry measures were performed at 20, 60, and 120 minutes after initial treatment. Surprisingly, continued treatment beyond the one initial treatment is not mentioned in the study publication, although the publication states that the evidence suggests that continued epinephrine treatment would not result in better outcomes, and some patients were withdrawn for failure or side effects. Additionally, the criteria for removal or rescue of patients are not stated, although the discussion section appears to

suggest that treatment failures after epinephrine were treated with an inhaled $beta_2$ agonist, such as fenoterol.

Baseline data for the two groups were comparable. Twenty-six patients received fenoterol and 24 patients received epinephrine followed by Sus-Phrine. Overall, there was a better response from fenoterol than from epinephrine treatment. Although both groups responded within 10 minutes and peak improvement was reached within one hour, FEV_1 and the FEF_{25-75} were greater at 20 minutes with fenoterol ($p < 0.05$), and improvement in PEF and clinical score were greater following fenoterol than epinephrine treatment in the first hour ($p < 0.05$). Those with more severe obstruction (FEV_1 <30%) had significantly greater improvement in the first 20 minutes after fenoterol than epinephrine treatment. The only treatment failures were in the epinephrine treatment group, with a combined failure/relapse rate of 34% for this treatment group. Four patients in the epinephrine treatment group who remained in the trial failed to respond and required additional medical attention within 24 hours.

Adverse reactions reported in the trial included tremor (2 fenoterol, 1 epinephrine), headache (1 fenoterol, 3 epinephrine), nausea (1 fenoterol, 1 epinephrine), palpitations (1 epinephrine), fatigue (1 epinephrine), sweating (1 epinephrine). One patient was withdrawn from the study due to a severe headache following epinephrine treatment.

Lin YZ, Hsieh KH, et al., 1996. Terbutaline nebulization and epinephrine injection in treating acute asthmatic children. Pediatr Allegy Immunol. 7(2): 95-99.

This was an unblinded, non-randomized, controlled study conducted in 90 children with acute asthma at the Pediatric Allergy Outpatient Clinic of the Taipei Municipal Chung Hsiao Hospital. The objective was to compare the efficacy and safety of nebulized terbutaline with injected epinephrine in the treatment of an acute asthma exacerbation. For one period of time, all eligible patients were given nebulized terbutaline, and for the other, subcutaneous epinephrine. The terbutaline group (n=45) received 2 ml (5.0 mg) terbutaline solution diluted with 2 ml 0.9% saline for inhalation by nebulization over 10 minutes; the epinephrine group (n=45) received 0.01 ml/kg of 1:1000 epinephrine (maximum 0.3 ml) via SC injection in the deltoid area. Spirometry (FVC, FEV_1, FEF_{25-75}%), pulse oximetry, and clinical severity scoring system were evaluated at baseline and again 15 minutes after treatment.

Baseline data for the two groups were comparable. Mean age was about 7 years (range 5-12 years). Clinical severity scores and spirometry measures significantly improved for both groups after treatment. Compared with the terbutaline group, the epinephrine group had better mean oxygen saturation (SaO2; $p<0.001$), frequency of oxygen desaturation ($p=0.0028$) and FEF_{25-75}% ($p=0.027$). For those patients with an initial FEV_1 <60% predicted, epinephrine was more effective in the improvement of FEV_1, FEF_{25-75}%, and oxygen saturation (SaO2) ($p=0.011$, 0.012, and 0.006, respectively). The findings in this study with regard to oxygen saturation are similar to those found in the Becker study (Becker 1983), i.e., that oxygen saturation was increased after epinephrine but not after the nebulized beta agonist, suggesting that beta agonist nebulization should be accompanied by oxygen supplementation. A significantly higher rate of adverse reactions were noted after epinephrine than

terbutaline administration (47% vs 11%, p=0.0002). For the epinephrine group, these included pallor (11), tremor (5), dizziness (5), headache (4), palpitation (4), soreness of legs (3), numbness of extremities (2), cold sweating (2), general weakness (1), and nausea (1). For the terbutaline group these included: dizziness (2), pallor (2), and tremor (1). The conclusion was that, although both treatments were effective, noninvasive therapy and adverse event profiles favor treatment with a nebulized $beta_2$ agonist, such as terbutaline, along with oxygen supplementation to prevent hypoxemia.

Lowell et al., 1987. Wheezing in Infants: The Response to Epinephrine. Pediatrics 79: 939-945.

Most studies evaluating the treatment of young children less than 2 years of age with bronchiolitis have used nebulized beta-adrenergics or racemic epinephrine. This study differed in that it used subcutaneous epinephrine. No safety concerns were noted with epinephrine use in this population.

This was a randomized, double-blind trial that compared subcutaneous injection of epinephrine or normal saline in 30 children <24 months of age who presented to the pediatric emergency room and primary care center at Yale-New Haven Hospital with wheezing and no prior history of bronchodilator therapy. Wheezing was defined as a high pitched, continuous, musical, respiratory sound. Patients were stratified by age (<12 months and 12-24 months) and randomized to two injections of epinephrine or placebo, 0.01 mL/kg, 15 minutes apart. Respiratory assessments were made at baseline and at 15 minutes after each injection using a Respiratory Distress Assessment Instrument developed for the study that scored changes in respiratory rate, wheezing (8 point scale), and retractions (9 point scale) using two simultaneous observers. After completion of assessments, the code was broken; patients who had received placebo could receive 2 doses of epinephrine, and patients who received epinephrine were eligible to receive a third dose of epinephrine in an unblinded fashion. Of note, the only safety variable that stated to have been followed in addition to respiratory status was the heart rate.

Baseline data for the two groups were comparable. Twenty-six of the 30 children receive 2 doses of treatment, and 4 received 1 dose. Nine of 16 children treated with epinephrine (56%) improved their respiratory status compared to one of 14 who received placebo (7%) (Fisher exact test, p = 0.0067). This was confirmed by paired data in those who received placebo and then epinephrine (Wilcoxon signed ranks test, p <0.01). The response was reasonably consistent across all age groups (63% of patients <12 months, 92% of those 12-24 months). Seven of 10 children with proven RSV bronchiolitis responded to epinephrine treatment with an improvement of ≥4 units in the respiratory status score. The study noted that no consistent pattern of change in heart rate was seen after either epinephrine or placebo treatment. The conclusion was that the study demonstrates the effectiveness of epinephrine in the treatment of acute wheezing in children <24 months of age.

Sharma A and Madan A, 2001. Subcutaneous Epinephrine vs Nebulized Salbutamol in Asthma. Indian J Pediatr. 68 (12): 1127-1130.

