CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209359Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation
and Research
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

Memorandum

Date:	April 24, 2017
From:	Rama Dwivedi, Ph.D. Pharmacologist
Through:	Thomas Papoian, PhD. Supervisory Pharmacologist
To:	NDA 209359 (Epinephrine Injection USP, 1mg/mL, Abboject Syringe™)
Indication:	Intravenous infusion for the treatment of hypotension associated with septic shock
Subject:	Safety Evaluation of Sodium Metabisulfite in Epinephrine Drug product (0.46 mg/mL)
Applicant:	Hospira (a Pfizer Company)
RLD:	NDA 205029 (Epinephrine, approved on July 29, 2014, DCRP)

Background Information

Hospira's New Drug Application (NDA) for Epinephrine Injection USP, 1mg/mL, Abboject Syringe™ is in accordance with 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The basis for this submission is the reference listed drug (RLD): Belcher Pharmaceutical's NDA 205029 Epinephrine Injection USP, approved on July 29, 2014. The active moiety, strength administered to the patient, indication, route of administration and dosage form are the same as the RLD (Belcher Pharmaceutical's NDA 205029 Epinephrine). The composition of Hospira's drug product differs from the RLD that it contains 0.46 mg/mL Sodium Metabisulfite, NF (Table 1). The present review is to determine if level of sodium metabisulfite (0.46mg/mL) in Hospira's drug product (epinephrine) is safe for human use.

Table 1 Comparison of Hospira's Epinephrine Injection USP and Belcher Pharmaceutical's Epinephrine Injection USP

Ingredients	Drug Product	
	Belcher Pharmaceuticals Epinephrine Injection USP (1 mg/mL) (NDA 205029)	Hospira Epinephrine Injection USP 0.1 mg/mL
Active Ingredient	1 mg/mL Epinephrine (b) (4) (b) (4)	0.1 mg/mL Epinephrine USP
Sodium Chloride USP	9 mg/mL	8.16 mg/mL
Hydrochloric Acid USP	q.s.	NA
(b) (4)		
Sodium Metabisulfite NF	NA	0.46 mg/mL
Citric Acid USP	NA	2.13 mg/mL
Sodium Citrate Dihydrate USP	NA	0.41 mg/mL
Fill Volume	1 mL	10 mL

NF=National Formulary; q.s.=quantity sufficient; USP=United States Pharmacopeia.

Sodium Metabisulfite (0.46 mg/mL)

CAS Number 7681-57-4

Other Name(s) Sodium pyrosulfite and Sodium disulfite

Molecular Formula $Na_2S_2O_5$

Molecular Weight 190.107 g/mol

Structure or Biochemical Description

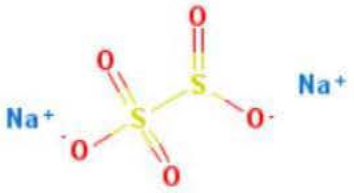

Figure 1: Sodium bisulfite (Pubchem)

Pharmacologic Class (b) (4)

Safety Evaluation of Sodium Metabisulfite

In 1982, sulfur dioxide, Sodium Sulfite, Sodium and Potassium Bisulfite, and Sodium and Potassium Metabisulfite were classified "generally recognized as safe" (GRAS) by the FDA. The

GRAS status was supported by an evaluation by the Federation of American Societies for Experimental Biology (FASEB).

By October 1986, FDA had received 767 reports of adverse reactions following ingestion of sulfites as preservatives on fresh fruits and vegetables, in packaged foods, shrimp, and alcoholic beverages. FDA analysis of 22 deaths allegedly associated with sulfite ingestion determined that 9 fatalities (all severe asthmatics) were probably and 5 fatalities (also asthmatics) were possibly due to sulfite ingestion (FDA1986).

These instances prompted a reevaluation of the GRAS status (FASEB 1985). The Committee concluded that there was no evidence that sulfite agents were a hazard "for the majority of the population." However, "for the fraction of the public that is sulfite sensitive," evidence was available to suspect that these agents were a "hazard of unpredictable severity to such individuals when they are exposed to sulfite agents in some foods at levels that are now current and in the manner now practiced."

