CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203340Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	5/8/13
From	Billy Dunn, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	203340
Applicant	Arbor Pharmaceuticals
Date of Submission	11/20/12
PDUFA Goal Date	5/20/13
Proprietary Name / Established (USAN) names	Nymalize/Nimodipine
Dosage forms / Strength	3 mg/ml oral solution (20 ml[60 mg] per dose)
Proposed Indication(s)	Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition
Recommended:	Approval

1. Introduction

On 11/18/11, the sponsor (Arbor Pharmaceuticals) submitted a 505(b)(2) new drug application (NDA) to support the marketing of nimodipine (Nymalize), a new oral drug with a proposed indication for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition. Nimotop (approved nimodipine – NDA 18869, approved in 1998) is the Reference Listed Drug for this application.

After review, the application was not approved and a Complete Response (CR) letter was issued on 8/16/12. All aspects of the initial application were acceptable except for facility inspections. I reproduce the facility inspections deficiency, as noted in the CR letter, below:

> During a recent inspection of the Enterprises Importfab manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional details of the reasons for failure are found in the previous reviews of the original application, but, in brief, concerned inadequate light protection and storage conditions at a site of manufacture. The current submission addresses the facility inspections deficiency. No other changes to the application were submitted.

I refer to my previous review, dated 8/16/12, along with the various primary reviews of the initial submission, for a detailed discussion of the initial application's acceptability. The remainder of my review will briefly repeat background material from my previous review and otherwise will address only the outstanding issues remaining from the CR, facility inspections and labeling.

Nimodipine has been previously approved as an oral capsule filled with nimodipine liquid. The current application is for a nimodipine oral solution, a new and heretofore unapproved dosage form. The proposed mechanism of action of nimodipine is inhibition of vascular smooth muscle contractility due to calcium channel blockade.

The review team for this resubmission included the following primary reviewers:

Chemistry – Donghao Lu, PhD
Division of Medication Error Prevention and Analysis – Liu Liu, PharmD
Office of Prescription Drug Promotion – Gina McKnight-Smith
Study Endpoints and Labeling Development – Elizabeth Donohoe, MD

I discuss below the key conclusions of each reviewer and provide my recommendations regarding this submission.

2. Background

Nimodipine is the only approved drug to improve outcome in subarachnoid hemorrhage (SAH). The innovator no longer markets Nimotop, but several generic versions are available. Nimotop was withdrawn (b) (4), but not for reasons of safety or effectiveness.

As patients with SAH are often obtunded, the marketed liquid-filled capsules may, on occasion, not be administered as designed due to swallowing difficulties. In these situations, it has become standard practice to administer the nimodipine by extracting the contents of the capsule with a needle and then administering the extracted contents via nasogastric tube (this procedure is described in approved labeling). Despite multiple warnings in labeling and via various communications over the years, the extracted contents are, rarely but recurrently, erroneously administered intravenously. Such intravenous administration may be expected to, and has, resulted in death.

The sponsor developed the oral solution that is the subject of this application in order to allow for a more reliable oral dosing form and regimen that should minimize, or ideally eliminate, the dosing errors described above.

The sponsor's original submission presented manufacturing and nonclinical information to support its approval. This resubmission presents facility inspections and labeling information.

One meeting with the sponsor focused on this submission was scheduled but did not take place, as the sponsor canceled the meeting after receiving preliminary comments. There are no significant outstanding issues from the canceled meeting. The clinical development program under the associated IND (110870) was granted Fast Track designation and the current application was granted Priority Review. The action date of the original submission was extended due to a major amendment concerning CMC and nonclinical data.

3. CMC/Device

Dr. Lu reviewed this submission and recommends approval. His review notes the "Acceptable" overall recommendation from the Office of Compliance, reflecting the resolution of the deficiencies associated with the previous facility inspections.

There are no outstanding CMC issues. There are no CMC post-approval recommendations.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

N/A

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

N/A

8. Safety

N/A

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

N/A

12. Labeling

The sponsor submitted proposed labeling. See the separate labeling document for the labeling negotiated with the sponsor.

Dr. Liu reviewed the final proposed trade name, Nymalize, and found it acceptable. She reviewed the proposed container labels and carton labeling, and, after negotiation, found the final proposed versions acceptable.

Ms. McKnight-Smith the proposed prescribing information and made labeling recommendations.

Dr. Donohoe reviewed the proposed prescribing information and made labeling recommendations.

13. Recommendations/Risk Benefit Assessment

I recommend approval of this application.

The sponsor has submitted adequate information to support approval, based on a biowaiver, discussed in the previous review cycle, allowing reliance on the findings of safety and effectiveness of previously approved nimodipine (Nimotop).

All outstanding issues have been resolved. Acceptable labeling has been negotiated with the sponsor.

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/s/

WILLIAM H Dunn
05/09/2013