CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208424Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA:	208424
Drug:	GoNitro (nitroglycerin) sublingual powder, 400 mcg per packet
Class:	Vasodilator
Applicant:	G. Pohl-Boskamp GmbH & Co. KG
Indication:	GoNitro is a nitrate vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.
Date of Submission:	06 August 2015
FDA Received Date:	10 August 2015
Approval date:	08 June 2015
PDUFA date:	10 June 2016

- **REVIEW TEAM**
  - Office of New Drugs, Office of Drug Evaluation I (ODE I)
    - Division of Cardiovascular & Renal Products (DCRP)
      - Norman Stockbridge, MD, PhD (Division Director)
      - Thomas Papoian, PhD (Team Leader, Pharmacology/Toxicology)
      - Philip Gatti, PhD (Pharmacology/Toxicology Reviewer)
      - Bridget Kane, MS (Regulatory Health Project Manager)
  - Office of Clinical Pharmacology (OCP)
    - Rajnikanth Madabushi, PhD (Cross-Discipline Team Leader – CDTL)
    - Venki ChithambaramPillai, PhD (Reviewer)
  - Office of Product Quality (OPQ)
    - Wendy Wilson-Lee, PhD (Branch Chief)
    - Mohan Sapru, PhD (Application Technical Lead – ATL)
    - Sithumalli Chandramouli, PhD (Drug substance)
    - Mariappan Chelliah, PhD (Drug product)
    - Jing Li, PhD (Biopharmaceutics)
    - Steven Hertz (Facilities)
    - Xuhong Li (Process)
  - Office of Surveillance and Epidemiology
    - Sarah Thomas, PharmD (DMEPA)
    - Janine Stewart, PharmD (DMEPA)
  - Office of Medical Policy
    - Office of Prescription Drug Promotion (OPDP)
      - Zarna Patel, PharmD
    - Patient Labeling
      - Karen Dowdy, RN, BSN (Instructions for Use)
  - Division of Pediatric and Maternal Health
    - Christos Mastroyannis, MD (Labeling review)

❖ BACKGROUND

The planned NDA 208424 submission was the subject of two Pre-NDA meetings held under IND 116608 (22 January 2013 and 18 September 2014). During the Pre-NDA meeting on 22 January 2013, the Division of Cardiovascular and Renal Products confirmed that to support their planned NDA submission, the applicant could:

- Rely on their own approved product, Nitrolingual Pumpspray (NDA 18705) to support the safety and efficacy of the sublingual powder
- Provide data from a pharmacokinetic bridging study to demonstrate the relative bioavailability of the new formulation when compared to the Registered Listed Drug (RLD), Nitrolingual Pumpspray

The pharmacokinetic bridging study (Study PL1302NL) was conducted under IND 116608 and found to be acceptable by the Division (Meeting minutes 7 October 2014) to support the submission of NDA 208424.

NDA 208424 was submitted on 6 August 2015 pursuant to section 505(b)(1) of the FD&C act and was received by the Division on 10 August 2015 and subsequently filed on 9 October 2015. The applicant is seeking approval for a new formulation, sublingual powder, of nitroglycerin (GTN) for the acute relief of an attack or prophylaxis of angina pectoris. The application was given a Standard Review with a PDUFA goal of 10 June 2016.

During the filing meeting on 23 September 2015, the review team initially thought that reliance on published literature would be needed to verify the safety of the excipients unique to GoNitro, making the application a 505(b)(2). However after further review, the pharmacology/toxicology team determined that the excipients could be verified using the Inactive Ingredient Database (IID), a public source of information. Therefore, a memorandum to file was written (22 October 2015) to document the Division's decision and rationale to file this application as a 505(b)(1) as originally intended by the applicant at the time of submission.

This NDA was reviewed by pharmacology/toxicology, OPQ and OCP. Several information requests were sent by OPQ and OCP during the review cycle. Both OPQ and OCP requested inspections (facilities and a biopharmaceutical site inspection for Study PL1302NL, respectively). In a review dated 10 November 2015 (Nkah), the Division of New Drug Bioequivalence Evaluation (DNDBE) recommended acceptance of Study PL1302NL data without an on-site inspection, stating "an inspection of the site will not be needed at this time" given the nature of the findings from the previous inspection.

By the end of the review cycle, the GoNitro review team concluded that 1) the safety of the excipients unique to GoNitro were acceptable, 2) the applicant's Chemistry, Manufacturing, and Controls procedures met the regulatory requirements for approval, 3) the manufacturing facilities were acceptable and 4) and the bioavailabity study (PL1302NL) supported the bridging of GoNitro to the applicant's approved Nitrolingual Pumpspray.

There were no post-marketing requirements/commitments issued and the application was recommended for approval by all reviewing disciplines.

❖ REGULATORY TIMELINE and GENERAL APPLICATION POINTS / MAJOR ISSUES

This section will cover general application milestones during the review cycle. The review of this application proceeded relatively smoothly, meeting all major 21st century review timelines.

- Pre-NDA Meeting: 22 January 2013 (minutes dated 5 February 2013)
- Pre-NDA Meeting: 18 September 2014 (minutes dated 7 October 2014)

- NDA 208424 Submitted: 6 August 2015
- NDA 208424 Received: 10 August 2015
- Filing Meeting: 23 September 2015
- Filing date: 9 October 2015
- 74-day Issues Letter with Comments: 21 October 2015
- Mid-cycle Meeting: 11 January 2016
- Facilities Inspection: 8 February - 11 February 2016
- Proprietary Name Granted: 1 June 2016
- PDUFA Date: 10 June 2016
- **Approval Letter**: 8 June 2016

User Fee
The user fee for this application was paid in full on 5 August 2015, prior to the submission of the application (ID 3015300).

Pediatric Review Committee (PeRC)
The PeRC meeting to discuss this application was held on 4 May 2016. The PeRC and the Division agreed with the applicant that angina pectoris due to coronary artery disease does not exist in pediatric patients and therefore studies with GoNitro in pediatric patients would be impossible and highly impractical. Therefore, a full pediatric waiver was granted for this application.

Trade name
GoNitro was deemed conditionally acceptable on 1 June 2016 after being resubmitted for review on 27 May 2016. This trade name was initially denied on 16 November 2015 due to potential confusion with another product under review. Per DMEPA, this potential conflict is no longer of concern.

Review Status
NDA 208424 was considered a Standard Review (10-month review).

Facilities
The Office of Process and Facilities has recommended overall approval for the manufacturing facilities (refer to OPQ review dated 23 May 2016).