Based on the new evaluation, FDA required that packaged sulfited foods that contain ≥10 ppm sulfite must list it on the ingredient label. GRAS status was revoked for use of sulfating agents on fresh fruits and vegetables (FDA 1986). The only produce exempt from the ban are precut or peeled (not whole raw) potatoes and grapes (Fisher 1997).

General Toxicity

The acute oral LD50 was 1131 and 1903 mg/kg for female and male rats, respectively (Eastman Kodak Co. 1980). Til et al. (1972a) reported that anemia developed in mice that had been dosed with ≥2% Sodium Metabisulfite for 10 to 56 days; increased hematopoiesis and splenomegaly were observed with doses ≥4%.

Hemorrhagic erosions, inflammation, and necrosis of the stomach were observed in rats fed 4%, 6%, or 8% Sodium Metabisulfite. In a review, Walker (1985) noted that the principal finding was local gastric irritant effects without systemic toxicity. Vitamin B12 deficiency was considered a possible contributor to the development of anemia.

A single exposure to low concentrations of a Sodium Sulfite fine aerosol produced dose-related changes in the lung capacity parameters of guinea pigs. A 3-day exposure of rats to a Sodium Sulfite aerosol (particle size of ~1 μm) produced: mild pulmonary edema following exposure to 5 mg/m3, and irritation of the tracheal epithelium with 15mg/m3. Severe epithelial changes were observed in dogs exposed for 290 days (Takenaka et al. 1990) to 1 mg/m3 of a Sodium Metabisulfite aerosol (MMAD of 0.63 μm).

Sodium Bisulfite (tested at 38%) and Sodium Metabisulfite (undiluted) were not irritants to rabbits following occlusive exposures of ≤24 h. Sodium Metabisulfite (tested at 50%) was irritating to guinea pigs following repeated exposure.

Numerous oral-dose reproductive and developmental toxicity studies have been conducted. In rats, Sodium Sulfite heptahydrate at large doses (up to 3.3 g/kg) produced fetal toxicity but not teratogenicity (FDA 1972b, 1974b). Sodium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite were not teratogenic for mice, rats, hamsters, or rabbits at doses up to 160 mg/kg.

IARC (1992) concluded that Sodium Sulfite, Sodium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite were not classifiable (group 3) as to their carcinogenicity for humans.

Calculation for the exposure of Sodium Metabisulfite in Hospira's Epinephrine Drug Product

Levels of sodium metabisulfite in Epinephrine (NDA 209359)
= 0.46 mg/ml (=10X solution).

50 ml of this 10X epinephrine solution at 0.1 mg/ml will be mixed in a 500 ml dextrose-containing solution to give a final concentration of 0.001 mg/ml (=1 mcg/ml).

Patients may be given up to 5000 ml of this final solution = 50 ml of the 10X solution that contains sodium metabisulfite at 0.46 mg/ml
= **23 mg sodium metabisulfite per day**.

Hospira's own Dopamine HCl product (40 mg/mL Injection, USP; NDA 18132) contains sodium metabisulfite at 9 mg/ml.

According to their label:

the maximum daily dose of epinephrine is 50 mcg/kg/min x 70 kg x 60 min/hr x 24 hours/day = 5040000 mcg /day = 5040 mg epinephrine/day
= **1134 mg sodium metabisulfite per day**.

The lowest strength dopamine they market to give the highest volume administered is 40 mg/ml = 126 ml of dopamine solution (=5040 / 40) x 9 mg/ml sodium metabisulfite = **1134** mg sodium metabisulfite (=126 x 9). When compared to **23** mg sodium metabisulfite in epinephrine, 1134 mg sodium metabisulfite in dopamine = **49.3X** higher (1134 / 23).

Recommendations
The level of sodium metabisulfite (23 mg) in Hospira's proposed Epinephrine drug product as per day use is 49.3 times (1134 / 23) lower than the previously approved DOPA hydrochloride (NDA 18132) from the same company (Hospira) and is reasonably safe for human use from Pharm/Tox perspective.

The applicant's reference to the following two other drug products containing sodium metabisulfite are not needed to support its safety:

1. PlenamineTM 15% Amino Acids Injection; B. Braun Medical Inc., ANDA 091112.

2. Dobutamine Hydrochloride in 5% Dextrose Injection (DOBUTamine, 250 mg/250 mL, Baxter Healthcare Corporation, NDA 020255.

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