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APPLICATION NUMBER:

21-780

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

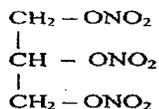
(505(b)(2) NDA)

NDA number: 21-780
Date of submission: Jun 17, 2004
Sponsor : NovaDel Pharma Inc.
25 Minneakoning Rd, Flemington, NJ

Reviewer : Belay Tesfamariam, PhD
Division : Cardio-Renal Drug Products, HFD-110
Review completion date: 10/22/04

Drug:

Trade name: Nitroglycerine lingual spray, 0.4 mg
Generic name: Nitroglycerine / Glycerol trinitrate / Nitroglycerol
Chemical name: 1,2,3-propanetriol trinitrate
CAS number: 55-63-0
Molecular formula: C₃H₅N₃O₉
Molecular weight: 227.09
Structure:



Relevant INDs/NDAs/DMFs: NDA 18-705

Nitrolingual[®] Pump spray 0.4 mg/spray (First Horizon Pharmaceuticals),
Nitrostat[®] sublingual nitroglycerin tablet (Southward Pharmaceuticals)

Drug class: Vasodilator

Indication: Acute relief and acute prophylaxis of angina pectoris due to coronary artery disease

Clinical formulation: Nitroglycerin lingual spray 0.4 mg/spray. ~~metered~~ metered sprays)
Inactive ingredients: caprylic/capric diglycerol succinate, peppermint oil, L(-)-menthol, n-butane.

Route of administration: Spray droplets into open mouth.

Proposed use: For acute relief and acute prophylaxis of angina pectoris.

Summary

I. Background :

This submission is a request for approval of the 15 mL (1.5 mL dose size) aerosol bottle of Nitroglycerin lingual spray (0.4 mg/spray). The product labeling is supported by data from published findings and clinical studies conducted by NovaDel Pharma Inc. and from other sources. The proposed labeling remains consistent with approved labeling for a similar nitroglycerin lingual spray product, Nitrolingual[®] pumpspray (First Horizon Pharmaceuticals) and the recently approved labeling for the sublingual nitroglycerin tablet Nitrostat[®] (Southward Pharmaceuticals, Inc.). The proposed labeling is typical for class labeling and reflect the current understanding of the mechanism of action and benefits and risks associated with nitroglycerin therapy for the acute relief and acute prophylaxis of anginal attacks. Preclinical and clinical information are extensively cross-referenced. There are no new preclinical tests submitted as part of this NDA.

The active ingredient, strength, dosage form and route of administration are identical to that of NDA 18-705 although the formulations differ in which dehydrogenated alcohol is a component of the NDA 18-705 product, whereas butane is used in this application. Nitroglycerin lingual spray is expected to have a safety and efficacy profile similar to that of currently marketed formulations, and the labeling for the aerosol spray closely resembles the labeling of similar nitroglycerin lingual spray product.

II. Recommendations

A. Recommendation on Approvability: Approvable

B. Recommendation for Nonclinical Studies: None

C. Recommendations on Labeling:

Updates based on recent review of the literature:

- Nitroglycerin forms nitric oxide (NO) which activates guanylate cyclase and increases cyclic GMP which is then degraded by phosphodiesterases (PDE). Thus, inhibitors of PDE could potentiate the hypotensive effects of nitroglycerin.

- Nitroglycerin was found to have reverse mutation activity in the *Salmonella typhimurium* strain TA1535 (Ames assay). A similar mutation in *S. typhimurium* strain TA1535 was reported for other NO donors indicating that NO may be responsible for the observed mutations. There was no evidence of chromosomal aberrations

observed in kidney cells or lymphocytes of rats after oral nitroglycerin dosing of approximately 60 mg/kg/day for five weeks followed by 230 mg/kg/day for eight weeks, in the kidney cells or bone marrow erythrocytes of rats that received 360 mg/kg/day (males) or 430 mg/kg/day (females) for 2 years.

- Lingual spray delivery of nitroglycerin may provide rapid onset of action because of increased surface area exposure. However, the possibility that lingual spray nitroglycerin may be inadequately absorbed and efficacy decreased in subjects with dry oral mucous membranes.

- Nitrate tolerance as a result of repeated administration is possible. As with other nitroglycerin formulations, a decrease in therapeutic effect may result from frequent and repeated use of nitrates.

III. Summary of Nonclinical Findings:

A. Brief Overview of Pharmacology:

The principal pharmacological action of nitroglycerin, an inorganic nitrite, is relaxation of vascular smooth muscle. Although venous effects predominate, nitroglycerin produces dilation of both arterial and venous beds in a dose-related manner. Dilation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood, decreases venous return to the heart, and reduces left ventricular end-diastolic pressure (preload). Nitroglycerin also produces arteriolar relaxation, thereby reducing peripheral vascular resistance and arterial pressure (afterload), and dilates large epicardial coronary arteries. Therapeutic doses of nitroglycerin may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, and pulmonary and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased and a more favorable supply-demand ratio can be achieved.

Mechanism of Action:

Nitroglycerin forms free radical NO[•] which activates guanylate cyclase, resulting in an increase of guanosine 3',5'-monophosphate (cyclic GMP) in smooth muscle and other tissues. This eventually leads to dephosphorylation of myosin light chains, which regulate the contractile state in smooth muscle, and result in vasodilatation.