Advisory Committee
An Advisory Committee (AC) Meeting was not convened for this application as the safety and efficacy of the active moiety is well-established and no issues arose during the review cycle that needed AC review.

❖ LABELING REVIEW

Labeling discussions began 25 April 2016 and concluded on 19 May 2016. Please see the final label appended to the approval letter.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the review team members, organized by role and/or discipline.

Divisional Memorandum (4 June 2016)
Dr. Stockbridge's memo conveys the Division's recommendation to approve NDA 208424 and concurrence with the CDTL's (Madabushi) recommendation for approval of NDA 208424.

Cross-Discipline Team Leader (CDTL) Memorandum (3 June 2016)
Recommendation: Approval

Dr. Madabushi summarized the basis of approval for NDA 208424 noting the acceptability of the pharmacokinetic bridging study (study P1302NL), the resolution of all identified CMC deficiencies during the review cycle, as well as qualification of all excipients of GoNitro sublingual powder. He reiterated the applicant's reliance on NDA 18705 to support safety and efficacy of the proposed sublingual powder formulation. Dr. Madabushi agreed with the primary reviewers' recommendation to approve NDA 208424.

Clinical Pharmacology Review (1 June 2016)
Recommendation: Approval
Dr. Chithambaram Pillai reviewed study P1302NL and concluded that the pharmacokinetic bridging between GTN oral powder and the RLD, Nitrolingual Pumpspray formulation is acceptable.

Office of Product Quality Review (23 May 2016)
Recommendation: Approval
The Integrated Quality Assessment was compiled by Dr. Sapru, Application Technical Lead for NDA 208424. NDA 208424 was found to be acceptable from a Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics and Microbiology perspectives. The Agency has recommended a shelf-life of 18 months for GoNitro when stored in the approved commercial container closure system between the temperatures of 20°C -25°C, with excursions permitted between 5 °C– 40 °C.

Pharmacology/Toxicology Review (21 December 2015)
Recommendation: Approval
There were no pre-clinical studies performed or reviewed for this application. Dr. Gatti concluded that, based on the IID, all inactive ingredients for GoNitro are qualified.

❖ CONSULT REVIEWS

Please see the following reviews and their corresponding dates:

- OSE/DMEPA: 29 May 2016, 25 May 2016, 23 March 2016, 10 February 2016, 15 November 2015
- OPDP: 4 May 2016
- Patient Labeling (Instructions for Use): 5 May 2016
- DPMH: 2 June 2016

❖ CONCLUSION

After considering all primary and consult reviews, the Division issued an approval letter for NDA 208424 on 8 June 2016. The approval letter was signed by Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products on 8 June 2016.

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

/s/

BRIDGET E KANE
06/08/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: May 18, 2016 **Date consulted:** September 10, 2015

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD,
Director, Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Nitroglycerin (GTN) powder for sublingual administration

NDA: 208424 (Original NDA)

Applicant: G. Pohl-Boskamp GmbH & Co. KG (Pohl-Boskamp)

Subject: Pregnancy and Lactation Labeling

Indication: For Acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease

Materials Reviewed:

- DPMH consult request dated September 10, 2015 in DARRTS.
- Applicant's submitted package for original NDA: 208424 dated August 10, 2015.
- Applicant's response to information request (IR) by the Division on October 21, 2015, dated November 27, 2015.

Consult Question:

DCRP requests that DPMH "determines if the PLLR format in the proposed Prescribing Information (PI) is acceptable".

INTRODUCTION

The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 10, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of GTN powder for sublingual administration [glyceryl tri-nitrate /nitroglycerin (GTN)] to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY

On August 10, 2015, Pohl-Boskamp (the Applicant) submitted the marketing application for GTN powder for sublingual administration (GTN powder), NDA 208424, indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease. This application is a 505(b)(1). This submission provides information from a single relative bioavailability study demonstrating the in vivo biopharmaceutical characteristics and bioavailability of GTN powder versus Nitrolingual® Pumpspray (NDA 18-705). This submission triggers a PLLR labeling conversion.

Nitrolingual® Pumpspray was approved on October 31, 1985. Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

DCRP sent Pohl-Boskamp an IR on October 21, 2015, to request that the Applicant provide:

- A review and summary of all available published literature regarding GTN use in pregnant and lactating women,
- A revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

In response, the Applicant submitted on November 27, 2015, a summary of available published literature related to GTN use in pregnant and lactating women and assessment of the proposed package insert for the Pregnancy and Lactation sections of the labeling in compliance with the PLLR.

BACKGROUND

Heart Disease and Pregnancy

Cardiovascular disease (CVD) complicates 1% to 4% of pregnancies,[1] with congenital heart disease (CHD) being the most common preexisting condition and hypertension the most common acquired condition. The incidence of maternal CVD appears to be growing, likely due to increasing maternal age, cardiovascular risk factors (i.e., obesity, diabetes, and hypertension,) and lifespan of patients with CHD. Studies suggest that pregnancy-related mortality has also increased over the last several decades, with deaths attributable to CVD increasing over the same time period. [2,3]

---

[1] Weiss BM, von Segesser LK, Alon E, Seifert B, Turina MI. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984-1996. Am J Obstet Gynecol 1998; 179:1643–53.

[2] Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. Obstet Gynecol 2010; 116:1302–09.

[3] Naderi S, Raymond R. Pregnancy and Heart Disease, Cleveland Clinic, Center for Continuing education

Acute myocardial infarction (AMI) during pregnancy is rare, occurring in approximately 1 in 35,000 pregnancies. Independent predictors of AMI during pregnancy include chronic hypertension, hyperlipidemia, smoking, advanced maternal age, diabetes, and preeclampsia. Most myocardial infarctions occur during the third trimester and are most common in multiparous women over the age of 33.[3] Maternal mortality is highest in the peripartum period. In a review of 68 reported cases, myocardial infarction during pregnancy was associated with a 35% mortality rate, and only 13% of patients were known to have had coronary artery disease before pregnancy. Two-thirds of the women suffered infarction in the third trimester; mortality for these women was 45%, compared with 23% in those suffering infarction in the first or second trimesters.[4] Maternal mortality after AMI is estimated at 5% to 7%, with improved survival since the advent of percutaneous coronary intervention.[5]

