

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203340Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE: May 10, 2013

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 203-340

SUBJECT: Action Memo for NDA 203-340, for the use of Nymalize Oral Solution (nimodipine 60 mg/20mL) in the treatment of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial aneurysms

NDA 203-340, for the use of Nymalize Oral Solution (nimodipine 60 mg/20mL) in the treatment of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial aneurysms, was submitted by Arbor Pharmaceuticals, Inc., on 11/18/2011. The division issued a Complete Response (CR) letter to the sponsor on 8/16/12. The basis for the CR was a number of deficiencies found on inspection of the Enterprises Importfab manufacturing facilities (see my memo of 8/16/12 for a detailed review of the application submitted at that time).

The sponsor has responded to the CR letter in a submission dated 11/20/12. This submission has been reviewed by Dr. Donghao Lu, Office of New Drug Quality Assessment, Dr. Liu Liu, Division of Medication Error Prevention and Analysis, Gina McKnight-Smith, Office of Prescription Drug Promotion, Dr. Elizabeth Donohoe, Study Endpoints and Labeling Development, and Dr. Billy Dunn, neurology team leader and Cross-Discipline Team Leader. The review team recommends that the application be approved.

The sole deficiency that was the basis of the CR decision has now been resolved; that is, the Office of Compliance now finds that the manufacturing facility is acceptable.

We have negotiated labeling with the sponsor, and we are in agreement with the labeling language.

For these reasons, then, I will issue the attached Approval letter, with appended agreed-upon labeling.

Russell Katz, M.D.

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

/s/

RUSSELL G KATZ
05/10/2013

MEMORANDUM

DATE: August 13, 2012-08-13

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 203-340

SUBJECT: Action Memo for NDA 203-340, for the use of Nymalize Oral Solution (nimodipine 60 mg/20 mL) in the treatment of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial aneurysms

NDA 203-340, for the use of Nymalize Oral Solution (nimodipine 60 mg/20 mL), a calcium channel blocker, in the treatment of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial aneurysms, was submitted by Arbor Pharmaceuticals, Inc. on 11/18/2011. Nimodipine is currently marketed in liquid-filled capsule forms for the same indication; the approved dosing regimen is 60 mg every 4 hours for 21 days, to be initiated within 96 hours after the subarachnoid hemorrhage.

In patients who cannot swallow the available capsules intact (e.g., patients with a nasogastric tube or PEG), the contents of the capsule can be drawn up via a needle attached to a syringe, and the contents can be delivered from the syringe, with the needle removed, into the tube. However, there have been reports of hospital personnel injecting the drug intravenously, with severe clinical consequences, including death. This inadvertent use results directly from the fact that the contents of the capsule are drawn into a syringe by needle; in some cases, when the needle is inadvertently left on the syringe, hospital staff has mistakenly injected the drug intravenously. Although various labeling changes warning of this possibility have been instituted over the years, the possibility of these events still occurring has led the Agency to encourage the development of an oral formulation that can be delivered to all patients without requiring the use of a needle at any stage to prepare the dosage.

This application proposes just such a formulation. An oral solution can be taken by patients who are able to swallow, and can also be given into an NG tube or PEG without the necessity of drawing it up with a needle.

This application contains the requisite chemistry and manufacturing controls (CMC) data, as well as short term animal toxicity studies. The sponsor has presented no clinical data, and has requested a waiver of the requirement to perform a bioequivalence study comparing the kinetics of this formulation to the marketed product.

The application has been reviewed by Jung Lee, Division of Medication Error Prevention and Analysis (DMEPA); Drs. Richard Siarey and Lois Freed, pharmacology/toxicology; Drs. Donghao Lu and Martha Heimann, Office of New Drug Quality Assessment (ONDQA; CMC); Dr. Kareen Riviere, ONDQA, Biopharmaceutics; Dr. Erika Pfeiler, Microbiology; Dr. Xinning Yang, Office of Clinical Pharmacology; Dr. John Marler, medical officer; and Dr. Billy Dunn, neurology team leader and Cross-Discipline Team Leader (CDTL).