This was a prospective, randomized, controlled trial that compared the efficacy of the subcutaneous epinephrine (1:1000, 0.01 mg/kg/dose, maximum 0.3 mL per dose) (n=25) with nebulized albuterol (0.03 mg/kg/dose, 0.5% solution, maximum 1 mL [5.0 mg] per dose diluted 1:1 in isotonic saline)(n=25) to be repeated twice at 20 minute intervals in 50 asthmatic children 6-14 years of age. Patients were excluded if they were considered to have a life-threatening attack, a PEFR <30%, had received a bronchodilator within 6 hours, or had a history of an ICU admission. Nasal oxygen was administered to both groups at 3 L/minute, and patients were observed at 15, 20, 30, 60, 120, 180 and 240 minute intervals. The primary outcome was the improvement in percent predicted PEFR, with a 20% increase from pretreatment sustained over all assessment timepoints considered to be a good response.

Baseline data for the two groups were comparable. Both the groups had comparable mean increase in PEFR % (epinephrine 27.7 ±0.7; albuterol 28.8 ±0.06, p >0.05). Eight patients in each group failed to respond and were placed on alternative treatments. In the epinephrine treatment group there was a significant increase in HR and systolic blood pressure at 30 minutes after the start of treatment, which was significantly higher than that observed after albuterol treatment (HR at 30 minutes: epinephrine 134, albuterol 118 bpm; SBP at 30 minutes: epinephrine 128, albuterol 119 mm Hg). There were no significant differences in subsequent HR or BP measures. Adverse reactions noted were similar in both groups: tremors (6 epinephrine, 8 albuterol), palpitation (13 epinephrine, 14 albuterol). The conclusion was that both the groups had satisfactory improvement in clinical parameters which continued up to 4 hours after start of treatment, and that SC epinephrine can be safely used if nebulizers are not available.

Simons FE and Gillies JD, 1981. Dose response of subcutaneous terbutaline and epinephrine in children with acute asthma. Am J Dis Child. 135(3): 214-217.

This was a randomized, double-blind dose response study conducted in the ER setting at the University of Manitoba, Canada, in 26 children 6-16 years of age with acute asthma and previously documented reversible airway obstruction. Subcutaneous doses of 3, 6, or 12 mcg/kg of terbutaline sulfate (0.5 mg/dL) were compared with SC doses of 10 mcg/kg (0.01 mg/kg) of epinephrine (1:1000) (maximum of 0.4 mg of either drug, regardless of weight). Evaluations included physical examinations, weight, vital signs, assessment of pulmonary index (composite score based on RR, amount of wheezing, inspiratory / expiratory ratio, and use of accessory muscles, each rated on a 0-3 score where 0 is the least and 3 is the most severe), PFTs, and radial artery blood for PaCO2, PaO2, and pH. Repeat PE, VS, assessment of pulmonary index, and PFTs were performed at 15, 30, 45, and 60 minutes after treatment. Humidified 30% oxygen was administered to all patients with a PaO2 <70 mm Hg, but stopped 10 minutes before a second radial artery puncture at 60 minutes after treatment.

Baseline data for the two groups were comparable. All groups improved clinically and no patients were withdrawn due to increasing respiratory problems. Mean FVC, FEV_1 and FEF_{25-75}. A log dose response was seen for FEF_{25-75}, but not for the other PFTs.

At 60 minutes, 66%, 38%, 44%, and 40% of patients on epinephrine, terbutaline 12, 6, and 3 mcg/kg, required a second drug injection, respectively. Mean HR increased in all treatment groups, but more so on terbutaline 3 mcg/kg. No significant changes were noted in PaCO2 or PaO2 for any group. No clinically significant effects on BP were noted, and no patients complained of palpitations. Adverse reactions are shown in the Table 6 below. Excitement, agitation, and headache were only noted after epinephrine treatment.

Table 6. Percent of patients with adverse reactions (Simons 1981)

Reaction	Epinephrine 10 mcg/kg	Terbutaline 12 mcg/kg	Terbutaline 6 mcg/kg	Terbutaline 3 mcg/kg
Excitement, agitation	50	0	0	0
Tremor	33	38	11	0
Headache	33	0	0	0

Sly RM, Badiei B, et al., 1977. Comparison of subcutaneous terbutaline with epinephrine in the treatment of asthma in children. J Allergy Clin Immunol. 59(2): 128-135.

This was a randomized, controlled trial comparing epinephrine and terbutaline, 0.01 mg/kg SC, maximum dose 0.25 mg, in 35 children 5-16 years of age with acute asthma. Measurements were made of BP, pulse, ECG, and PEFR at 5, 15, 30, 60, 120, 180, and 240 minutes after treatment. Twenty children returned with acute asthma attaches on other days to receive treatment with the alternative drug, 8 received terbutaline only, and 7 received epinephrine only, and 6 children required additional therapy and were discontinued prior to 4 hours post-dosing. The study was conducted in the pediatric allergy clinical of Charity Hospital of Louisiana at New Orleans, Louisiana State University Division. Significant increases in PEFR occurred within 5 minutes and were maintained for 4 hours after treatment with both drugs, although the percent change from baseline in PEFR was higher from 5 to 180 minutes (peak at 30 minutes) after terbutaline treatment. Increases in heart rate were noted from 5-30 minutes after treatment with terbutaline but not epinephrine. Small increases in systolic BP and decreases in diastolic BP were noted from 5-30 minutes after treatment with both drugs.

Adverse reactions reported in the 20 children who had both treatments included: 5 reports of sleep or drowsiness, 1 tremor, and 1 nervousness after epinephrine; 9 sleep or drowsiness, 4 tremor, 1 nervousness, 1 headache, and 1 vomiting after terbutaline.

Turpeinen M, Kuokkanen J, et al., 1984. Adrenaline and nebulized salbutamol in acute asthma. Arch Dis Child. 59(7): 666-668.

This was a randomized, controlled trial comparing epinephrine (10 mcg/kg IM) (n=20) with albuterol (0.15 mg/kg diluted with 2 mL of isotonic saline delivered by nebulization) (n=26) in 46 children ≥7 years of age with acute asthma. Measurements were made of PEFR, RR, HR, and BP at 10 and 30 minutes after treatment. Baseline data for the two groups were comparable. Although both treatment groups showed significant improvement in % predicted PEFR at 10 and 30 minutes, the response was significantly

greater after albuterol than epinephrine. Nine patients (45%) in the epinephrine group and five patients (19%) in the albuterol group required hospitalization. No significant changes in RR, HR, and BP were noted for either group. Muscle tremor was noted in five children in the epinephrine group and two children in the albuterol group.

9.1.2.6 Gas Gangrene

Association for Professionals in Infection Control and Epidemiology. Guide to the Elimination of Clostridium difficile in Healthcare Settings. Association for Professionals in Infection Control and Epidemiology, Washington, DC (2008).

Harvey PW and Purnell GV, 1968. Fatal case of gas gangrene associated with intramuscular injections. Br Med J. 1(5594): 744-746.

Stuart Hannah RC, Heddle R, et al., 2011. Fatal gas gangrene related to self-injection treatment of anaphylaxis. Ann Allergy Asthma Immunol. 106(6): 538.

9.1.2.7 Nasal Decongestion

Biaggioni I and Robertson D, 2012. Adrenoceptor Agonists & Sympathomimetic Drugs. *Basic & Clinical Pharmacology*. B. G. Katzung, S. B. Masters and A. J. Trevor. New York, McGraw-Hill.