Coronary spasm, coronary thrombosis, and spontaneous coronary artery dissection occur more often than classic obstructive atherosclerosis. Angina pectoris rather than acute myocardial infarction is the most common symptom of initial presentation of coronary artery disease during pregnancy. Though incidence of cardiovascular disease is low in pregnant women, the balance of demand and supply of myocardial oxygen should be managed and if need exists, it should be corrected. Anxiety or high levels of physical activity may aggravate the condition. Under normal circumstances, drug therapy involving the use of calcium channel blockers, beta adrenergic blockers or GTN may be recommended for treating angina in women during pregnancy.[6] Angina pectoris is an age-related disease with a continuous increase in prevalence with greater age. In the age group between 35 - 44 years, the prevalence of angina pectoris is less than 2.5 %. [7]

Coronary artery spasm is defined as a dynamic, transient reduction in the luminal diameter of the epicardial coronary arteries due to increased vasomotor tone leading to myocardial ischemia.[8,9]

The pathogenesis of coronary spasm is complex. It is thought to be a multifactorial process involving several mechanisms[10] including endothelial dysfunction, hyper-reactivity of coronary smooth muscle cells to constrictor stimuli (catecholamines, acetylcholine, and histamine), and other triggering factors, such as activation of the parasympathetic nervous system and alpha-adrenergic receptors.[11]

---

[4] Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 36: Cardiac Diseases in Pregnancy, pp: 260-275, Jan 14, 2008

[5] James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study [published online ahead of print March 13, 2006]. Circulation 2006; 113:1564–71

[6] Elkayam U., Gleicher N. Cardiac problems in pregnancy: Diagnosis and management of maternal and fetal heart disease, 3rd Edition, Wiley-Liss, 1998, P:125-7

[7] Shurin S. Morbidity and Mortality: 2012 chart book on cardiovascular, lung, and blood diseases. 2012. National Heart, Lung and blood Institutes website. 2012

[8] Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris I. A variant form of angina pectoris. Preliminary report. The American Journal of Medicine. 1959;27(3):375–88

[9] Yasue H, Kugiyama K. Coronary spasm: clinical features and pathogenesis. Internal Medicine. 1997;36(11):760–5

[10] Koneru J, Cholankeril M, Patel K, Alattar F, Alqaqa A, Virk H, Shamoon F, Bikkina M. Postpartum coronary vasospasm with literature review. Case Rep Cardiol. 2014

[11] Hiroki T, Kenji N, Yukihito H, et al. Treatment of coronary spastic angina, particularly medically refractory

Long acting nitrates have long been used in patients with coronary spasm for their vasodilatory effects. GTN is an endothelium-independent vasoactive agent with the capacity to diminish myocardial oxygen demand by dilating peripheral arteries and veins,.[12]

Nitroglycerin (GTN) Drug Characteristics[13]
GTN powder for sublingual administration is a powder containing GTN. GTN, an organic nitrate, is a vasodilator which has effects on both arteries and veins. GTN forms free radical nitric oxide (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 regulates the contractile state in smooth muscle and results in vasodilatation.

The compound has a molecular weight of 227.09. Each packet of the drug delivers 400 mcg of GTN when administered under the tongue.[14] Elimination half-life of GTN is 1.7 to 2.9 minutes. When glyceryl tri-nitrate (GTN) was given sublingually, peak plasma concentrations appeared within 4 minutes and at least half of the intact GTN was cleared from the blood in 1 to 3 minutes.[15]

Common adverse events that have occurred with use of GTN include headache, dizziness, and paresthesia. The following adverse reactions have been identified during post-approval use of other GTN drugs:

- Neurologic: weakness, drowsiness,
- Dermatologic: cutaneous vasodilation, flushing, drug rash, exfoliative dermatitis,
- Gastrointestinal: nausea, vomiting,
- Respiratory: transient hypoxemia
- Cardiovascular: tachycardia

Pregnancy and Lactation Labeling
On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,"*[16] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[17] format to include information about the risks and benefits of using these products during pregnancy and lactation.

---

spasm. Clinical Medicine: Cardiology. 2008;2:181–9.
[12] May D, Popma JJ, Black WH, et al. In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. The New England Journal of Medicine. 1987;317(13):805–9
[13] Nitrolingual Pumpspray labeling, Sections 11 (Description) and 12 (Clinical Pharmacology), Lanuary 23, 2015
[14] Proposed nitroglycerin labeling
[15] https://toxnet nlm nih.gov/cgi-bin/sis/search2/f?./temp/~IAAHTq:1
[16] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labelin*g (79 FR 72063, December 4, 2014)
[17] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*,

REVIEW

The Applicant provided a literature assessment related to the administration of GTN in pregnant and lactating women. The following databases were searched for scientific evidence for GTN use in pregnant and lactating women:

Table 1: relevant database

database	link, commentary
PubMed	- http://www.ncbi.nlm.nih.gov/pubmed - more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans	- http://monographs.iarc.fr/ENG/Classification - The IARC Monographs identify environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors.
HSDB, Hazardous Substances Data Bank	- http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm - Peer-reviewed toxicology data for over 5,000 hazardous chemicals
LactMed, Drugs and Lactation Database	- http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm - Drugs and other chemicals to which breastfeeding mothers may be exposed
DART, Developmental and Reproductive Toxicology Database	- http://toxnet.nlm.nih.gov/newtoxnet/dart.htm - Developmental and Reproductive Toxicology Database. References to developmental and reproductive toxicology literature
CCRIS, Chemical Carcinogenesis Research Information System	- Carcinogenicity and mutagenicity test results for over 8,000 chemicals - Archived, no longer updated - http://toxnet.nlm.nih.gov/newtoxnet/ccris.htm
ChemIDplus	- http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp - Chemical database of over 400,000 chemicals (names, synonyms, and structures).

From Applicant's response to IR, dated November 2015, Table 1, P:8

Many publications were identified. For references considering clinical off-label use of GTN, a large number of publications are available. In this case, the publication was considered as relevant if it was the broadest systematic review and/or the publication was recent. Searches included the terms GTN, and pregnancy or pregnant women or lactation or breast feeding or lactating women, and infertility. DPMH also conducted a review of PubMed, ReproTox[18], and TERIS[19] for published literature regarding GTN and pregnancy, teratogenicity, and birth defects or lactation or females of reproductive potential. The results of the literature search are described below.

The Applicant did not provide a Pharmacovigilance report because they don't have a marketed product.

PREGNANCY

Nonclinical Experience

published in the Federal Register (71 FR 3922; January 24, 2006).

[18] ReproTox database, Truven Health analytics, Micromedex solutions, 2016

[19] TERIS database, Truven Health Analytics, Micromedex Solutions, 2016

Animal teratology studies have not been conducted with the specific product, GTN powder, the subject of this application. However, animal data are available for other GTN products. For example, topically applied GTN ointment in rats and rabbits at doses up to 80 mg/kg/day and 240 mg/kg/day respectively, demonstrated no toxic effects on dams or fetuses were seen at any dose tested.
The delivery of nitroglycerin by sublingual, transdermal and anal fissure application (ointment) are not equivalent.