In brief, Dr. Riviere has concluded that the sponsor can be granted a waiver of the requirement to demonstrate bioequivalence to a marketed nimodipine dosage form, based on several criteria, including the fact that the marketed dosage form can be given as an oral solution (see above; this implies that the oral solution is bioequivalent to the drug given in the capsule) and there are no inactive ingredients expected to affect the bioavailability of the oral solution.

Further, as has been described by Drs. Lu, Siarey, and Freed, the proposed product, when the application was submitted, had 6 impurities, the proposed acceptance criteria for which exceeded the threshold for qualification of NMT (b) (4) % (the sponsor asserted that one of the impurities, so-called (b) (4) (b) (4) . Ultimately, the sponsor lowered the specifications for 3 of the impurities to acceptable levels, leaving 3 (including (b) (4) with proposed specifications above the qualification threshold (the proposed specification for (b) (4) was (b) (4) %; for the other two, (b) (4) %).

To establish the acceptability of the proposed specifications for the two non-(b) (4) impurities, the sponsor performed a two-week toxicity study in rat intended to qualify the impurities. Drs. Siarey and Freed find this study acceptable.

To qualify (b) (4), the sponsor submitted literature reports that ostensibly demonstrate that (b) (4) is, indeed, (b) (4) and that the amounts of (b) (4) circulating at therapeutic doses are considerably greater than the amounts present in the product at the proposed specification. Dr. Yang has concluded that the literature report does establish these facts.

The Office of Compliance (OC) has performed inspections of several of the manufacturing sites. An inspection of the site of the manufacturer of the finished dosage form, Enterprises Importfab of Pointe-Claire, Canada, has revealed numerous deficiencies that have led OC to recommend that the application not be approved.

In brief, nimodipine is light-sensitive, and must be protected from light. At numerous steps in the manufacture of the finished dosage form, the inspection revealed that the company had not ensured that the API was adequately

protected by light. For example, [REDACTED] (b) (4)

[REDACTED] during various phases of the manufacture were not adequately protected from light. In addition, the physical inadequacies of the plant led to the possibility of contamination of the Nymalize product with another product being manufactured there.

These deficiencies were presented to the site, and the sponsor has responded; however, OC has found these responses to be inadequate.

Therefore, despite the conclusion that the CMC and toxicology data, as well as the pharmacokinetic considerations, support the approval of the application, the findings on inspection are sufficiently serious to question the integrity of the product, and for this reason, I will issue the attached Complete Response (CR) letter.

Russell Katz, M.D.

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

/s/

RUSSELL G KATZ
08/16/2012

Cross-Discipline Team Leader Review

| | |
|--|---|
| Date | 8/16/12 |
| From | Billy Dunn, MD |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 203340 |
| Supplement# | |
| Applicant | Arbor Pharmaceuticals |
| Date of Submission | 11/18/11 |
| PDUFA Goal Date | 8/18/12 |
| | |
| 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: | Complete Response |

1. Introduction

The sponsor (Arbor Pharmaceuticals) has 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.

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 NDA included the following primary reviewers:

Chemistry – Donghao Lu, PhD
 Chemistry (Biopharmaceutics) – Kareen Riviere, PhD
 Chemistry (Microbiology) – Erika Pfeiler, PhD
 Nonclinical – Richard Siarey, PhD
 Clinical Pharmacology – Xinning Yang, PhD
 Clinical – John Marler, MD

OSE (DMEPA – Carton and Container Labeling) – Jung Lee, RPh

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 the drug, but several generic versions are available.

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 application presents manufacturing and nonclinical information to support its approval.

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 was extended due to a major amendment concerning CMC and nonclinical data.

3. CMC/Device

Dr. Lu reviewed this submission and does not recommend approval due to a "Withhold" recommendation for the manufacturing facility from the Office of Compliance. This "Withhold" recommendation stems from a failure on the part of the manufacturer to provide necessary protection from light during the manufacture of the drug product. I have reviewed the Establishment Inspection Report related to this deficiency and find it consistent with Dr. Lu's recommendation. Dr. Lu's recommendation has supervisory endorsement.