ISMP, 2009 "ALERT: Fatal Outcome after Inadvertent Injection of Epinephrine Intended for Topical Use." ISMP Canada Safety Bulletin 9.

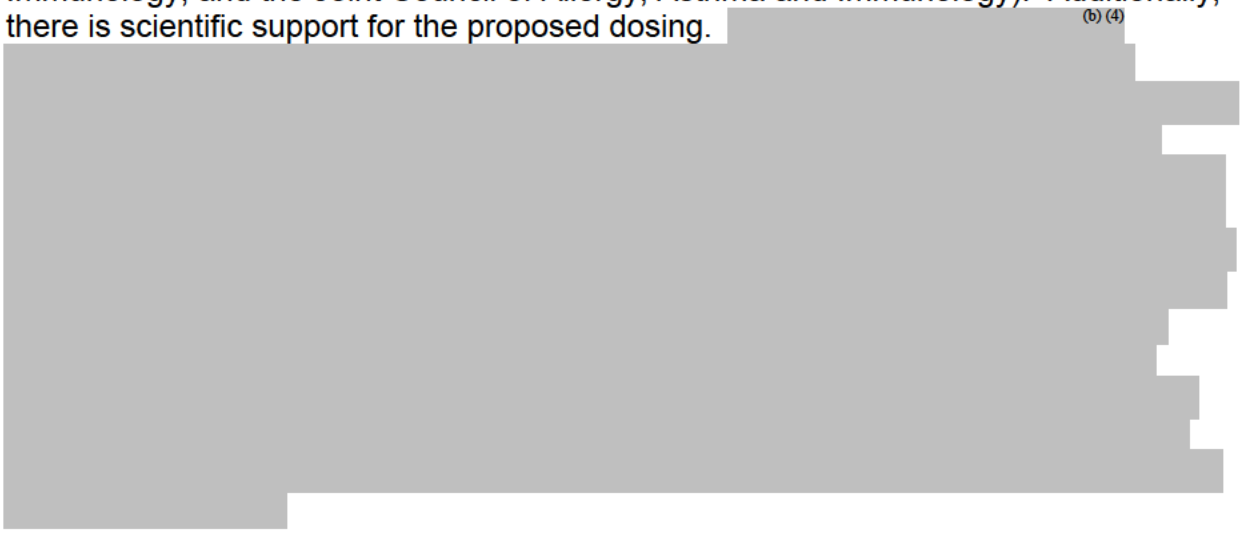
9.2 Labeling Recommendations

Labeling recommendations will be finalized subsequent to completion of this review. Nevertheless, several general labeling comments may be made here.

As noted elsewhere in this review, two indications have been requested for this product, the second of which is being reviewed in a different Division within the Agency. If approved for both indications, the Divisions will coordinate the labeling reviews to ensure that the final labeling is satisfactory for both indications.

The sponsor has submitted a label that is ported to Physician Labeling Rule (PLR) format from its current unapproved labeling. The unapproved Adrenalin product is marketed for a number of indications, most of which are not being sought with this application. Therefore, the sponsor has made an effort to drop labeling statements that apply to those indications and only leave labeling appropriate for the indications sought. Nevertheless, some extraneous information is still present. Further, much of the information in the label has been present for many years and contains inappropriate or out-of-date statements (e.g., the Drug-Drug Interactions section). It therefore needs significant updating.

The sponsor has made dosing recommendations that are in keeping with the literature and are consistent with the latest anaphylaxis dosing and treatment recommendations from the Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology). Additionally, there is scientific support for the proposed dosing. (b) (4)



Approved labeling for the epinephrine auto-injector products for the indication of anaphylaxis is available to be used as reference labeling. Auvi-Q, for example, was recently approved, and is the only epinephrine auto-injector product approved in PLR labeling format. The Division has previously made significant efforts to ensure that the labeling for all of the epinephrine auto-injectors are as similar as possible in order to avoid confusion among the products, and this product would not be an exception. With regard to the anaphylaxis indication, similar efforts will be made for this product, with the

understanding that there are and will be critical differences between this label and the labels for the epinephrine auto-injectors due to differences in the intended population and use of this product compared with those products. As a result, while certain sections of the auto-injector labels may be able to be used as a reference, others (e.g., the Dosing and Administration section) will not, and will significantly differ from those of the current products.

9.3 Advisory Committee Meeting

No advisory committee was convened to discuss this application.

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

/s/

PETER R STARKE
10/29/2012

THERESA M MICHELE
10/29/2012

CLINICAL REVIEW of NDA 204-200

For Administrative Purposes NDA 204-200 Original-2

Application Type	NDA
Application Number(s)	204-200
Priority or Standard	Priority (for Original-2)
Submit Date(s)	March 7, 2012
Received Date(s)	March 7, 2012
PDUFA Goal Date	September 7, 2012
Division / Office	Division of Transplant and Ophthalmology Products, Office of Antimicrobial Products
Reviewer Name(s)	Wiley A. Chambers, MD
Review Completion Date	September 5, 2012
Established Name	Epinephrine Injection
(Proposed) Trade Name	Adrenalin®
Therapeutic Class	Sympathomimetic catecholamine
Applicant	JHP Pharmaceuticals, LLC (JHP)
Dosing Regimen	For intracameral administration during intraocular surgery
Indication(s)	Hypersensitivity reactions: severe acute anaphylactic reactions (b) (4) Ophthalmic use: induction and maintenance of mydriasis during intraocular surgery (Original-2) The product has been proposed to be indicated for two indications (treatment of hypersensitivity reactions and induction and maintenance of mydriasis during intraocular surgery). Only the mydriasis indication will be presented in this review. Separate reviews, goal dates and action are proposed for the hypersensitivity reaction indication.
Intended Population(s)	Patients undergoing intraocular surgery

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 204-200, Adrenalin (epinephrine injection, USP) is recommended to be approved from a clinical prospective for the induction and maintenance of mydriasis during intraocular surgery with labeling recommended in this review.

1.2 Risk Benefit Assessment

The benefits of using epinephrine injection when administered in concentrations between 1:10,000 and 1:1,000,000 inclusive to dilate the pupil during the performance of intraocular surgery outweigh the potential risks associated with the use.

1.3 Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies

No additional information is needed to evaluate the risks associated with using epinephrine injection intracamerally during intraocular surgery.

1.4 Recommendations for Post-marketing Requirements and Commitments

No additional studies are recommended in association with this application.

2 Introduction and Regulatory Background

2.1 Product Information

Adrenalin® currently marketed by JHP Pharmaceuticals, LLC (JHP) is reported by JHP to be 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 or identical to the current formulation described below.

