CENTER FOR DRUG EVALUATION AND RESEARCH

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Memorandum

Date: March 20, 2013

From: Thomas Papoian, PhD, DABT
Supervisory Pharmacologist

To: NDA 203496 (Treprostinil diethanolamine)

Subject: Listing of diethanolamine (diolamine) as known by the State of California to cause cancer (according to Proposition 65) - June 22, 2012

1. Background

Treprostinil diethanolamine (NDA 203496; United Therapeutics Corp.), an analogue of prostacyclin (PGI_2) with potent vasodilatory as well as platelet antiaggregatory effects, was submitted to this Division (DCRP) on Dec. 24, 2011, as a sustained release oral tablet for the treatment of pulmonary arterial hypertension (PAH). Treprostinil had been approved previously for the treatment of PAH by the subcutaneous, intravenous, and inhalational routes of administration. The current oral formulation is different from the previous sodium salt formulations in that it uses the diethanolamine salt (b) (4)

On March 7, 2013, this reviewer was notified by Mr. Dan Brum (DCRP Regulatory Project Manager) that on June 22, 2012, diethanolamine (CAS No. 111-42-2) was listed by the Office of Environmental Health Hazard Assessment (OEHHA) of the State of California as a chemical known to cause cancer. During the course of the NDA review cycle, the sponsor coincidentally changed the name of the drug to treprostinil diolamine, one of several commonly used chemical names for diethanolamine.

Other chemical names for diethanolamine include:

- Diolamine
- Bis(hydroxyethyl)amine
- N,N-Bis(2-hydroxyethyl)amine
- 2,2'-Dihydroxydiethylamine
- β,β'-Dihydroxydiethylamine
- N-Ethylethanamine
- 2-[(2-Hydroxyethyl)amino]ethanol

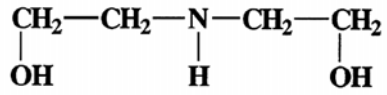
- 2,2'-Iminobisethanol
- Iminodiethanol

Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986, was enacted as a California State ballot initiative in November 1986. The Proposition was intended to protect California citizens and the state's drinking water sources from chemicals known to cause cancer, birth defects or other reproductive harm, and to inform citizens about exposures to such chemicals. Proposition 65 requires the Governor to publish, at least annually, a list of chemicals known to the State to cause cancer or reproductive toxicity.

The safety, particularly carcinogenic risk, of treprostinil diethanolamine (now diolamine) when given to PAH patients at recommended doses is reviewed below.

2. Toxicity Profile of Diethanolamine

Diethanolamine



CAS No. 111-42-2
Chemical formula: $C_4H_{11}NO_2$
MW: 105.14

Diethanolamine (DEA) is an organic compound synthesized from a reaction of ethylene oxide and ammonia. In contrast to naturally-occurring ethanolamine (monoethanolamine; MEA), a common head group for cell membrane phospholipids that is synthesized endogenously, diethanolamine is not known to occur naturally. However, it is widely used in the preparation of diethanolamides and diethanolamide salts of long-chain fatty acids, such as coconut oil diethanolamine condensates (cocomide DEA), that are formulated into soaps, detergents, cosmetics, shampoos, hair conditioners, and in many other industrial uses (reviewed in IARC, 2012). For example, diethanolamine as a contaminant can constitute up to 18% of cocomide DEA.

CFSAN/FDA permits use of diethanolamine as a component of adhesives in food packaging and as an indirect food additive when food comes into contact with paper products containing diethanolamine (21 CFR Parts 175.105, 176.170, 176.180).

A search of currently approved drug labels did not find any drugs stating that they contained diethanolamine or diolamine. However, according to the FDA's database of inactive ingredients used in approved brand-name and generic drug products (i.e., Inactive Ingredient Guide), 1.5% aqueous diethanolamine solutions are used as solvents for drugs given intravenously, in topical creams at 0.3%, and in ophthalmic solutions.

Animal toxicity studies with diethanolamine have been conducted going back many decades (reviewed in Mathews et al., 1997; IARC 2000, 2012a). In 1992, the National Toxicology

Program (NTP) conducted 13-week subchronic toxicity studies with diethanolamine in B6C3F$_1$ mice and F344/N rats following dermal and oral (via drinking water) administration (Melnick et al., 1994a and 1994b). Doses administered were as follows:

- Mice:
  - Drinking water = 630-10,000 ppm = 100-1700 mg/kg
  - Dermal (5X/wk) = 80-1250 mg/kg
- Rats:
  - Drinking water = 160-5000 ppm = 15-440 mg/kg
  - Dermal (5X/wk) = 32-500 mg/kg

Results (as stated in the PubMed abstracts) showed that diethanolamine induced dose-dependent toxic effects in multiple organs in both species (Table 1).