In addition, Dr. Lu's review discusses the presence of impurities, (b) (4), that exceeded the qualification threshold, and the studies conducted to qualify those impurities. There are no obstacles to approval in this regard.

Dr. Riviere reviewed this submission and recommends approval. She notes that the sponsor requested a biowaiver and she recommends that it be granted.

Dr. Pfeiler reviewed this submission and recommends approval.

The only outstanding CMC issue is the “Withhold” recommendation. There are no CMC post-approval recommendations.

4. Nonclinical Pharmacology/Toxicology

Dr. Siarey reviewed this submission and recommends approval.

His review (along with that of his Team Leader, Lois Freed, PhD) discusses the presence of impurities, [REDACTED] ^{(b) (4)}, that exceeded the qualification threshold, and the studies conducted to qualify those impurities. There are no obstacles to approval in this regard.

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

5. Clinical Pharmacology/Biopharmaceutics

Dr. Yang reviewed this submission and found it acceptable.

Her review discusses the presence of [REDACTED] ^{(b) (4)}, one of the above noted impurities [REDACTED] ^{(b) (4)} and concludes the risk of exposure to this compound has been adequately characterized and that exposure confers no additional risk.

There are no outstanding clinical pharmacology issues. There are no clinical pharmacology post-approval recommendations.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Dr. Marler reviewed this submission and recommends approval. It should be noted that the “Withhold” recommendation was not known to Dr. Marler at the time his review was filed.

His review is not intended to address this recommendation. There was no clinical data submitted in this application.

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

8. Safety

See Section 7.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

N/A

12. Labeling

The sponsor submitted proposed labeling. As a Complete Response action is anticipated, a detailed clinical review of the proposed labeling was not completed.

Ms. Lee reviewed the carton and container labeling submitted by the sponsor. Her comments and recommendations have been communicated to the sponsor throughout the review period

Ms. Lee reviewed the proposed proprietary name and found it acceptable.

13. Recommendations/Risk Benefit Assessment

I do not recommend approval of this application. Based on the “Withhold” recommendation summarized in this review and detailed in Dr. Lu’s review, I recommend the following deficiencies serving as the basis for a Complete Response be communicated to the sponsor in

the action letter (the following reflects standardized language concerning “Withhold” recommendations resulting from facility inspections):

FACILITY INSPECTIONS

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.

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

/s/

WILLIAM H Dunn
08/16/2012

CLINICAL REVIEW

Application Type Type 3
Application Number(s) NDA 203340
Priority or Standard Priority

Submit Date(s) November 18, 2011
Received Date(s) November 18, 2011
PDUFA Goal Date August 18, 2012
Division / Office Division of Neurology Products

Reviewer Name(s) John Marler
Review Completion Date March 18, 2012

Established Name Nimodipine
(Proposed) Trade Name Nymalize
Therapeutic Class calcium channel blocker
Applicant Arbor Pharmaceuticals

Formulation(s) Oral solution 3mg/ml
Dosing Regimen 20 mL (60 mg) every 4 hours
for 21 consecutive days
Indication(s) Subarachnoid hemorrhage
Intended Population(s) Adults