JHP at Rochester, MI manufactures the drug product, Adrenalin® (epinephrine injection, USP) 1 mg/mL (b) (4)

Name	Adrenalin® (epinephrine injection, USP)
Strength	1 mg/mL (1:1000)
Dosage Form	Injection (solution)
Route of	Intramuscular, subcutaneous (b) (4)
Description	Clear, colorless to light yellow solution

2.2 Currently Available Treatments for Proposed Indications

Epinephrine injection is an unapproved, currently marketed product. There are currently no alternative products which can be administered intracamerally to dilate the pupil.

2.3 Availability of Proposed Active Ingredient in the United States

Epinephrine is currently marketed in the United States in products which are the subject of approved applications and products which are not the subject of approved applications. Applications which are the subject of approved applications include:

NDA	Name	Ingredient Summary	Indication
21-504	Lidosite Topical	Anesthetic and Epinephrine	Dermal Anesthesia
20-971	Septocaine	Anesthetic and Epinephrine	Infiltration or Nerve Block Anesthesia
22-010	Septocaine	Anesthetic and Epinephrine	Infiltration or Nerve Block Anesthesia
20-530	Iontocaine	Anesthetic and Epinephrine	Local Anesthesia
21-381	Lidocaine	Anesthetic and Epinephrine	Local Anesthesia
21-383	Prilocaine	Anesthetic and Epinephrine	Local Anesthesia
22-466	Orabloc	Anesthetic and Epinephrine	Local Anesthesia
6-488	Xylocaine and Epinephrine	Anesthetic and Epinephrine	Local Anesthesia
19-430	Epipen	Epinephrine	Emergency Treatment of Allergic Reactions
201-739	Auvi-Q	Epinephrine	Emergency Treatment of Allergic Reactions
20-800	Twinject	Epinephrine	Emergency Treatment of Allergic Reactions

Unapproved Epinephrine Injection products include the product which is the subject of this application and additionally: (partial list)

Epinephrine injection- American Reagent
Epinephrine injection- Amphastar
Epinephrine injection- Claris Lifesciences
Epinephrine injection- Greenstone
Epinephrine injection- Hospira
Epinephrine injection- Physicians Total Care

2.4 Important Safety Issues with Consideration to Related Drugs

Not applicable.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

A Pre-IND (PIND 111712) meeting was held on July 5, 2011.

2.6 Other Relevant Background Information

The product is currently marketed by JHP (b) (4)

This application includes two different indications, only the induction and maintenance of mydriasis during intraocular surgery indication is considered a priority review. It is considered a priority review because there are currently no approved products which can be given to dilate the pupil after a surgical incision has been made in the cornea.

Induction and maintenance of the mydriasis, as the phrase is used in this review and proposed labeling of the drug product is considered one indication. Pupillary dilation in response to direct application of epinephrine intracamerally occurs within seconds, but without continued administration rapidly wears off. The phrase "induction and maintenance" is meant to describe an increase in pupillary diameter over the diameter that would have occurred during the entire intraocular surgical procedure as long as the drug product is continuing to be administered.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application references literature studies in support of the safety and efficacy of the new drug product. These studies are considered to be adequate and well controlled studies of adequate quality and integrity.

3.2 Compliance with Good Clinical Practices

The submitted studies were conducted in a manner which is consistent with good clinical practices.

3.3 Financial Disclosures

None – Based on literature references not conducted by the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Formulation (b) (4)

Ingredient	Grade	Function	Batch Quantity	Unit Formula
Epinephrine	USP	Active	(b) (4)	(b) (4)
Sodium Chloride	USP	Tonicity adjustor		9.0 mg
Sodium Metabisulfite	NF	Antioxidant		1.0 mg
(b) (4) Hydrochloric Acid	USP	(b) (4)		(b) (4)
Water for Injection	USP	(b) (4)		(b) (4)

(b) (4)

Reviewer's Comments: (b) (4)

The 1 mL (b) (4) *provides more than enough epinephrine for a single patient and ophthalmic operating room procedures prohibit the use of the same bottle for more than one patient. There would be no need to have more than 1 mL in the operating room.*

Drug Product Specifications:

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

Reviewer's Comments: *Concur with current proposed specifications. Due to the small volume and expected dilution prior to use, it is unlikely that the current specifications will lead to any ocular harm and* (b) (4)

4.2 Clinical Microbiology

Not applicable. The product is not an antimicrobial drug product.

4.3 Preclinical Pharmacology/Toxicology

There were no significant issues raised as a result of the non-clinical studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The effects of epinephrine are dependent on the type of adrenergic receptor found in the body system. In the eye, adrenergic sympathetic activity of epinephrine on the dilator pupil musculature of the iris produces mydriasis.

4.4.2 Pharmacodynamics
Pupillary dilation occurs within seconds of adrenergic stimulation.

4.4.3 Pharmacokinetics
The product is administered directly to the site of action (intracamerally). Pupil dilation occurs within seconds of administration.

5 Sources of Clinical Data
5.1 Tables of Studies/Clinical Trials

Study	Authors	Title	Doses Studied	Number of Patients
1	Liou and Chen, 2001	Maintenance of Mydriasis with One Bolus of Epinephrine Injection During Phacoemulsification	0.1 mL injection, 1:25,000; 1:50,000; 1:100,000; 1:200,000; 1:400,000	70 patients; Mean Age 69 (55-83); 10 control; 11 group 1; 13 group 2; 10 group 3; 14 group 4; 12 group 5
2	Corbett and Richards, 1994	Intraocular adrenaline maintains mydriasis during cataract surgery	1:1,000,000 epinephrine in intraocular irrigation fluid	70 patients; Mean Age 75
3	Gimbel, 1988	The Effect of Treatment with Topical Nonsteroidal Anti-inflammatory drugs with and without Intraoperative Epinephrine on the Maintenance of Mydriasis during Cataract Surgery	1:1,666,667 epinephrine in intraocular fluid; 6 treatment groups; Ocufen plus epinephrine, Ocufen without epinephrine; Indocid plus epinephrine, Indocid without epinephrine; Placebo with epinephrine; Placebo without epinephrine	216 patients randomly distributed between 6 groups (approx 36 per group)
4	Liou and Chen, 1998	The Effect of Intracameral Adrenaline Infusion on Pupil Size, Pulse Rate, and Blood Pressure During Phacoemulsification	1:1,000,000 epinephrine in intraocular irrigation fluid	42 eyes (30 with 0.25 mL added to 250 mL BSS Plus), 12 control eyes (BSS Plus)
5	Backstrom and Behndig, 2006	Redilation with intracameral mydriatics in phacoemulsification surgery	1:1,666,667 epinephrine in intraocular fluid in epinephrine group. Additional 150 microliters of 1.5% in Intracameral mydriatic (ICM)group	80 patients; Mean Age 76; 30 eyes epi+ ICM; 30 eyes epi + no-ICM; 10 eyes no-epi + ICM; 10 eyes no-epi + no-ICM.
6	Duffin, Pettit and Straatsma, 1983	Maintenance of Mydriasis with Epinephrine During Cataract Surgery	1:16,000 to 1:96,000	55 patients, Mean Age 72 (range 55 to 93)

5.2 Review Strategy

Intracameral epinephrine has been widely used for decades. The company provided literature references of adequate and well controlled studies to support their position that epinephrine when added to an ophthalmic irrigating solution was safe and efficacious. While the company did not provide a systemic plan for reviewing the literature, independent searches have the literature have failed to provide any inconsistencies in the studies provided by the applicant. Representative studies have been included in this review. Studies 1-4 and 6 were included in the applicant's original submission. Study was identified during additional Medline searches.

