CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208424Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208424
Supporting document/s:	EDR
Applicant's letter date:	August 10, 2015
CDER stamp date:	August 10, 2015
Product:	Nitroglycerin Powder for sublingual use
Indication:	Acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease
Applicant:	G. Pohl-Boskamp
Review Division:	Division of Cardiorenal Products
Reviewer:	Philip Gatti, Ph.D.
Supervisor/Team Leader:	Thomas Papoian, Ph.D., D.A.B.T.
Division Director:	Norman Stockbridge, M.D., Ph.D.
Project Manager:	Bridget Kane

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208424 are owned by G. Pohl-Boskamp or are data for which [name of applicant] has obtained a written right of reference.
Any information or data necessary for approval of NDA 208424 that G. Pohl-Boskamp does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208424.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Nitroglycerin is a nitrate vasodilator indicated for relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.
G. Pohl-Boskamp has developed a formulation of nitroglycerin powder for sublingual administration. Each (b) (4) contains nitroglycerin powder with 400 mcg GTN per (b) (4) Glyceryl trinitrate (GTN) is a well-known nitric oxide donor and sublingual routes in particular have a well-established medicinal use throughout the world, with recognized efficacy in patients with angina pectoris and an acceptable level of safety. Hence, the product characteristics of GTN can be considered a well-established medicinal drug.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were performed for this application.

1.3 Recommendations

1.3.1 Approvability

Approvable from a pharmacology/toxicology perspective

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

8.1 Pregnancy

There have been no reports of any adverse developmental outcome(s) associated with maternal use of [Brand name]. Animal teratology studies have not been conducted with [Brand name]. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. A teratogenicity study was conducted in the third mating of F0 generation female rats administered dietary nitroglycerin for gestation day 6 to day 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 probably reflects delayed development rather than a potential teratogenic effect, thus indicating no clear evidence of teratogenicity of nitroglycerin. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to pregnant women only if clearly needed.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenesis studies with sublingual 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 high dose, the incidences of hepatocellular carcinomas in both

sexes were 52 % vs. 0 % in controls, and 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. Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. There was no evidence of mutagenicity in an in vivo dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in in vitro cytogenic tests in rat and dog tissues and for chromosomal aberration in Chinese hamster ovary cells. In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for six months prior to mating of the F0 generation with treatment continuing through successive F1and F2generations. The high dose was associated with decreased feed 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 aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

2 Drug Information

2.1 Drug

CAS Registry Number 55-63-0

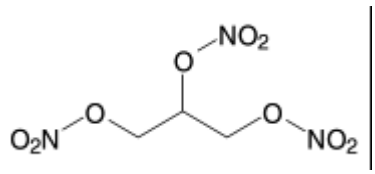
Generic Name (b) (4)

Code Name none

Chemical Name (b) (4)

Molecular Formula/Molecular Weight $C_3H_5N_3O_9$; 227.087 g/mol

Structure or Biochemical Description



Pharmacologic Class Vasodilator

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 18705

2.3 Drug Formulation

Table 1. Drug formulation

Ingredient	Quantity [mg]	Standard	Function
Active substance			
Nitroglycerin	8.0		
	0.4		active ingredient
Excipients			
Medium chain triglycerides[2]		USP - NF	
Isomalt		USP - NF	
Anhydrous dibasic calcium phosphate[3]		USP - NF	
Oleoyl Polyoxylglycerides		USP - NF	
Peppermint oil		USP - NF	
Total	200		

2.4 Comments on Novel Excipients

All the inactive ingredients in this formulation are listed in the Inactive Ingredient Database (IID). All of them are qualified based on the data below:

1) Peppermint oil (CAS # 8006904)

   There is (b) (4) of this ingredient in each (b) (4)). In the Inactive Ingredient Database (IID), an oral capsule in application # 202644 (4/25/2013 approval date) had (b) (4) as the maximum potency.

2) Medium chain triglycerides

   There is (b) (4) of this ingredient in each (b) (4) In the IID, an oral capsule in application # 91356 (12/12/2014 approval date) had (b) (4) as the maximum potency.

3) Isomalt

   There is (b) (4) mg of this ingredient in each (b) (4) In the IID, an oral tablet, uncoated in application # 20747 (11/04/1998 approval date) had (b) (4) mg as the maximum potency.

4) Dibasic anhydrous calcium phosphate

There is (b) (4) of this ingredient in each (b) (4)
In the IID, an oral capsule in application # 78878 (06/05/2009 approval date) had (b) (4) as the maximum potency.

5) Lauroyl polyoxyglycerides

There is (b) (4) of this ingredient in each (b) (4)). In the IID, an oral capsule in application # 21612 (01/11/2006 approval date) had (b) (4) as the maximum potency.

Conclusion
Based on the IID, all inactive ingredients of NitroGo in NDA 208424 are qualified.

Table 2 Safety summary of inactive ingredients (excipients) in Nitroglycerin powder

Excipients	NDA 18-705		GTN oral powder	safety limit	conclusion
Units	[mg/1 puff]	[mg/3 puffs]	(b) (4)		
Medium chain triglycerides			(b) (4)	tox. uncritical	safe
Isomalt				tox. uncritical	safe
Anhydrous dibasic calcium phosphate				(b) (4)	safe
Oleoyl Polyoxylglycerides					safe
Peppermint oil				tox. uncritical	safe
					(b) (4)

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Patients with coronary artery disease who manifest angina pectoris. Drug will be administered by patient PRN.

2.7 Regulatory Background

Pohl-Boskamp has an approved NDA (NDA 18705) for the currently US marketed product to Nitroglycerin powder, namely Nitrolingual Pumpspray. In 2 meetings with the FDA (on January 22, 2013 and September 18, 2014) it was agreed that Pohl-Boskamp's NDA 18705 could be cross-referenced in the current Nitroglycerin powder NDA.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies have been performed or submitted.

3.2 Studies Not Reviewed

Not applicable

3.3 Previous Reviews Referenced

NDA 18705

4 Pharmacology

4.1 Primary Pharmacology

Nitroglycerin is an arteriolar and venodilator.

4.2 Secondary Pharmacology

Not performed

4.3 Safety Pharmacology

Not performed

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Not performed

5.2 Toxicokinetics

Not performed

6 General Toxicology

6.1 Single-Dose Toxicity

Not performed

6.2 Repeat-Dose Toxicity

Not performed

7 Genetic Toxicology

Not performed

7.4 Other Genetic Toxicity Studies

Not performed

8 Carcinogenicity

Not performed

9 Reproductive and Developmental Toxicology

Not performed

10 Special Toxicology Studies

Not performed

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

/s/

PHILIP J GATTI
12/21/2015

THOMAS PAPOIAN
12/21/2015
Concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208424 **Applicant: G. Pohl-Boskamp** **Stamp Date: 10 August 2015**

Drug Name: Nitroglycerin Powder for sublingual use **NDA/BLA Type: 505 b(2)**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The sponsor is referencing data from NDA 21134 for nonclinical data.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Literature to support the use of the excipients such as peppermint oil (b) (4) isomalt, medium chain triglycerides and anhydrous dibasic calcium phosphate have been provided.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		Sponsor is relying on extensive clinical experience with nitroglycerin for efficacy and safety. Also, the sponsor has submitted literature to qualify the excipients listed above. A clinical PK bridging study will be performed.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes__

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

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

None.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

APPEARS THIS WAY ON ORIGINAL

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

/s/

PHILIP J GATTI
09/28/2015

THOMAS PAPOIAN
09/28/2015
Concur.