Table of Contents

| | | |
|----------|---|----------|
| 1 | RECOMMENDATIONS/RISK BENEFIT ASSESSMENT | 4 |
| 1.1 | Recommendation on Regulatory Action | 4 |
| 1.2 | Risk Benefit Assessment..... | 4 |
| 1.3 | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ... | 4 |
| 1.4 | Recommendations for Postmarket Requirements and Commitments | 4 |
| 2 | INTRODUCTION AND REGULATORY BACKGROUND | 4 |
| 2.1 | Product Information | 5 |
| 2.2 | Tables of Currently Available Treatments for Proposed Indications | 5 |
| 2.3 | Availability of Proposed Active Ingredient in the United States | 5 |
| 2.4 | Important Safety Issues With Consideration to Related Drugs..... | 5 |
| 2.5 | Summary of Presubmission Regulatory Activity Related to Submission | 5 |
| 2.6 | Other Relevant Background Information | 6 |
| 3 | ETHICS AND GOOD CLINICAL PRACTICES..... | 6 |
| 3.1 | Submission Quality and Integrity | 6 |
| 3.2 | Compliance with Good Clinical Practices | 6 |
| 3.3 | Financial Disclosures..... | 6 |
| 4 | SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES | 6 |
| 4.1 | Chemistry Manufacturing and Controls | 6 |
| 4.2 | Clinical Microbiology..... | 6 |
| 4.3 | Preclinical Pharmacology/Toxicology | 6 |
| 4.4 | Clinical Pharmacology | 6 |
| 5 | SOURCES OF CLINICAL DATA..... | 7 |
| 6 | REVIEW OF EFFICACY | 7 |
| | N/A since there was no clinical data submitted for review..... | 7 |
| 7 | REVIEW OF SAFETY..... | 7 |
| 8 | POSTMARKET EXPERIENCE..... | 7 |
| 9 | APPENDICES | 8 |
| 9.1 | Literature Review/References | 8 |
| 9.2 | Labeling Recommendations | 8 |
| 9.3 | Advisory Committee Meeting..... | 8 |

Table of Tables

| | |
|--|---|
| Table 1 Literature References for Four Clinical Trials in Label..... | 8 |
|--|---|

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval

1.2 Risk Benefit Assessment

Nymalize nimodipine oral solution is expected to be safer than the Nimotop gelatin capsule formulation approved in 1988. In order to administer nimodipine to patients who cannot swallow, the contents of Nimotop gelatin capsules are removed with hypodermic needles for administration through a gastric tube. On rare occasions the liquid extracted from the capsules has been accidentally administered intravenously. These accidents are less likely to occur with the Nymalize oral solution since hypodermic needles will not be used.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

No recommendations.

2 Introduction and Regulatory Background

Spontaneous subarachnoid hemorrhage is often fatal. In those who survive, nimodipine given for 21 days after the hemorrhage reduces the severity of long term disability. Nimodipine is regarded as part of standard care for most patients who survive the initial hemorrhagic event. Because the patients are often seriously ill, many cannot swallow the gelatin capsules which are the only available form of nimodipine. To treat them hospital staff use hypodermic needles to withdraw the liquid contents of the capsule for delivery via gastric tube.

Rarely, accidental intravenous administration of the liquid contents of nimodipine gelatin capsules has caused serious injury and death. The addition of a black box warning and other label changes has not reduced the number of accidental IV administrations.

The sponsor developed an oral solution to address this problem.

2.1 Product Information

FDA approved oral nimodipine liquid-filled gelatin capsules in 1988. The approved indication is to improve neurological outcome in patients with subarachnoid hemorrhage due to ruptured aneurysms. The sponsor proposes a new formulation of nimodipine as an oral solution for the same indication.

2.2 Tables of Currently Available Treatments for Proposed Indications

Nimodipine gelatin capsules are the only available treatment for the indication.

2.3 Availability of Proposed Active Ingredient in the United States

On the “Drugs@FDA” website, FDA identifies three companies that manufacture generic nimodipine gelatin capsules: Banner, Sun, and Barr. The innovator, Bayer, has withdrawn their NDA for marketing reasons.

2.4 Important Safety Issues With Consideration to Related Drugs

In response to a Division of Medication Errors Prevention and Analysis (DMEPA) review, on August 2, 2010, FDA posted a Drug Safety Communication to remind healthcare professionals to avoid accidental IV administration of nimodipine capsule contents. “FDA identified 31 cases of medication errors associated with the use of nimodipine that were reported to FDA's Adverse Event Reporting System (AERS), the Pennsylvania Patient Safety Reporting System (PA-PSRS), the Institute for Safe Medication Practices' (ISMP) Quantros MEDMARX database, and the Council for International Organizations of Medical Sciences (CIOMS) II database, and published in the medical literature between 1989 (initial marketing of nimodipine) and 2009. Of the 31 medication errors, 25 involved erroneous intravenous nimodipine prescribing or administration. Four of the patients who mistakenly received nimodipine intravenously died; five patients were characterized as having near-death events; and one patient was characterized as having suffered permanent harm as a result of the inadvertent intravenous administration of nimodipine.”