Table 1

Results of 13-Week Toxicity Studies with Diethanolamine in Mice and Rats
(Melnick et al., 1994a and 1994b)

Species	**Tissue**	**Effects**	**NOAEL Dose Achieved? (Yes/No)**
Mouse	Liver	Hepatocellular cytological alterations and necrosis; multiple hepatocyte changes, including enlarged cells that were frequently multinucleated, increased nuclear pleomorphism, increased eosinophilia and disruption of hepatic cords	No
	Kidney	Nephropathy and tubular epithelial necrosis in males	Yes
	Heart	Cardiac myocyte degeneration	Yes
	Skin	Site of application: ulceration, inflammation, hyperkeratosis, and acanthosis	No
Rat	Blood	Poorly regenerative, microcytic anemia	No
	Kidney	Increased weight, tubular necrosis, decreased renal function, and/or tubular mineralization	No
	Brain and spinal cord	Demyelination	Yes
	Testis	Degeneration of the seminiferous tubules	Yes
	Skin	Site of application: ulceration, inflammation, hyperkeratosis and acanthosis	No

The predominant target organs of toxicity were liver in mice, and kidney in both species, the two tissues with the highest concentrations (up to one-third of the administered oral dose) of diethanolamine. Interestingly, no liver lesions were seen in rats by either route of exposure. In rats, diethanolamine produced greater toxicity when given in the drinking water when compared to topical application. This was attributed largely to the limited dermal absorption of the

chemical through rat skin. However, little difference in toxicity between the two routes (oral or dermal) was noted in mice, which was thought to be due to thinner skin in mice vs. rats.

Subsequent absorption and bioavailability studies in mice and rats were conducted using oral, dermal and intravenous dosing in rats, and dermal dosing only in mice (Mathews, et al., 1997). Dermal application of diethanolamine used a wire mesh to prevent oral absorption through grooming, in contrast to the NTP carcinogenicity studies were grooming of the applied area was allowed. Results showed that diethanolamine is 100% absorbed from the GI tract, absorption through skin increased with increasing doses (i.e., diethanolamine enhances its own absorption), absorption of total dose through thinner mouse skin (26.8-58.1%) is greater than thicker rat skin (2.9-16.2%), and that diethanolamine has significant potential for bioaccumulation following repeated exposure, a reflection of diethanolamine's long half-life (7 days for various tissues and up to 54 days in blood). Published exposure estimates of diethanolamine from human daily use of shampoo products (e.g., cocomide DEA) varied widely from 8-200 mg/kg/day to 0.2-2.0 µg/kg/day (reviewed in IARC, 2012a).

Diethanolamine is excreted essentially unchanged, whereas the naturally-occurring ethanolamine is converted to CO_2 (10-15%), with the remainder incorporated into phospholipids. The toxicity of diethanolamine was thought to be due to high tissue accumulation, and incorporation and accumulation of *O*-phosphorylated and *N*-methylated diethanolamine into aberrant phospholipids resulting in alterations in membrane structure and function (Mathews, et al., 1997; reviewed in IARC, 2012).

Due to this reported toxicity in subchronic animal studies and continuing widespread human exposure, particularly in the industrial workplace and through skin care products, diethanolamine was selected by NTP for carcinogenic evaluation (NTP, 1999). Male and female $B6C3F_1$ mice and F344/N rats were administered diethanolamine in ethanol dermally 5 days/week for 2 years. Mice received diethanolamine at 0, 40, 80, or 160 mg/kg, and rats received 0, 16, 32, or 64 mg/kg (males) or 0, 8, 16, or 32 mg/kg (females).

Other than irritation at the site of application, no significant pathologic findings or increased tumors were seen in rats, presumably due to limited dermal absorption of diethanolamine through rat skin.

In mice, however, incidences of the following tumors, when compared to vehicle controls, were either significantly increased or showed a positive trend:

Male mice:

- Hepatocellular adenoma and hepatocellular adenoma and carcinoma (combined) in all dose groups (significantly increased).
- Hepatoblastoma in mid-dose (80) and high-dose (160 mg/kg) groups (significantly increased).
- Renal tubule adenoma (positive trend).

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