(1) Sublingual GTN powder (0.8 mg): Cmax: 1.67 ng/ml at a Tmax: 7 minutes. (NDA208424)
(2) Transdermal patch of GTN (In vivo release rate: 0.5 mg/cm2/24 h; for 20 cm2 patch): Cmax: ~1 ng/ml at a Tmax: ~60 min. The Cmax is maintained until the patch is removed after 8 hr.
(3) GTN ointment (0.4% =1.5 mg GTN) [rectal application]: Absolute bioavailability: 50%, Cmax: 0.183 ng/ml at a Tmax: 30 min. (NDA21359)

The sublingual absorption would achieve rapid Cmax compared to the other routes. However, the transdermal application would also be able to achieve comparable Cmax as that of sublingual but maintain the concentration over ~18 hr. It is generally recommended to remove the patch after 12 hr of application on every day.

For more detailed review, the reader is referred to the Pharmacology Toxicology review by Philip Gatti, Ph.D. in DARRTS dated December 21, 2015.

Review of the Literature on use of GTN during Pregnancy
The Applicant identified no information on GTN use in pregnancy according to the proposed indication "for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease," because angina pectoris due to coronary artery disease occurs rarely during pregnancy. DPMH in a review of PubMed did not identify any published literature on use of GTN powder for this indication.

Off-label use
GTN has been used in the research setting, off label, for: acute tocolysis[23], pregnancy induced (gestational) hypertension[25], inhibition of preterm labor[20], external cephalic version, cervical relaxation in breech delivery[22], severe preeclampsia[21], and myocardial infarction during pregnancy.[22]

Acute tocolysis:

- Black RS *et. al*.[23] Sixty women in preterm labor were enrolled in this study that was part of a multicenter study of GTN. Once randomized, the women received transdermal GTN

[20] Conde-Agudelo A,, Romero R. Transdermal nitroglycerin for the treatment of preterm labor: a systematic review and metaanalysis. American J of Obstet Gynecol. 2013 Dec; 209(6): 551.e1-551.e18
[21] Trapani A, Jr., Goncalves LF, Pires MM. Transdermal nitroglycerin in patients with severe pre-eclampsia with placental insufficiency: effect on uterine, umbilical and fetal middle cerebral artery resistance indices. Ultrasound in obstetrics & gynecology, 2011;38(4):389-94.
[22] 23th edition, Williams Obstetrics, 2010, The McGraw-Hill Companies P: 741, 826, 539, 977
[23] Black RS; Lees C; Thompson C; Pickles A; Campbell S. Maternal and fetal cardiovascular effects of transdermal glyceryl trinitrate and intravenous ritodrine. Obstet Gynecol. 1999, Oct; 94(4):572-6

or intravenous ritodrine for acute tocolysis. At doses required for acute tocolysis, transdermal GTN had minimal effects on maternal pulse, blood pressure (BP), and fetal heart rate, and significantly fewer adverse cardiovascular effects than intravenous ritodrine. The authors concluded that transdermal GTN might be a safer treatment for women in preterm labor than ritodrine.

- Schleussner E *et. al*.[24] Fifty pregnant women between 27 and 35 weeks of gestation with preterm labor were treated with either transdermal GTN (0.4-0.8 mg/h) or fenoterol (60 - 120 µg/h). Outcome parameters were (1) the effects on fetal and maternal heart frequency (FHF/MHF) and blood pressure, and (2) subjective experiences of adverse effects assessed by utilizing a questionnaire. The authors concluded that transdermal GTN appears to be a "safe" therapy for the mother and fetus and is a promising new option for the treatment of preterm labor.

Pregnancy induced hypertension (gestational hypertension):

- Iqbal K *et. al*.[25]; In this double-blind, placebo-controlled study, sixty pregnant women with severe hypertension at or beyond 36 weeks of gestation were randomized to receive either GTN or a matched placebo infusion. Patients with severe gestational hypertension (BP >= 160/110 mmHg) despite oral antihypertensive treatment, with or without superimposed pre-eclampsia or eclampsia were admitted to the study. They received either intravenous GTN as a continuous infusion, starting at 5µg/min with increments of 5µg/min until the goal BP or a dose of 300µg/min was reached or equivalent drop rate of plain fluid in the placebo group. Maternal BP, maternal heart rate, fetal heart rate and any signs of fetal distress were monitored. Condition of the newborn babies was estimated by APGAR score. The goal was to achieve a systolic BP of 120-140mmHg and /or diastolic BP of 90-100mmHg. There was a statistically significant fall in blood pressure in both groups. However, BP control was achieved faster in NTG group. The time to delivery in both groups was similar. There was no significant change in fetal heart rate in the 2 groups. Maternal tachycardia in response to nitroglycerin was observed, which was transient. There was no maternal or fetal death. The authors concluded that parenteral nitroglycerin given in continuous infusion of incremental doses is an effective agent in acute lowering of high blood pressure in term gravidas. The drug was well tolerated by both, the mother and the fetus.

Inhibition of preterm labor

- Conde-Agudelo and Romero [21] conducted a systematic review and meta-analysis of transdermal nitroglycerin for the treatment of preterm labor. They included 13 randomized controlled trials in which transdermal nitroglycerin was used for tocolysis in patients with preterm labor compared with placebo, no treatment, or alternative tocolytic agents. Trials were excluded if they were quasi-randomized, if they evaluated nitroglycerin for tocolysis administered intravenously, sublingually or orally. A total of

---

[24] Schleussner E; Möller A; Gross W; Kähler C; Möller U; Richter S; Seewald HJ. Maternal and fetal side effects of tocolysis using transdermal nitroglycerin or intravenous fenoterol combined with magnesium sulfate. Eur J Obstet Gynecol Reprod Biol. 2003, Jan 10; 106(1):14-9

[25] Iqbal K; Dar MA; Tramboo NA; Firdous N; Naikoo BA; Mohiuddin K; Mir S; Ali SM; Lone AA; Rizvi M. Treatment of Pregnancy Induced Hypertension With Intravenous Nitroglycerine: A Randomized, Double Blind Placebo Controlled Study. J Am Coll Cardiol 2005 Feb;45(3 Suppl):375A

1302 women met the inclusion criteria. Overall, nitroglycerin dosing regimens were similar across the trials. The authors concluded that based on the findings of this systematic review, there is insufficient evidence to recommend the use of transdermal nitroglycerin for the treatment of preterm labor. If tocolysis is considered for women in preterm labor, nifedipine is preferable to transdermal nitroglycerin. Information about the long-term growth and development of the child exposed in utero to transdermal nitroglycerin is needed. Regarding the safety, as reflected in the relevant endpoints of delivery, neonatal outcome, and the neuro-developmental status of 24 months old children, the authors concluded, that there are no statistically significant differences between nitroglycerin and placebo.