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Under IND 110870, the sponsor requested a type C meeting on December 10, 2010, to discuss the submission of an NDA application for an oral formulation of nimodipine. After receiving DNP pre-meeting comments, the sponsor withdrew the meeting request. DNP granted Fast Track Designation on July 20, 2011.

2.6 Other Relevant Background Information

August 8, 2010, FDA issued a drug safety communication: “Serious medication errors from intravenous administration of nimodipine oral capsules.” FDA announced its intention to “continue working with the manufacturers of nimodipine and with outside groups to evaluate and implement additional ways to prevent medication errors with this product.”

3 Ethics and Good Clinical Practices

N/A since there was no clinical data submitted for review.

3.1 Submission Quality and Integrity

N/A since there was no clinical data submitted for review.

3.2 Compliance with Good Clinical Practices

N/A since there was no clinical data submitted for review.

3.3 Financial Disclosures

N/A since there was no clinical research performed.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the CMC review.

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

Please see the clinical pharmacology and toxicology review.

4.4 Clinical Pharmacology

N/A since there was no clinical data submitted for review.

5 Sources of Clinical Data

N/A since there was no clinical data submitted for review.

6 Review of Efficacy

N/A since there was no clinical data submitted for review.

7 Review of Safety

N/A since there was no clinical data submitted for review.

8 Postmarket Experience

N/A since there was no clinical data submitted for review.

9 Appendices

9.1 Literature Review/References

In 2008, the Cochrane Library published an online review entitled “Calcium antagonists for aneurysmal subarachnoid haemorrhage.”¹ After reviewing the results of 16 trials, the authors concluded that “calcium antagonists reduce the risk of poor outcome and secondary ischaemia after aneurysmal SAH. The results for 'poor outcome' depend largely on a single large trial of oral nimodipine; the evidence for other calcium antagonists is inconclusive. ... Overall, calcium antagonists reduced the risk of poor outcome: the relative risk (RR) was 0.81.”

The tables in the approved and proposed drug label do not identify the four clinical trials. The following table gives references for the four trials mentioned in the label.

Table 1 Literature References for Four Clinical Trials in Label

| ID for Trial In Label | Trial Description in Label | Literature reference from Cochrane Review | Nimodipine | Placebo |
|-----------------------|----------------------------|---|------------|---------|
| Trial #1 | US | Allen 1983 | 56 | 60 |
| Trial #2 | French | Philippon 1986 | 31 | 39 |
| Trial #3 | UK | Pickard 1989 | 278 | 276 |
| Trial #4 | Canadian | Petruk 1988 | 72 | 82 |

9.2 Labeling Recommendations

The sponsor did not submit any clinical data to support their application other than the information contained in previous approved product labels for the Nimotop gelatin capsule formulation of nimodipine. There is no need to change the clinical trial section of the previous label. The sponsor has modified the previous label format to meet new PLR requirements.

9.3 Advisory Committee Meeting

DNP determined that no Advisory Committee Meeting is necessary.

¹ <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000277.pub3/abstract> . Sanne Dorhout Mees, Gabriel JE Rinkel, Valery L Feigin, Ale Algra, Walter M van den Bergh, Marinus Vermeulen, Jan van Gijn. “Calcium antagonists for aneurysmal subarachnoid haemorrhage”

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

/s/

JOHN R MARLER
07/17/2012

WILLIAM H Dunn
08/16/2012
See CDTL memo for my recommendation.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|----------------------|---|-----|----|----|---------|
| | proposed draft labeling? | | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | | | X | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | X | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | | | X | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | | | X | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | | | X | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | | | X | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | | | X | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | | | X | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | | | X | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | X | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | | | X | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | | | X | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|---------|
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | X | ° |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | | | X | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | | | X | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | | | X | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | | | X | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | | | X | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | | | X | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | | | X | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | | | X | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? N/A

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The application is fileable.

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

1) None.

John Marler, M.D.

 Reviewing Medical Officer


 Date 6-Feb-2012

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Billy Dunn, M.D.

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

JOHN R MARLER
03/23/2012

WILLIAM H Dunn
04/02/2012