B. Pharmacokinetics:

Nitroglycerin is rapidly absorbed following lingual spray administration. A liver reductase enzyme is of primary importance in the metabolism of nitroglycerin to glycerol di- and mononitrate metabolites and ultimately to glycerol and organic nitrate. Known sites of extrahepatic metabolism include red blood cells and vascular walls. In addition to nitroglycerin, 2 major metabolites, 1,2- and 1,3-dinitroglycerin are found in plasma. The mean elimination half-life of both 1,2- and 1,3-dinitroglycerin is 40 minutes. The 1,2- and 1,3-dinitroglycerin metabolites have been reported to possess approximately at least 10% of the pharmacological activity of nitroglycerin, whereas glycerol mononitrate metabolites of nitroglycerin are essentially inactive.

The half-life of disappearance of the nitroglycerin ($t_{1/2\beta}$) (5.16 minutes) was significantly less than the half-life of appearance ($t_{1/2\alpha}$) of the 1,2- and 1,3-dinitroglycerin metabolites suggesting the possibility of an additional compartment into which the nitroglycerin disappears from plasma prior to being metabolized into the dinitroglycerin metabolites.

Nitroglycerin is well absorbed in rodents, dogs, and monkeys and is mainly excreted in the urine with significant fecal excretion seen only in mice. Metabolism of GTN to dinitroglycerins (GDN) and mononitroglycerins (GMN) metabolites is rapid in all species, being most complete in mice. The risk of toxicity is minimal when GTN is administered intermittently as one or two doses, as it would be in the clinical management of angina.

C. Brief Overview of Genetic Toxicology, Carcinogenicity, and Reproductive Toxicology:

Genetic Toxicology:

In vitro Bacterial reverse mutation assay:

Glyceryl trinitrate (GTN) is a mutagen in the *Salmonella typhimurium* strain TA1535 in the presence of rat liver S9 fraction at concentrations of 0.5 to 1.5 mg/plate (EPA 2003). Reproducible mutagenicity in other *S. typhimurium* strains (TA100, TA102, TA1538, TA1975) was not observed. A similar mutational spectrum in the *S. typhimurium* strain TA1535 was reported with a complex of spermine which releases NO indicating that NO is responsible for the observed mutations (Mutat Res. 298(3):187, 1993).

***In vitro* chromosomal aberration assay in CHO:**

No *in vitro* mutagenic activity of nitroglycerin was observed in Chinese hamster ovary KI cells.

***In vivo* chromosomal aberration assay:**

No evidence of chromosomal aberrations was seen in the kidney cells or lymphocytes of rats after oral dosing at approximately 60 mg/kg/day for five weeks followed by 230 mg/kg/day for eight weeks, or in the kidney cells or bone marrow erythrocytes of rats that received 360 mg/kg (males) or 430 mg/kg (females) per day for 2 years, or in the kidney cells or lymphocytes of dogs that received 1 mg/kg/day for four weeks and 5 mg/kg/day for a subsequent nine weeks (EPA 2003).

There was no evidence of mutagenicity in an *in vivo* dominant lethal assay of male rats treated with oral doses of up to about 363 mg/kg/day or in *ex vitro* cytogenic tests of rat and dog tissues.

Rat dominant lethal assay: There was no evidence of genetic damage to sperm based on embryo viability in females inseminated by males which received up to 363 mg/kg/day of dietary GTN for 13 weeks prior to mating.

Carcinogenicity:

Carcinogenicity studies with sublingually administered or lingual spray nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At the highest dose, the incidences of hepatocellular carcinomas was 52% compared to 0% in untreated controls. Incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Reproductive and developmental toxicology:

In a 3-generation reproduction study, rats received dietary nitroglycerin at doses up to about 408 mg/kg/day (males) to 452 mg/kg/day (females) for 5 months (females) or 6 months (males) prior to mating of the F₀ generation with treatment continuing through successive F₁ and F₂ generations. The highest dose was associated with decreased food intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F₀ generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and

aspermato genesis in the high dose males. No reduction in male fertility was observed in the rat dominant lethal assay when males were fed up to 363 mg/kg/day of GTN for 13 weeks prior to mating, and gravid females autopsied for embryo viability.

Pregnancy category C:

Animal reproduction and teratogenicity studies have not been conducted with Trade name or nitroglycerin sublingual tablets. It is also not known whether Trade name can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. A teratogenicity study was conducted in the third mating of F₀ generation female rats administered dietary nitroglycerin for gestation days 6 to 15 at dose levels used in the 3-generation reproduction study. In offspring of the high dose nitroglycerin group, increased incidence of diaphragmatic hernias and decreased hyoid bone ossification were seen. The latter finding was considered to reflect delayed development rather than a potential teratogenic effect, thus indicating no clear evidence of teratogenicity of nitroglycerin.

D. Nonclinical Safety Issues Relevant to Clinical Use:

- Nitroglycerin forms nitric oxide which activates guanylate cyclase and increases cyclic GMP which is then degraded by phosphodiesterases (PDE). Thus, inhibitors of PDE could potentiate the hypotensive effects of nitroglycerin.
- Nitrate desensitization as a result of repeated administration is possible. As with other nitroglycerin formulations, a decrease in therapeutic effect may result from frequent and repeated use of nitrates.

Reviewer _____
Belay Tesfamariam, PhD

Supervisor _____ Concurrency: Yes ___ No ___
Al DeFelice, PhD (see memo attached)

cc: Division files, HFD-110

**This is a representation of an electronic record that was signed electronically and
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/s/

Belay Tesfamariam
10/22/04 12:37:50 PM
PHARMACOLOGIST

Albert Defelice
10/28/04 11:42:56 AM
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Appears This Way
On Original