Severe preeclampsia

- Trapani A. Jr. *et. al*. studied prospectively 30 singleton pregnancies (gestational age range: 24–31 weeks) with severe pre-eclampsia and abnormal uterine and umbilical artery Doppler waveforms. They compared maternal blood pressure as well as the resistance index and the pulsatility index of the uterine, umbilical and fetal middle cerebral arteries before and after application of a transdermal nitroglycerin patch (average dose 0.4 mg/h) for a period of 3 days. They concluded that application of a 50-mg transdermal GTN patch to the maternal abdomen was associated with a significant decline in the resistance index of the uteroplacental (uterine arteries) and fetoplacental (umbilical arteries) circulation. No change was observed in the resistance index of the cerebral circulation (middle cerebral artery). None of the patients developed severe hypotension or tachycardia in this study. Headache was the most common adverse effect, and it was observed in 79% of the patients. It remains to be determined whether or not transdermal GTN could be used in association with other drugs to control arterial pressure in patients with pre-eclampsia.

Summary

Overall, the published literature includes off-label use of GTN for various conditions occurring later in pregnancy; these publications do not provide any information to evaluate the effects of GTN on early pregnancy and the developing fetus; the risk of miscarriages; or major birth defects. When GTN was used in later pregnancy, no adverse outcomes to the mother or the fetus were reported. There is no new information to support additional information to be included in labeling at this time. Therefore, this reviewer does not recommend any changes to the Nitrolingual® Pumpspray aside from a changes to comply with PLLR format.

LACTATION

Nonclinical Experience

There are no studies performed in animals evaluating any formulation of GTN during lactation.

Review of the Literature on use of GTN during Lactation

There is no information on the use of GTN in lactation except of one study found in the LactMed[26] database on topical use of GTN for anal fissures by nursing mothers. Forty nursing mothers used

[26] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels,

GTN ointment (dosage not specified) topically for the treatment of postpartum anal fissures for durations ranging from 1 use to 12 months of intermittent use. All but nine of the women reported side effects from therapy, primarily headache, but also dizziness or lightheadedness. None of the mothers reported any side effects in their breastfed infants. [27] Sublingual and intravenous GTN have not been studied during breastfeeding.

In Thomas Hale's Medication and Mother's Milk,[28] , cases are reported of nitrate (GTN is a subset of nitrates) induced methemoglobinemia in infants exposed to well water with high levels of nitrates when they were fed foods/formulas prepared with contaminated water. The author states that "it is less certain that the oral ingestion of nitrates can penetrate into human milk in clinically relevant amounts". A study by Dusdieker LB *et. al*.,[29] concluded that "mothers who ingest nitrate of 100 mg/d or less do not produce milk with elevated nitrate levels". The study was conducted using nitrates in water and may not correlate with ingestion of high and prolonged concentration of nitrates from medications administered orally, buccally, or transcutaneously. The available data are not sufficient to conclude whether GTN is present in human milk, the effects of GTN has effects on milk production, or any effects on nursing infants.

Summary
There is limited information about GTN and lactation following topical administration; however, no information exists regarding other routes of administration. This reviewer does not recommend any changes to the Nitrolingual® Pumpspray aside from a change to comply with PLLR format. From the review above, there is no information to conclude that breastfeeding may be harmful to the breastfed infant. No adverse reactions have been observed to the breastfed infant. The following statement should be included in the GTN Powder labeling: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GTN and any potential adverse effects on the breastfed child from GTN or from the underlying maternal condition.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Animal teratology studies have not been conducted with the specific product, GTN powder, the subject of this application. However, animal data are available for transdermal GTN. A published report of transdermal GTN in 30 pregnant rabbits from day 6 to 18 of gestation at dose levels of 15, 60, and 240 mg/kg/day, identified no adverse findings regarding the reproductive performance of dams and the development of the fetuses at any dose level compared to the vehicle control.[30] A fertility study in rats demonstrated no reproductive effects following intraperitoneal doses up 20 mg/kg/day in males 63 days prior to mating and in females.[30]

---

any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[27] Taylor T, Kennedy D. Safety of topical glyceryl trinitrate in the treatment of anal fissure in breastfeeding women. Birth Defects Research Part a-Clinical and Molecular Teratology. 2008;82:411. Abstract
[28] Hale, T. Medications and Mother's Milk. Hale Publishing, 2012
[29] Dusdieker LB, Stumbo PJ, Kross BC, Dungy CI. Does increased nitrate injestion elevate nitrate levels in human milk? Arch Pediatr Adolesc Med 1996; 150(3): 311-14
[30] Applicant's response to IR, dated November 2015,

GTN 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, orally, or in in vitro cytogenic tests in rat and dog tissues and for chromosomal aberration in Chinese hamster ovary cells.

Review of the Literature on use of GTN on Females and Males of Reproductive Potential
The Applicant did not report any publications on the use of GTN regarding Females and Males of Reproductive Potential. DPMH conducted a review of PubMed from 1990 to today and Repro Tox. The use of GTN patches or a 2% GTN paste applied topically to the penile shaft has been investigated as a potential treatment for some forms of impotence. [31],[32] This therapy has been associated with beneficial effects in men with moderate erectile disturbances, [33] but it has not proved useful in diabetic patients.[32] Transdermal GTN has also been reported for treatment in a pilot study of 64 women with primary dysmenorrhea with successful outcomes.[34]

Summary
There is limited information about GTN on Females and Males of Reproductive Potential. No new safety information was identified to update the labeling.