6 Review of Efficacy

6.1 Indication- Intraoperative mydriasis

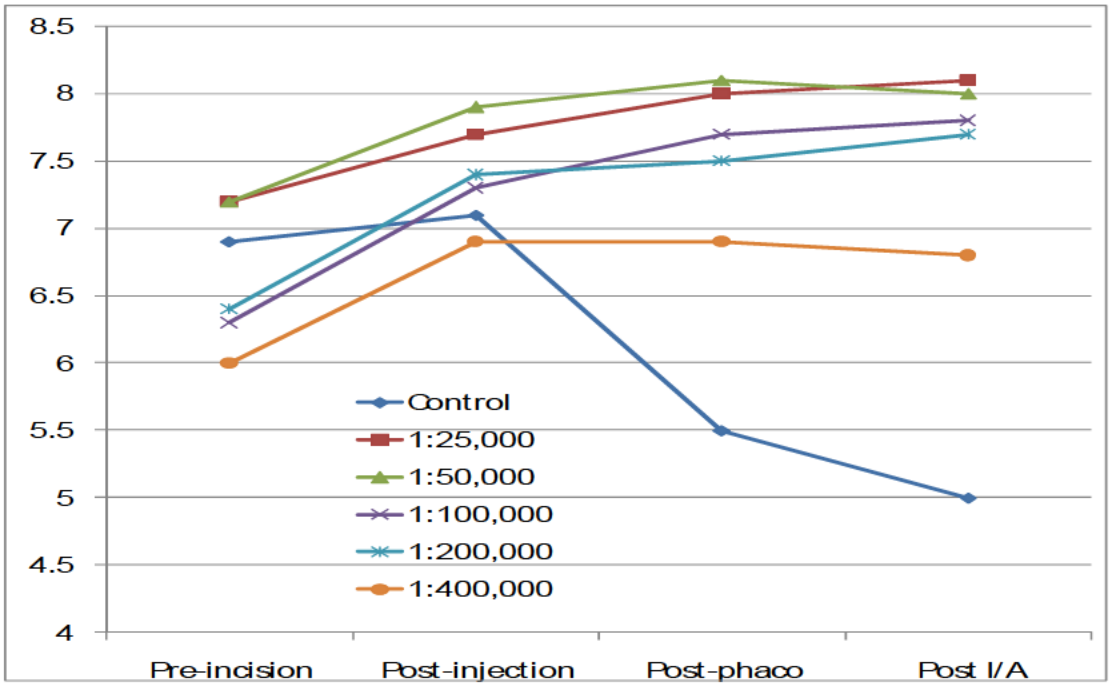
Methods – Measurements made through operating room microscope

Analysis of Primary Endpoint – Pupil Size

Published literature includes adequate and well controlled studies demonstrating the safety and efficacy of epinephrine when injected intracamerally or added to balanced salt solution during intraocular surgery.

A representative sample of these literature studies and the study results is included below.

Study 1: Liou SW and Chen CC. Maintenance of Mydriasis with One Bolus of Epinephrine Injection During Phacoemulsification. *J Ocular Pharmacology.* 2001; 17:249-253.



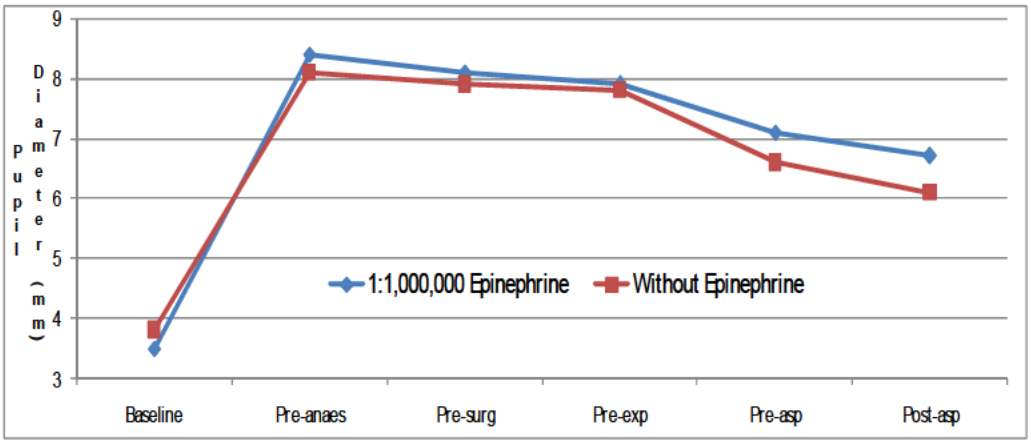
	Pre-incision	Post-incision	Post-phaco	Post I/A
Control Group	6.9 ± .5	7.1 ± .5	5.5 ± .4	5.0 ± .4
1:25,000	7.2 ± .5	7.7 ± .5	8.0 ± .6	8.1 ± .6
1:50,000	7.2 ± .6	7.9 ± .7	8.1 ± .8	8.0 ± .5
1:100,000	6.3 ± .4	7.3 ± .5	7.7 ± .7	7.8 ± .6
1:200,000	6.4 ± .5	7.4 ± .6	7.5 ± .7	7.7 ± .6
1:400,000	6.0 ± .6	6.9 ± .6	6.9 ± .9	6.8 ± .2

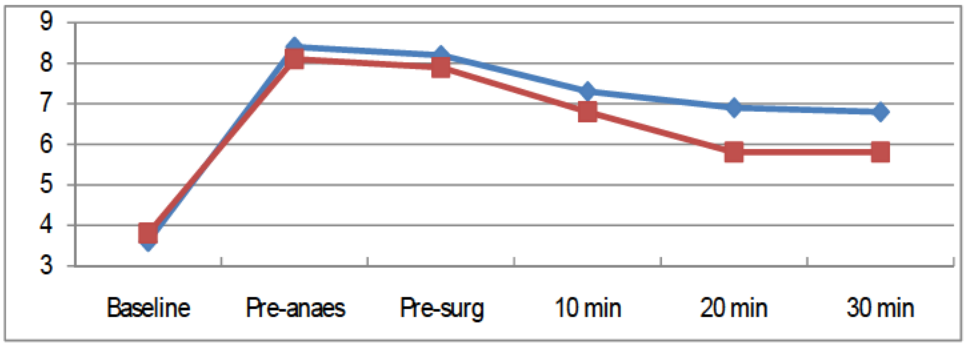
Reviewer's Comments: *While all concentrations were effective, there is a small difference due to concentration. Increased pupil size allows for increased surgical visibility.*

Study 2: Corbett MC and Richards AB. Intraocualr adrenaline maintains mydriasis during cataract surgery. *Br J Ophthalmol.* 1994; 78:95-98.

