CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208424Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 03, 2016
From	Rajanikanth Madabushi, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208424
Type	505(b)(1)
Applicant	G. Pohl-Boskamp GmbH & Co.KH
Date of Submission	August 06, 2015
PDUFA Goal Date	June 10, 2016
Proprietary Name / Established (USAN) names	GoNitro™ (nitroglycerin)
Dosage forms / Strength	Oral powder for sublingual use - 400 µg per packet
Proposed Indication(s)	Acute relief of an attack or prophylaxis of angina pectoris
Recommended:	**Approval**

This secondary review is based, on the primary reviews of:

- OPDP (Patel), 05/04/2016
- OSE/DMEPA (Stewart, Tu), 11/13/2015, 05/29/2016
- OSE/DMEPA (Thomas), 02/10/2016, 03/23/2016
- DPMH (Mastroyannis), 06/02/2016
- Patient Labeling (Dowdy), 05/05/2016
- OPQ (Sapru), 05/23/2016
- Pharmacology/Toxicology (Gatti), 12/21/2015
- Clinical Pharmacology (Pillai), 06/01/2016

Cross Discipline Team Leader Review Template

1. Introduction

In the current new drug application (NDA), G. Pohl-Boskamp GmbH & Co.KH is seeking authorization to market GoNitro, nitroglycerin (GTN) oral powder in a packet, a new formulation, under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic Act and 21 CFR §314.54. The product is intended for sublingual use. The proposed indication is acute relief of an attack or prophylaxis of angina pectoris.

Pohl-Boskamp has an approved NDA (NDA 18705) for the currently US marketed predecessor product to Nitroglycerin powder, namely Nitrolingual Pumpspray®. Nitrostat® tablets, Nitromist® metered dose aerosol and Nitrolingual Pumpspray® are currently available FDA approved sublingual formulations of GTN in the market.

The primary basis in support of this new drug application comes from a single pharmacokinetic bridging study (PL1302NL) in adult healthy subjects evaluating the relative bioavailability of nitroglycerin oral powder (test) and the approved Nitrolingual Pumpspray®.

2. Background

GTN is a nitric oxide donor and exerts its therapeutic action by means of cGMP-mediated venous and arteriolar vasodilatation resulting in reduced cardiac pre- and afterload, myocardial wall tension and oxygen demand. The efficacy of sublingual nitroglycerin for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease is well established.
During the IND stage, the Applicant had several meetings with the Agency (01/22/2013 and 09/18/2014) to discuss the development of nitrolycerin oral powder.

It was agreed that Pohl-Boskamp's NDA 18705 could be cross-referenced in the current nitroglycerin powder NDA under the 505(b)(1) approach. It was agreed that the results of an adequate comparative bioavailability study comparing Nitroglycerin powder to the Nitrolingual Pumpspray product and a complete drug product quality section (Module 3) would support the bridging to NDA 18705.

3. CMC

Based on the chemistry, manufacturing, and controls (CMC) and biopharmaceutics information provided in this submission, the Office of Pharmaceutical Quality (OPQ) reviewer states that the information is adequate for the drug substance and drug product. For the drug substance, the applicant has cross-referenced DMF No.: (b) (4) DMF No.: (b) (4), and subsequent annual reports have been previously reviewed and found adequate. The establishments for the commercial manufacturing, packaging and testing were inspected and were found to be acceptable. From a biopharmaceutics perspective, the review recommends the applicant perform a comparative solubility study, using a validated method, to support post-approval changes in formulation or drug product manufacturing process. Specifically, for the pre-change and post-change drug

product batches, not less than (b) (4)% of the drug product should be dissolved in 30 mL of the phosphate buffer (pH 6.8) in 5 minutes. The reviewer recommends approval of the product with a shelf-life of 18 months for the product when stored in the approved commercial container closure system at 20°C - 25°C (68°F-77°F), with excursions permitted between 5°C – 40°C (41°F – 104°F). The Office of Process and Facilities has recommended overall approval for manufacturing facilities concerning this NDA. The Applicant has satisfactorily addressed all the deficiencies that were communicated during the review and as such from a CMC perspective, OPQ recommends approval.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical studies submitted for this application. The Pharmacology/Toxicology reviewer concludes that all the inactive ingredients listed in the formulation are qualified.