CONCLUSIONS
GTN powder for sublingual administration labeling has been updated to comply with the PLLR. DPMH has the following recommendations for GTN labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of GTN labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" subsections[35].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of GTN labeling was formatted in the PLLR format to include: the "Risk Summary".[36]

(b) (4)

- **Patient Counseling Information, Section 17**

[31] Gramkow J, Lendorf A, Zhu J, Meyhoff HH: Transcutaneous nitroglycerine in the treatment of erectile dysfunction: a placebo controlled clinical trial. Int J Impot Res 1999;11:35-9
[32] Negelev S: Re: Topical nitroglycerin: a potential treatment for impotence. J Urol 143:586, 1990
[33] Claes H, Baert L: Transcutaneous nitroglycerin therapy in the treatment of impotence. Urol Int 44:309-312, 1989
[34] The Transdermal Nitroglycerine/Dysmenorrhea Study Group, Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhea: a multinational pilot study. J Int Med Res 25 (1997), pp. 41-44
[35] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[36] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.
[37] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

- The “Patient Counseling Information” section of GTN labeling has no information to include regarding pregnancy, lactation or infertility and contraception.

RECOMMENDATIONS

DPMH revised sections 8.1, and 8.2 of GTN labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed GTN powder for sublingual administration Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Limited published data on the use of nitroglycerin are insufficient to determine a drug associated risk of major birth defects or miscarriage. The majority of the published data were in pregnant women during later stages of pregnancy (i.e., third trimester). In animal reproduction studies, there were no adverse developmental effects when nitroglycerin was administered intravenously to rabbits or intraperitoneally to rats during organogenesis at doses greater than 64-times the human dose *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
No embryotoxic or postnatal development effects were observed with transdermal application in pregnant rabbits and rats at doses up to 240 mg/kg/day for 13 days, at intraperitoneal doses in pregnant rats up to 20 mg/kg/day for 11 days, and at intravenous doses in pregnant rabbits up to 4 mg/kg/day for 13 days during organogenesis at doses greater than 64-times, the human dose (based on body weight).

8.2 Lactation
Risk Summary
Nitroglycerin has not been studied in lactating women. It is not known if nitroglycerin is present in human milk, the effects on the breastfed infant, or the effects on milk production. There is no information to conclude that breastfeeding may be harmful to the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for nitroglycerin and any potential adverse effects on the breastfed child from nitroglycerin or from the underlying maternal condition.

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

/s/

CHRISTOS MASTROYANNIS
06/01/2016

TAMARA N JOHNSON
06/01/2016

LYNNE P YAO
06/02/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 5, 2016
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	Brand name (nitroglycerin)
Dosage Form and Route:	powder, for sublingual use
Application Type/Number:	NDA 208424
Applicant:	G. Pohl-Boskamp GmbH & Co. KG c/o Espero Pharmaceuticals, Inc.

1 INTRODUCTION

On August 6, 2015, G. Pohl-Boskamp GmbH & Co. KG c/o Espero Pharmaceuticals, Inc. submitted for the Agency's review original New Drug Application (NDA) 208424 for Brand name (nitroglycerin) powder. The proposed indication for Brand name (nitroglycerin) powder is for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Cardiovascular and Renal Products (DCRP) on September 10, 2015, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for Brand name (nitroglycerin) powder.

DMPP conferred with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on February 10, 2016.

2 MATERIAL REVIEWED

- Draft Brand name (nitroglycerin) powder IFU submitted on August 6, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 26, 2016.
- Draft Brand name (nitroglycerin) powder Prescribing Information (PI) submitted on August 6, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 26, 2016.
- Division of Medication Error Prevention and Analysis (DMEPA) Label and Labeling Review for Nitroglycerin Sublingual Powder dated February 10, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KAREN M DOWDY
05/05/2016

ZARNA PATEL
05/05/2016

MARCIA B WILLIAMS
05/05/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: May 4, 2016

To: Bridget Kane, MS
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Nitroglycerin Powder**
NDA: 208424
Comments on draft product labeling

In response to your consult dated September 10, 2015, OPDP has reviewed the attached substantially complete version (emailed to us on April 26, 2016) of the draft prescribing information (PI), and we do not have any comments on the draft PI at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ZARNA PATEL
05/04/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	March 22, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 208424
Product Name and Strength:	Nitroglycerin Sublingual Powder, 400 mcg per packet
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	G. Pohl- Boskamp GmbH & Co. KG
Submission Date:	March 4, 2016
OSE RCM #:	2015-2037-1
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling for Nitroglycerin sublingual powder submitted on March 4, 2016 (Appendix A) from a medication error perspective. The revisions are in response to our previous review of the labels and labeling for the proposed Nitroglycerin sublingual powder 400 mcg per packet product (See DARRTS Labeling Review dated February 10, 2016).[1]

[1] Thomas S. Label and Labeling Review for Nitroglycerin Sublingual Powder (NDA 208424). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Feb 10. 14 p. OSE RCM No.: 2015-2037.

2 CONCLUSION

G. Pohl- Boskamp GmbH & Co. KG incorporated the majority of our recommendations from the previous review, with the exception of relocating the numerical "XXXXXXXX/X" designation. Per G. Pohl- Boskamp GmbH & Co. KG, this represents the placeholder for the internal Pohl Boskamp material (article) number, with "XXXXXXXX" standing for the unique material number and "X" after the backslash representing the version. Due to technical reasons, the material number has to be placed close to the lot number and expiry date, (b) (4) The presentation of the expressions "LOT:" and "EXP:" ensures that the material number can be clearly distinguished from the lot number and expiry date, respectively. Hence, G. Pohl- Boskamp GmbH & Co. KG believes that any confusion is avoided by these expressions. Of note, G. Pohl- Boskamp GmbH & Co. KG made some additional formatting changes to the labels and labeling as well. After review of the revised labels and labeling, we find them acceptable from a medication error perspective.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SARAH E THOMAS
03/22/2016

CHI-MING TU
03/23/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 10, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 208424
Product Name and Strength:	Nitroglycerin Sublingual Powder, 400 mcg (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	G. Pohl- Boskamp GmbH & Co. KG
Submission Date:	August 10, 2015; November 27, 2015; January 27, 2016
OSE RCM #:	2015-2037
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the NDA review process for Nitroglycerin sublingual powder, the Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed container label and carton labeling, prescribing information, and instructions for use for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Nitroglycerin is currently available in many dosage forms, including sublingual tablet and sublingual aerosol solution. G. Pohl- Boskamp GmbH & Co. KG is proposing a new dosage form, sublingual powder, with a proposed strength of 400 mcg (b) (4). The proposed strength, route, and dosing of nitroglycerin sublingual powder is similar to that of the sublingual tablet and aerosol solution. However, our review of the proposed prescribing information (PI) found that the current description of the usual recommended dosage in the highlights section and section 2 of the PI may potentiate confusion. We recommend that the sponsor provide specification of the "dose" alluded to in section 2.1 of the PI, because as currently stated, the maximum dose recommended before warranting prompt medical attention could fall within the range of (b) (4). Additional improvements can be made to the PI to clarify and better convey important information to the end-user, and we provide our recommendations in section 4.1 and Appendix H. We also reviewed the proposed container label and carton labeling, and found additional formatting changes and improvements that can be made to mitigate the risk of medication error with this product (see section 4.2).