Pre-defined endpoint: Percentage of patients with pupil less than 5 millimeter

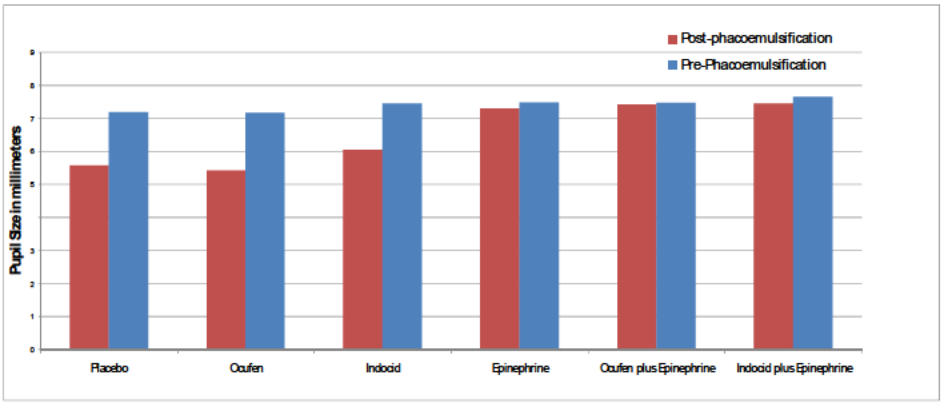
Time or stage of surgery	Without Epinephrine	With Epinephrine
Total number of patients	43	27
Before expression	None	None
Before aspiration	7 (16%)	None
After aspiration	9 (21%)	2 (7%)
10 min	4 (9%)	1 (4%)
20 min	9 (21%)	1 (4%)
30 min	9 (21%)	3 (9%)





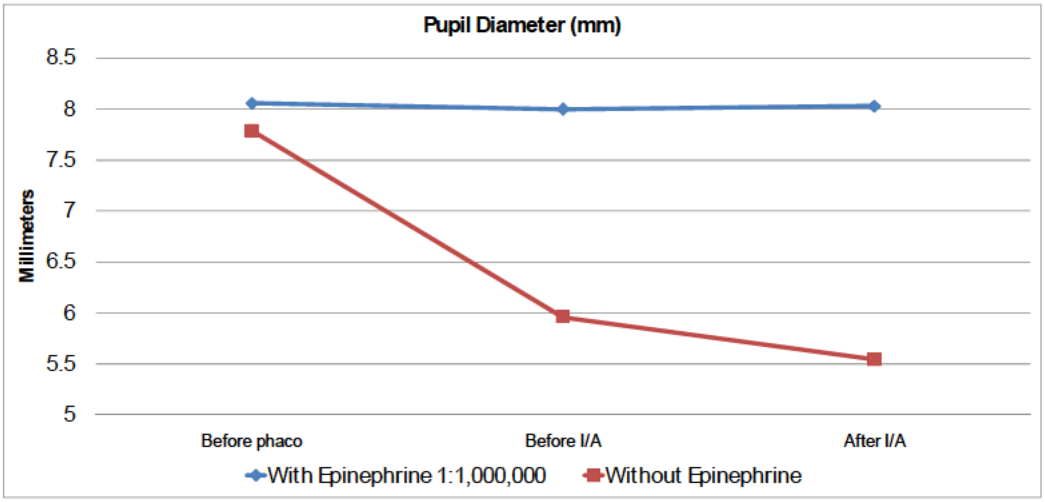
Reviewer's Comments: *As noted above, pupil dilation is maintained to a greater extent by the use of epinephrine at the critical times of the operation, at a 1,000,000 dilution. Increased pupil size allows for increased surgical visibility.*

Study 3: Gimbel HV. The Effect of Treatment with Topical Nonsteroidal Antiinflamatory Drugs with and without Intraoperative Epinephrine on the Maintenance of Mydriasis during Cataract Surgery. *Ophthalmol.* 1989; 96:585-588.



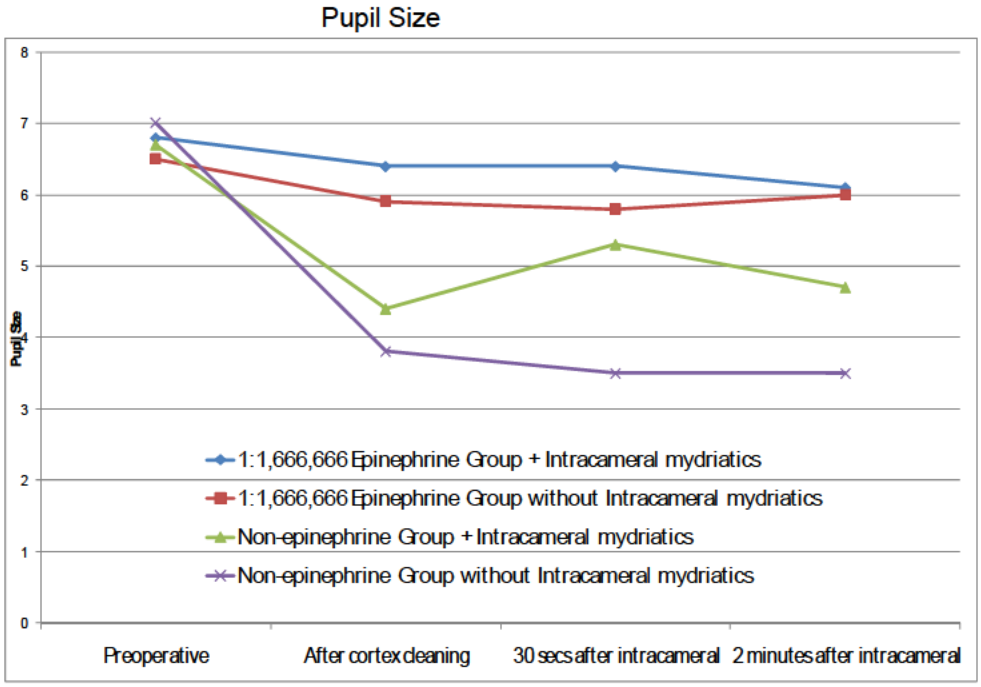
Reviewer's Comments: *As displayed above, each of the 3 groups which included epinephrine demonstrated statistically significantly larger pupil diameters than the any of the 3 groups which did not include epinephrine. The differences are statistically significant even after a Bonferroni correction for multiplicity. Increased pupil size allows for increased surgical visibility.*

Study 4: Liou SW and Yang CY. The effect of Intracameral Adrenaline Infusion on Pupil Size, Pulse Rate, and Blood Pressure During Phacoemulsification. *J Ocular Pharmacology Therapeutics.* 1998; 14(4): 357-361.



