CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Bayer

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-800
Epinephrine Injection, USP (1:1000)

SUBMISSION DATE:
12/05/96 (Serial No. 000)
02/24/97

BRAND NAME:

SPONSOR: Bayer Corp.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original NDA Submission

Code: 3S

TITLE: "Review of NDA of Epinephrine for Emergency Use"

BACKGROUND:

Emergency epinephrine (Epi) injection units have been marketed by Bayer for over 30 years in the Ana-Kit Anaphylaxis Emergency Kit form in many countries. Sales of the drug component, [redacted] assembly manufactured by [redacted] precede this time by many years. The AnaGuard (the same syringe unit in a "pen holder") was introduced in 1989. Both Ana-Kit and AnaGuard deliver two manual doses of Epi USP (1:1000). They are indicated for allergic reactions including **1)** anaphylactic shock due to stinging insects, **2)** severe allergic or anaphylactic reactions due to allergic injection, exposure to pollens, dusts, molds, foods, drugs, exercise, or unknown substances, and **3)** severe life-threatening asthma attacks. However, it should be noted that although the drug component, [redacted] was used for many years (a grandfather drug), it has never been approved by the Agency.

Note: EpiPen (Epi USP, 1:1000) and EpiPen, Jr. (Epi USP, 1:2000) with autoinjector that was filed under NDA 19-430 on 01/30/85 by Survival Tech Inc. was approved by the Agency on 12/22/87 for the same indications. The formulations of EpiPen and EpiPen Jr. (containing [redacted]) are slightly different from that of [redacted] (containing [redacted] instead of [redacted]). Included in NDA 19-430 were literature articles for safety and efficacy review. No pharmacokinetic (PK) information on Epi was submitted. Prior to its approval, NDA 19-430, however, has never been reviewed by The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (OCPB/DPE II).

SYNOPSIS:

This epinephrine product is a pure levo-isomer of synthetic catecholamine obtained by separation from synthetically produced racemate. [redacted] that was filed under NDA 20-800 on 12/05/96 by Bayer is an improved design which delivers the first dose

(0.3 ml) of Epi automatically and the second dose (0.3 ml) manually, if needed. The same drug component, [redacted] is used except the drug delivery system. Please see Figure 1 for the delivery system of [redacted] for details. The same indication as for AnaGuard and Ana-Kit is being sought for approval by the sponsor. [redacted] is to be given by intramuscular (IM) or subcutaneous (SC) injection as the currently marketed Ana-Kit and AnaGuard. However [redacted] is different from Ana-Kit and AnaGuard in:

1. **Indications and Usage:**

[redacted] is only indicated for patients [redacted] and two fixed doses (0.3 ml) are to be given automatically (first) and then manually (second), if needed. Ana-Kit and AnaGuard are for patients from infants to adults and the two doses to be given manually are 0.3 ml for adults and children over 12 years; 0.2 ml for 6-12 years; 0.15 ml for 2-6 years; 0.05 to 0.1 ml for infants to 2 years.

2. **Dosage and Administration:**

By IM or SC injection, [redacted] is to be given into the anterolateral aspect of the thigh only, while Ana-Kit and AnaGuard are given into the deltoid region of the arm or the anterolateral aspect of the thigh.

No PK studies were submitted under Human Pharmacokinetics and Bioavailability section of this NDA. Very little/limited PK information was obtained from published sources/articles. For the proposed package insert (PI; Oct, 96 version), please see Appendix 1 for details.

The results obtained from the reported PK information of Epi that were submitted on 12/05/96 are summarized below:

1. Epi acts rapidly after IM or SC injection, but is also rapidly inactivated by processes including uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues by catechol-o-methyl-transferase (COMT) and/or monoamine oxidase (MAO). [Goodman and Gilman's The Pharmacological basis of Therapeutics, 7th edi. and Biopharmaceutics and Drug Disposition, 10:1-14, 1989].

2. After a SC dose of 480 μg Epi, the maximum urinary excretion rate is reported to be 240 $\pm$ 55 ng per min as compared to baseline 10 $\pm$ 4 ng per min. [J. Allerg. 46: 336-339, 1970].

Additional PK information through Medline Search (1990-1997) were submitted 02/24/97 upon the Agency's request. The results that were reported by the authors are summarized below:

1. After IV infusion of Epi at 0.01, 0.06, 0.10, 0.14, and 0.20 μg/kg/min for 30 min to 16 normal healthy volunteers, 1) mean (± standard deviation) steady-state arterial plasma Epi levels (at 28th min during infusion) were increased from baseline, 0.29 (±0.24), to 1.75 (±0.44), 8.06 (±1.84), 12.2 (±1.47), 17.6 (±5.95), and 23.9 (±4.49) nmol/liter and those for venous plasma levels were baseline, 0.28 (±0.26), to 1.40 (±0.70), 5.08 (±1.86), 8.50 (±1.48), 12.5 (±1.70), and 19.3 (±4.14) nmol/liter, 2) the corresponding mean total clearance values obtained from arterial and venous blood were independent to rates of infusion (0.06 to 0.20 μg/kg/min) or steady-state plasma levels and they were calculated to be 49 (± 15), 52 (±8), 58 (±21), and 53 (±12) ml/kg/min from arterial data and 92 (± 50), 76 (±14), 70 (±13), and 66 (±15) ml/kg/min from venous data, 3) mean extraction ratio [(arterial-venous)/arterial plasma level x 100%] was calculated to be around 27%, and 4) similar results were obtained for norepinephrine (Nepi). [Eur. J. Clin. Pharmacol. (Germany) 43(3): 245-249, 1992].