4 CONCLUSION & RECOMMENDATIONS

The proposed container label, carton labeling, prescribing information (PI), and instructions for use (IFU) can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

We recommend changes to the PI and IFU in tracked changes in Appendix H be implemented prior to the approval of this NDA.

4.2 RECOMMENDATIONS FOR G. POHL- BOSKAMP GMBH & CO. KG

We recommend the following changes to the container label and carton labeling be implemented prior to approval of this NDA:

A. General Recommendations (container labels and carton labeling)
   1. Ensure the final container labels and carton labeling contain the conditionally accepted proprietary name.
   2. Revise the established name so that it is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21CFR201.10(g)(2).
   3. Revise the usual dosage statement (b) (4) to read "Usual dose: See Prescribing Information" because the proposed product can be dosed as one or two (b) (4).

B. Container Labels
   1. Provide clarification regarding the intent of the "X/XXXXXXXXX" designation on the individual (b) (4) container label. If this is a numerical designation, ensure that it is not located in close proximity to the lot number or expiration date where it can be mistaken as the lot number or expiration date.[1]

C. Carton Labeling
   1. Increase the prominence of the strength statement. As currently presented, the strength lacks prominence on the carton labeling.

[1] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nitroglycerin sublingual powder that G. Pohl-Boskamp GmbH & Co. KG submitted on January 27, 2016.

Table 2. Relevant Product Information for Nitroglycerin sublingual powder	
Initial Approval Date	N/A
Active Ingredient	Nitroglycerin
Indication	Nitrate vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.
Route of Administration	Sublingual
Dosage Form	Sublingual powder
Strength	400 mcg (0.4 mg) (b) (4)
Dose and Frequency	• 1-2 (b) (4) (400 mcg (b) (4)) administered at the onset of an attack under the tongue, and a dose may be repeated approximately every five minutes as needed up to three doses within a fifteen minute period. • Prophylactic dosing may be performed 5 to 10 minutes prior to engaging in activities that may precipitate an acute attack.
How Supplied	Each (b) (4) contains 400 mcg of nitroglycerin. Nitroglycerin powder is available in packs of 12, 36, or 96 (b) (4), and is also available in a physician sample carton containing 3 sample (b) (4).
Storage	Store up to 25°C (77°F). Excursions permitted to 5-40°C (41-104°F).
Container Closure	Exempt from CRC requirements per 16 CFR 1700.14(a).

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 5, 2016, we searched the [L:Drive] [AIMS] using the term "nitroglycerin powder" and the current proposed proprietary name (b) (4) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one proprietary name review[2] in the L:Drive search, but the review is not applicable to this label and labeling review.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2]Stewart, Janine. Proprietary Name Review for GoNitro (Nitroglycerin) Sublingual Powder (NDA 208424). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 13. 31 p. RCM No.: 2015-1272651.

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

/s/

SARAH E THOMAS
02/10/2016

CHI-MING TU
02/10/2016

M E M O R A N D U M

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

DATE: 11/10/2015

TO: Division of Cardiovascular and Renal Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208424

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the nature of the findings from the last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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

/s/

SHILA S NKAH
11/10/2015

Memorandum

Date: November 10, 2015

To: NDA 208424

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP's Review of a Potential Promotional Claim on Carton & Container Labeling (Email Response to DMEPA)

****** Pre-decisional Agency Information******

DMEPA requested OPDP's input on a potential promotional claim on the carton & container labeling for NDA 208424 (Nitroglycerin Powder for sublingual use). OPDP provided the following email response to DMEPA on November 10, 2015.

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ZARNA PATEL
11/10/2015

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Memorandum to File

NDA:	208424
Drug:	GoNitro (nitroglycerin powder) for sublingual use
Class:	Vasodilator
Applicant:	G. Pohl-Boskamp GmbH & Co. KG
Proposed Indication:	Acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease
Date of submission:	06 August 2015
FDA Received:	10 August 2015
PDUFA date:	16 June 2016

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Cross Discipline Team Leader:
    - Raj Madabushi
  - Pharmacology/Toxicology
    - Tom Papoian, Team Leader
    - Phil Gatti, Reviewer
  - Clinical Pharmacology
    - Venki ChithambaramPillai, Reviewer
  - Regulatory Health Project Manager
    - Bridget Kane, MS
- Office of Product Quality
  - Chemistry, Manufacturing, and Controls
    - Mohan Sapru, Team Leader
    - Sithumalli Chandramouli, Drug Substance Reviewer
    - Mariappan Chelliah, Drug Product Reviewer
    - Jing Li, Biopharmaceutics Reviewer
    - Steven Hertz, Facilities Reviewer
    - Xuhong Li, Process Reviewer

❖ BACKGROUND

Nitroglycerin is an approved treatment for angina pectoris. G. Pohl-Boskamp markets Nitrolingual pumpspray (NDA 18705) and they submitted an NDA for a new dosage form as an oral powder for sublingual administration in August 2015. The applicant first met with the Division in January 2013 to discuss both the clinical and CMC development program to ensure adequate support for an NDA submission. At the Pre-NDA meeting (under IND 116608) for this indication on 18 September 2014 (minutes dated 07 October 2014), the Division confirmed that the sponsor could cross-reference their own NDA 18705 to support their proposed NDA and be considered a 505(b)(1), but stated that if reliance on published literature was required to support this new application, the appropriate regulatory pathway would be 505(b)(2).

FILING REVIEW

During the internal filing meeting on 23 September 2015, it was decided that NDA 208424 would be filed as a 505(b)(2) because of its reliance on published literature to verify the safety of the excipients unique to the GoNitro formulation. The RPM Filing Review was uploaded to DARRTS on 07 October 2015 and reflected this decision.

However, upon further review of the application and discussions with Colleen Locicero, Associate Direction for Regulatory Affairs for Office of Drug Evaluation I, as well as the non-clinical reviewers, it was determined that NDA 208424 would be filed as a 505(b)(1) based on the following:

- NDA 18705 (Nitrolingual pumpspray), the applicant's product and referenced NDA, is a 505(b)(1).
- The safety of the excipients can be determined from the Inactive Ingredient Database (IID) which is referenced by the applicant.
- No reliance on data from published literature is required for this application

❖ **CONCLUSION**

Since the applicant submitted the Form 356h indicating 505(b)(1) as the NDA type (box 17), no modification of the 356h will be requested from the applicant, as was indicated in the RPM Filing Review. The 505(b)(1) regulatory pathway for this application will be conveyed to the applicant in the 74-day letter.