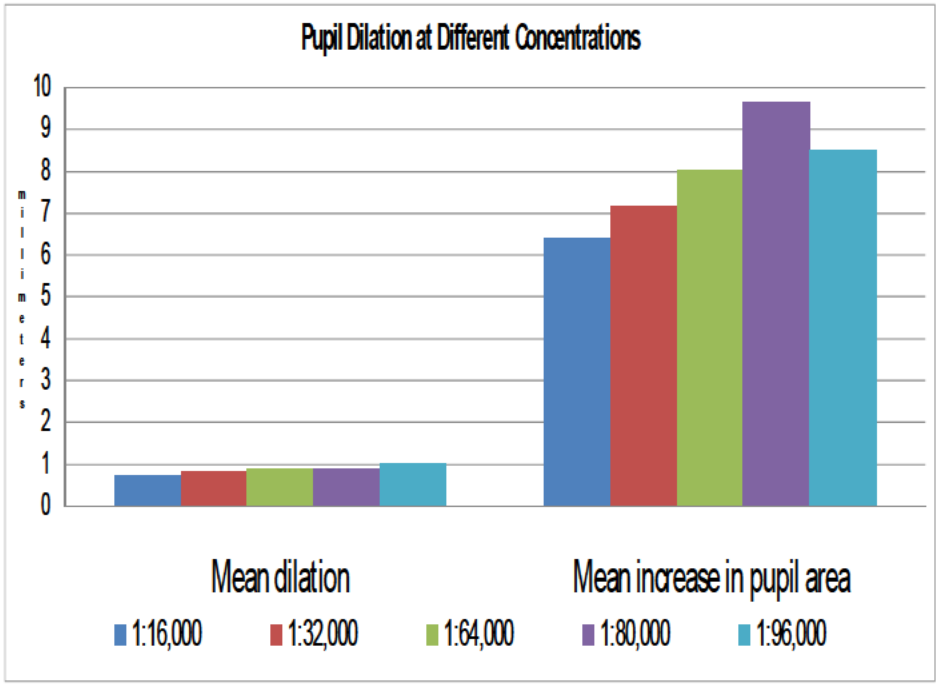
Reviewer's Comments: *As noted above, pupil dilation is maintained to a greater extent by the use of epinephrine, at a 1,000,000 dilution. Increased pupil size allows for increased surgical visibility.*

Study 5: Backstrom G and Behndig A. Redilation with intracameral mydriatics in phacoemulsification surgery. *Acta Ophthalmol Scand.* 2006; 84:100-104.



Reviewer's Comments: *Pupil size is reported in millimeters. Epinephrine added to the irrigating solution maintained pupil diameter and precluded the need for additional intracameral mydriatics. Increased pupil size allows for increased surgical visibility.*

Study 6. Duffin RM, Pettit TH and Straatsma BR. Maintenance of Mydriasis with Epinephrine During Cataract Surgery. *Ophthalmic Surgery*. 1983; 14:41-43.



Reviewer's Comments: *All concentrations lead to significant increases in pupil size. Increased pupil size allows for increased surgical visibility. Pupil area is reported as square millimeters.*

7 Review of Safety

7.1 Methods

The safety profile was evaluated from the published literature, adverse events reported to the applicant during marketing of the product and a review of MedWatch reports.

7.2 Adequacy of Safety Assessments

The potential adverse consequences of intracameral epinephrine when administered as intended (diluted into the ophthalmic irrigating solution) are difficult to evaluate because of the short onset of effect (seconds), short duration of effect (minutes) and the potentially confounding factors associated with using it as an admixture to balanced salt solution in intraocular surgery. There have been very few adverse reports to the Agency after millions of doses of used over decades.

7.3 Ocular Safety

As reported by Hull et al [*Am J Ophthalmol*. 1975 Feb;79(2):245-50] commercial epinephrine 1:1000 with its preservative sodium bisulfite damaged corneal endothelial function and ultrastructure in rabbit and monkey eyes with sodium bisulfite the source of the damage. Endothelial damage can be prevented with a 1:5000 dilution of commercially available epinephrine in 0.1% sodium bisulfite or freshly prepared epinephrine bitartrate 1:1000 with a bicarbonate Ringers. Cakmak et. al. [*Cutaneous and Ocular Toxicology.* 2010; 29(1):41-49] reported the safe use of 1:100,000 dilution of sodium bisulfate preserved epinephrine. Their clinical trial evaluated the effects on the corneal endothelial cells in patients treated with or without 1:100,000 epinephrine and they did not detect any differences.

Bozkurt et. al. [*J Cataract Refract Surg* 2010; 36:1380–1384] performed a randomized clinical trial evaluating the safety of an intracameral 0.2 mL injection of 1:5000 epinephrine. The clinical trial focused on the macular safety and demonstrated no difference with or without epinephrine.

7.4 Pediatrics

Wilson et al. [*J Cataract Refract Surg* 2007; 33:1325–1327] have reported on the safety of their routine use of epinephrine [0.5 mL in 500 mL of 0.1% epinephrine]. Included in this report is a case of intraoperative floppy-iris syndrome (IFIS) which occurred when the epinephrine was inadvertently left out of the irrigating solution.

7.5 Routine Clinical Testing

None.

7.6 Major Safety Results

7.6.1 Deaths
None.

7.6.2 Nonfatal Serious Adverse Events
None reported.

7.6.3 Dropouts and/or Discontinuations
None.

7.6.4 Significant Adverse Events
None when administered as directed. Corneal edema when administered in without dilution.

7.7 Supportive Safety Results- Vital Signs

Study 1:

Pulse Rate

	Pre-incision	Post-incision	Post-phaco	Post I/A
Control Group	75 ± 8	77 ± 7	73 ± 10	73 ± 8
1:25,000	76 ± 8	77 ± 9	77 ± 7	75 ± 8
1:50,000	74 ± 8	79 ± 8	78 ± 10	78 ± 7
1:100,000	75 ± 7	76 ± 7	79 ± 8	76 ± 9
1:200,000	72 ± 8	75 ± 8	76 ± 9	74 ± 7
1:400,000	74 ± 8	76 ± 8	76 ± 8	76 ± 5

Systolic Blood Pressure

	Pre-incision	Post-incision	Post-phaco	Post I/A
Control Group	141 ± 18	146 ± 14	143 ± 20	143 ± 18
1:25,000	140 ± 28	144 ± 19	143 ± 17	141 ± 18
1:50,000	141 ± 23	144 ± 18	139 ± 20	140 ± 27
1:100,000	144 ± 22	145 ± 27	141 ± 18	144 ± 19
1:200,000	140 ± 18	142 ± 18	139 ± 19	141 ± 17
1:400,000	140 ± 18	143 ± 18	140 ± 18	138 ± 25

Diastolic Blood Pressure

	Pre-incision	Post-incision	Post-phaco	Post I/A
Control Group	67 ± 12	70 ± 12	73 ± 10	69 ± 9
1:25,000	66 ± 13	73 ± 12	72 ± 7	75 ± 10
1:50,000	69 ± 9	72 ± 11	68 ± 11	68 ± 9
1:100,000	66 ± 10	70 ± 11	71 ± 11	68 ± 13
1:200,000	72 ± 10	72 ± 13	69 ± 10	74 ± 10
1:400,000	71 ± 10	73 ± 9	76 ± 9	72 ± 11

Reviewer's Comments: *As noted above there were no significant changes in pulse or blood pressure. Pulse or blood pressure was also measured in Studies 2 and 4. No significant changes were noted in these studies.*

7.8 Postmarketing Experience
The Office of Safety Evaluation provided a summary of the reported adverse events associated with the use of epinephrine when administered intracamerally.