2. After IV infusion of Epi at 0.03 to 0.20 μg/kg/min to critically ill children, 1) mean steady-state venous plasma level was 22.0 ± 7.5 nmol/liter (normalized to infusion rate of 0.1 μg/kg/min) and 2) the corresponding total clearance was independent to rates of infusion (29.3 ± 16.1 ml/kg/min) [Crit. Care Med. (US) 21(1):111-117, 1993].

3. After IV infusion of ^{3}H-Nepi to subjects, 1) steady state was reached at 12 min post infusion, 2) around 95.7 ± 0.7% was extracted from arterial plasma across hepatosplanchnic circulation and 78.9 ± 1.4% across coronary circulation, 3) its mean total clearance from arterial plasma was calculated to be around 2.3 liter/min, and 4) uptake into, storage in, and release from sympathetic nerves (trace recycling) was found to be around 5% compared to steady-state plasma levels. [Am. J. Physiol. (US) 261(4 Pt 1): E505-515, 1991].

4. After IV infusion of ^{3}H-Nepi to normotensive and untreated hypertensive black and white male subjects receiving high (200 meqi) and low (20 meqi) dietary sodium, 1) dietary sodium and blood pressure had no effects on the PK of ^{3}H-Nepi and 2) blacks appear to have significantly higher clearance value for Epi. [Life Sci. (UK) 49(6);427-433, 1991]

5. After IV infusion of ^{3}H-Nepi to 12 normal subjects at baseline and with lower body negative pressure (LBNP) of -15 mmHg, 1) mean arterial plasma levels of Nepi increased significantly, 22-25%, during LBNP compared to baseline

infusion, 2) corresponding mean total clearance values decreased significantly, 12-19%, 3) cardiac output also decreased significantly, 15-19%, and 4) therefore, the increase in arterial plasma Nepi levels was due to the decrease in cardiac output with resultant decrease in its total clearance. [Am. J. Physiol. (US) 260(5 Pt 2): H1708-1712, 1991].

6. After administration of ^{3}H-Epi and ^{3}H-Nepi to healthy subjects, 1) 51 ± 3% of plasma Epi was extracted during one pass through the coronary circulation and 2) significant higher extraction value, 78 ± 1%, was found for plasma Nepi. In patients with cardiovascular disorders, the extraction ratios were found to be 34 ± 3% an 63 ± 2% for Epi and Nepi, respectively. For subjects receiving desipramine to block neuronal uptake, the mean extraction ratios decreased to ranges of 12 to 28% and 20 to 49% for Epi and Nepi, respectively. The authors concluded that the neuronal uptake/removal of circulating Epi was 44-64% less avidly than that of Nepi. [J. Clin. Endocrinol. Metab. (US) 70(6):1710-1720, 1990].

7. After a 2-hr IV infusion of ^{3}H-Nepi to normal subjects, mildly depressed or absent renal function, 1) its mean total clearance in normals was calculated to be 1.5 ± 0.1 liter/min, 2) after infusion stopped, plasma ^{3}H-Nepi followed a pattern of two exponential decay with a mean terminal half-life ($T_{1/2}$) of 63 min, and 3) mean total clearance of Nepi decreased 20% and 40% in mildly renal failure and in patients with hemodialysis, respectively and mean $T_{1/2}$ values increased accordingly when compared to those for normal subjects. [Kidney Int. (US) 37(5):1357-1362, 1990].

8. In vitro equilibration between read blood cell (RBC) and plasma for Epi or Nepi was conducted. The results showed that for Epi, 1) mean ratio of RBC/plasma for Epi was estimated to be 3.21 ± 0.85, 2) the mean ratio decreased (to 1.26 and 1.19) as plasma concentrations increased, 3) the influx/efflux is a reversible process, and 4) the equilibration between two compartments was not instantaneous. For Nepi, 1) the R/P ratio was 0.91 ± 0.29, 2) it did not changed (0.92-0.94) as plasma Nepi levels increased, 3) the influx/efflux process is also reversible, and 4) a similar delay in equilibration was observed. [J. Cadiovasc. Pharmacol. (US) 23(4):525-531, 1994].

9. In vitro protein binding (f_b) of Epi and Nepi in plasma of healthy volunteers and Type I and II diabetic patients was conducted. The results showed that 1) the f_b values in these patients were not significantly different from that of healthy subjects (≈29% for Epi and ≈32% for Nepi) and 2) the f_b values of Ep and Nepi were correlated with albumin levels. [Eur. J. Clin. Pharmacol. (Germany) 43(3):265-268, 1992].

RECOMMENDATION:

The literature articles for PK of Epi that were submitted on 12/05/96 and 02/24/97 by Bayer for NDA 20-800 (— Epi injection USP, 1:1000) have been reviewed by OCPB/DPE II. It should be noted that variations in the reported PK parameters were found among different studies. They are acceptable provided that the assay methodologies are validated. Finally, OCPB/DPE II is of the opinion that the above PK information provided is very limited, yet it is helpful for better understanding the PK of Epi. However, due to the emergency use of Epi injection product, the above cited PK information is less pertinent to the subject of approval for this NDA. Therefore, a revision/update of its labeling is not attempted.

LSI

06/23/97
Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD/FT initialed by Dale P. Conner, Pharm.D. LSI

cc: NDA 20-800, HFD-570 (Nicklas, Toyer), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), CDR (B. Murphy).