5. Clinical Pharmacology

The clinical pharmacology review states that the information submitted to the application is sufficient to characterize and bridge the exposure of nitroglycerin oral powder to Nitrolingual Pumpspray®. The review recommends approval from a clinical pharmacology perspective.
The key findings are briefly described below:

- Following sublingual administration of two (b) (4) packs of GTN oral powder each containing 0.4 mg GTN (a total dose of 0.8 mg GTN), GTN oral powder shows higher maximum plasma concentration (Cmax) (geometric mean ratio (GMR): 2.07-fold) and area under the plasma concentration-time curve (AUC0-∞) (GMR: 1.56-fold) of GTN when compared to 0.8 mg Nitrolingual® Pumpspray.
- There is no difference in time to reach maximum plasma concentration (Tmax) or half-life (t1/2) between the two products.
- The systemic exposure to GTN following the administration of GTN oral powder is within the range of previous clinical trial experience with Nitrolingual Pumpspray®. Dose dependent increase in exercise tolerance, time to onset of angina and ST-segment depression were seen following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pumpspray as compared to placebo. The drug showed a profile of mild to moderate adverse events. As such the increased exposure with GTN oral powder is not expected to result in altered efficacy or safety profile compared to Nitrolingual Pumpspray®. Further, given the short half-life of nitroglycerin and dosing instructions to titrate till relief of chest pain (up to a maximum of 1200 mcg in 15 minutes over 5 minutes intervals) provides a strategy for safe use of GTN oral powder. Therefore, the efficacy and safety of GTN oral powder is expected to be similar to Nitrolingual Pumpspray®.
- Although Cmax of 1,2-GDN and 1,3-GDN was higher (GMR: 1.43 and 1.34-fold, respectively) following administration of GTN oral powder compared to RLD, the AUC0-∞ and t1/2 are similar between both products. The Tmax of 1,2-GDN and 1,3-GDN occurs slightly earlier for GTN oral powder compared to reference.
- The between subject variability of GTN following administration of test formulation (Cmax: 68% and AUC0-∞: 78%) is relatively lower compared to Nitrolingual Pumpspray® (Cmax: 115% and AUC0-∞: 118%).

6. Clinical Microbiology

There are no specific clinical microbiology issues in the current submission.

7. Clinical /Statistical Efficacy and Safety

There were no new clinical studies submitted for this application. During the IND, it was agreed that the applicant could cross-reference NDA 18705 for efficacy and safety.

8. Advisory Committee Meeting

The submission did not contain issues that required input from an Advisory Committee. Hence there was no Advisory Committee Meeting for this application.

9. Pediatrics

The applicant did not conduct pediatric studies. In order to meet the requirements of the Pediatric Research Equity Act (PREA), the Applicant is requesting a full waiver of pediatric studies in patients ages 0 to 17 years. The basis for requesting full waiver is that there is no objective evidence for the presence of coronary artery disease associated angina pectoris in the pediatric population. As such, studies in pediatric population are impossible to carry out. The Division and Pediatrics Review Committee (PeRC meeting on 05/04/2016) agree with the applicant's rationale for full waiver.

10. Other Relevant Regulatory Issues

There are no significant issues related to financial disclosure or inspections. There were 5 investigators that participated in the Study PL1302NL and these investigators did not have disclosable financial arrangements for the study sponsored by the applicant as per Form 3454 provided with the submission.

11. Labeling

There are no outstanding labeling related issues at this time. The proposed proprietary name GoNitro® has been reviewed by the Division of Medication Error Prevention and Analysis and is found acceptable from both a promotional and safety perspective.

12. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:**
  All the primary reviews are unanimous in their recommendation for approval. I concur with the primary reviewers. The recommended regulatory action is approval of GoNitro® (nitroglycerin oral powder), a new formulation for sublingual delivery of nitroglycerin for acute relief of an attack or prophylaxis of angina pectoris.
- **Risk Benefit Assessment:**
  The risk-benefit of GoNitro® when used as directed in the proposed labeling is not expected to be any different compared to Nitrolingual Pumpspray®.
- **Recommendation for other Postmarketing Requirements and Commitments:**
  There are no specific recommendations for post-market risk evaluation and mitigation strategies.

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/s/

RAJANIKANTH MADABUSHI
06/03/2016