78 ocular reports were retrieved (after removing duplicates). Of those, 26 involved epinephrine use with lidocaine or bupivicaine as a periorbital block. The vast majority of intracameral use (42) involved epinephrine admixed with BSS. The reported events included:

- Endophthalmitis – 15
- Toxic Anterior Segment Syndrome (TASS) – 9
- Corneal disorder – 6
- Blurred vision & edema – 6
- Vision loss – 4
- Cataract formation (post-vitrectomy) – 3
- Corneal opacity – 2
- Staph eye infection – 2
- Keratitis – 1
- Failed corneal graft secondary to osmotic shock – 1

There were three cases reporting inadvertent intraocular administration in which the events were vitreous hemorrhage, vision loss, and a decompensated cornea.

Reviewer's Comments: *The cases have been reviewed. Each of the cases has multiple potentially contributing causes and all events listed above have also been reported with the use of balanced salt solution (BSS) without epinephrine. None of the reported cases suggest that the cause of the adverse event was related to epinephrine use.*

8. Advisory Committee Meeting
The application raised no new issues of safety or efficacy which would likely benefit from an Advisory Committee discussion.

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

---

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

/s/

WILEY A CHAMBERS
09/05/2012

CLINICAL FILING CHECKLIST FOR NDA 204200/Mydriasis

NDA Number: 204200 **Applicant:** JHP Pharmaceuticals **Stamp Date: March 7, 2012**

Drug Name: Adrenalin **NDA/BLA Type: 5**

On initial overview of the NDA/BLA application for filing:

	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			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
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			
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			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) based on literature
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Mydriasis	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA 204200/Mydriasis

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication: Mydriasis				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) 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			
23.	Has the applicant submitted the coding dictionary[2] 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			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

[1] 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.

[2] 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).

CLINICAL FILING CHECKLIST FOR NDA 204200/Mydriasis

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, 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			
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 available and complete?		X		
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	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA 204200/Mydriasis

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

None.

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

WILEY A CHAMBERS
04/19/2012

WILLIAM M BOYD
04/19/2012

CLINICAL FILING CHECKLIST FOR NDA 204-200

NDA:	**204-200**
Applicant:	**JHP Pharmaceuticals, LLC**
Drug Name:	**Adrenalin® (epinephrine injection, USP)**
NDA Type:	**505(b)(2)**
Stamp Date:	**March 7, 2012**
Date of Review:	**April 11, 2012**

Introduction and Background

This is a 505(b)(2) new drug application (NDA) submitted by JHP Pharmaceuticals, LLC (JHP) for Adrenalin® (epinephrine injection, USP), referencing EpiPen® Auto-Injector (epinephrine injection, USP) (NDA 19-430) [1] as the reference listed drug (RLD). Epinephrine is a pre-1938 drug that has been marketed under the trade name Adrenalin® since shortly after the turn of the 20th Century. The drug product 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.

Although the product is being marketed for other indications, only two indications are proposed with this application: the emergency treatment of severe allergic reactions (anaphylaxis) by IM or SC injection (b) (4) and a new indication for ophthalmic clinical use (maintenance of mydriasis in cataract surgery) by topical irrigation or intraocular bolus injection. The application will therefore be reviewed by two review divisions within the Center for Drug Evaluation (CDER), Office of New Drugs (OND): the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the anaphylaxis indication, and the Division of Transplant and Ophthalmology Products (DTOP), for the mydriasis in cataract surgery indication. Because of differences in the two indications, the application carries two PDUFA dates, one for a standard review timeline for the anaphylaxis indication because there are other products approved for this indication, and one for a priority review timeline for the mydriasis in cataract surgery indication because there are no other products approved for this indication.

A pre-IND teleconference was held with the company on July 5, 2011. The teleconference included members of both DPARP and DTOP, as well as other relevant Offices within the Agency. The teleconference was prompted by a Notice of FDA Action sent by the Office of Compliance and received by JHP on July 23, 2009, regarding shipment of the active pharmaceutical ingredient (API), epinephrine, pending release from US Customs. JHP was requested to provide documentation of the grandfather status of their Adrenalin drug products, i.e., to clarify the linage of the Adrenalin drug product currently marketed by JHP with respect to the Adrenalin drug product initially marketed by Parke-Davis prior to June 25, 1938. JHP provided the requested information and the API was released from Customs

[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.

on October 9, 2009, after which the Office of Compliance urged JHP to contact OND to discuss the filing of a new drug application for the product.

The submission is in eCTD format. JHP has not performed any clinical trials to support the application. Instead, JHP submitted a relevant literature searches (in Module 5) and relevant overview documents (in Module 2) to support efficacy and safety for the two proposed indications. This is in conformance with discussion held at a pre-IND teleconference, at which time the Agency expressed the position that clinical trials would not be required, and that submission of relevant literature reviews would be acceptable for both of the proposed indications, with the proviso that the RLD would only support two proposed doses of epinephrine for anaphylaxis (b) (4) administered by the SC and IM routes, and that any differences in dosing and administration for the proposed product (indications, weight ranges, alternative dosing regimens, (b) (4)) would need to be supported by either clinical trial data or data from the literature. Of not, the literature review includes clinical trials to support efficacy and safety for the ophthalmic indication, but only historical use to support efficacy and safety for the anaphylaxis indication.

As recommended by the Agency, JHP has requested a waiver of *in vivo* bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is an injection solution (b) (4) To support the nonclinical pharmacology and toxicology, JHP conducted a literature review supplemented by four studies designed to assess genotoxicity and to qualify (b) (4) as an impurity.

With the application, JHP initially did not submit a Pediatric Assessment, as required under 21 CFR 314.55. After being informed that they needed to submit this, JHP submitted a request for a waiver of pediatric studies in all pediatric age ranges for both indications. I

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			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
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			
LABELING					
7.	Has the applicant submitted the design of the development	X			

	Content Parameter	Yes	No	NA	Comment
	package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?				
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Within the clinical overview
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Within the clinical overview
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Within the clinical overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) with reference to EpiPen Auto-Injector
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			Literature references included in submission
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval			X	

	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			
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			
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			
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
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, 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			Not initially submitted, but submitted after being requested by DPARP
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			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).

	Content Parameter	Yes	No	NA	Comment
	complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?			X	
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.

Potential Review Issues and Clinical 74-Day Comments

None

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

/s/

PETER R STARKE
04/11/2012

THERESA M MICHELE
04/11/2012