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

/s/

BRIDGET E KANE
10/22/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: 208424

Application Type: NDA

Name of Drug/Dosage Form: GoNitro (nitroglycerin for sublingual use) 400 mcg (b) (4)

Applicant: G. Pohl-Boskamp GmbH & Co. KG

Receipt Date: 10 August 2015

Goal Date: 10 June 2016

1. Regulatory History and Applicant's Main Proposals

G. Pohl-Boskamp GmbH & Co. KG submitted NDA 208424, nitroglycerin for sublingual use (proposed proprietary name 'GoNitro') for the indication of acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease. G. Pohl-Boskamp GmbH & Co. KG currently markets nitrolingual Pumpspray (NDA 18705). NDA 208424 was filed on 09 October 2015.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Label does not fully comply with PLLR, recommendations from PMHS will be forwarded to the applicant in the 74 day letter.

   All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by 13 November 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Margins do not meet requirements*

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Horizontal lines do not extend over entire column width*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Numbers are included, however not consistent with parentheses being inside or outside the period and spacing is inconsistent. Please place parentheses with numbers outside the period.*

YES 7. Section headings must be presented in the following order in HL:

Selected Requirements of Prescribing Information

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A

13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

NO

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *Item # 4.5 in FPI - Circulatory Failure and Shock not included in Highlights*

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Subsections should be in title case.*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics

12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *Verbatim*

NO 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Dash between post and approval (should read post-approval)*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

BRIDGET E KANE
10/15/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208424 BLA# N/A	NDA Supplement #: S- N/A BLA Supplement #: S- N/A	Efficacy Supplement Category: N/A
Proprietary Name: GoNitro Established/Proper Name: nitroglycerin (for sublingual use) Dosage Form: powder Strengths: 400 mcg (b) (4)		
Applicant: G. Pohl-Boskamp GmbH & Co. KG Agent for Applicant (if applicable): Espero Pharmaceuticals Inc.		
Date of Application: 06 August 2015 Date of Receipt: 10 August 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 10 June 2016	Action Goal Date (if different): N/A	
Filing Date: 09 October 2015	Date of Filing Meeting: 23 September 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed change: New dosage form: nitroglycerin powder for sublingual use (400 mcg (b) (4))		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): 116608	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Standard
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		This application was

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				determined to be a 505(b)(2) application; will need an updated 356H form
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested:	☐	☒	☐	

Note: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

(*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☒	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the***	☒	☐		

supporting document category, "Form 3674." ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		Consulted PeRC on 09 SEP 2015; PeRC review scheduled for 06 APR 2016.

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	20JAN15 – waiver granted
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Sponsor submitted GoNitro in SD3 on 18 Aug 2015.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☒	☐	Application does not include a summary of the available pregnancy and lactation data. Consult submitted to maternal health 29 SEP 2015 via DAARTS.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	Consult in DARRTS on 10 SEP 2015
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	Consult in DARRTS on 10 SEP 2015
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	OSI consult for inspection of bridging study # P1302NL in preparation; Consult to Patient Labeling in DARRTS 10 SEP 2015.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 22 JAN 2013 ***If yes, distribute minutes before filing meeting***	☒	☐		PIND 116608 meeting – 22 JAN 2013 (minutes dated 05FEB13)
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 18 SEP 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		Pre-NDA meeting – 18 SEP 2014 (minutes dated 07 OCT 2014)
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 23 September 2015

NDA #: 208424

PROPRIETARY NAME: GoNitro

ESTABLISHED/PROPER NAME: nitroglycerin powder (for sublingual use)

DOSAGE FORM/STRENGTH: 400 mcg (b) (4)

APPLICANT: G. Pohl-Boskamp GmbH & Co. KG

PROPOSED INDICATION: acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease

BACKGROUND: Nitroglycerin is an established treatment for angina pectoris. G. Pohl-Boskamp GmbH & Co. KG markets nitrolingual Pumpspray (NDA 18705). They are developing a new dosage form as an oral powder for sublingual administration. The sponsor met with the Division in January 2013 to discuss both the clinical and CMC development program to ensure adequate support for an NDA submission. The Pre-NDA meeting for this indication, under IND 116608, was 18 September 2014 (minutes dated 07 October 2014).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Bridget Kane	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Raj Madabushi		Y
Division Director	Norman Stockbridge		Y
Office Deputy	N/A		N/A
Clinical	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	TBD	N/A
	TL:	Raj Madabushi	Y
• Genomics	Reviewer:	N/A	N/A
• Pharmacometrics	Reviewer:	N/A	N/A
Biostatistics	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Phil Gatti	Y
	TL:	Thomas Papoian	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC) Review Team:	ATL:	Mohan Sapru	Y
	RBPM:	Maryam Changi	Y
• Drug Substance	Reviewer:	Sithumalli Chandramouli	N
• Drug Product	Reviewer:	Mariappan Chelliah	N
• Process	Reviewer:	Xuhong Li	N
• Microbiology	Reviewer:	N/A	N/A
• Facility	Reviewer:	Steven Hertz	N
• Biopharmaceutics	Reviewer:	Jing Li	N
• Immunogenicity	Reviewer:	N/A	N/A
• Labeling (BLAs only)	Reviewer:	N/A	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		N/A
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Karen Dowdy	Y
	TL:	Marcia Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Zarna Patel	N
	TL:	N/A	N/A

OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Janine Stewart	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	Kimberly Lehrfeld	N
OSE/DPV	Reviewer:	Amy Chen	N
	TL:	Susan Lu	N
OSE/OPE/DEPI	Reviewer:	Veronica Sansing	N
	TL:	Margie Goulding	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers/disciplines			
Other attendees	Darrell Lyons, OSE SRPM		Y
	Tri Bui Nguyen, OSE SRPM		Y
	Michael Montelone, ADL DCRP		N
	Alison Blaus, DCRP RPM		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO The Sponsor conducted a Phase 1 study (P1302NL) entitled "A randomized, controlled, open, crossover study in healthy volunteers to describe and compare the in vivo biopharmaceutical properties of an investigational nitroglycerin oral power."
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**: Drug Substance and Drug Product facilities will be inspected. Inspection date has not been provided	☐ Not Applicable ☒ YES ☐ NO

at this time.	
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge, MD, PhD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 11 Jan 16 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

BRIDGET E KANE
10/07/2015