

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205919Orig1s000

MEDICAL REVIEW(S)

Secondary (Team Leader) Review

| | |
|--|---|
| Date | April 10, 2014 |
| From | Albert Deisseroth, MD, PhD |
| Subject | Secondary Review |
| NDA Number | NDA 205919 |
| Applicant | NOVA Laboratories Limited |
| Date of Submission | July 10, 2013 |
| PDUFA Goal Date | May 10, 2014 |
| Established Name/Proprietary Name | 6-mercaptopurine/Purixan |
| Dosage Forms/Strength | Suspension 20 mg/ml |
| Applicant's Proposed Indication | Component of multi-drug (b) (4) therapy of acute lymphoblastic leukemia |
| Recommended: | Approval |

| Material Reviewed/Consulted | Reviewer/Author |
|-----------------------------|---|
| Medical Officer Review | Patricia Dinndorf, MD |
| Pharmacology/Toxicology | Rama Gudi, PhD/Haleh Saber, PhD |
| CMC | Danuta Gromek-Woods, PhD/Janice Brown, PhD |
| Biostatistics | Kyung Lee, PhD, Lie Nie, PhD |
| Clinical Pharmacology | Jeffrey Huang, DPharm/Julie Bullock, DPharm |
| Regulatory Program Manager | Kris Kolibab |

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1. EXECUTIVE SUMMARY: (This was excerpted from the review of Dr. Patricia Dinndorf):

On July 9, 2013, NOVA Laboratories Limited submitted a NDA for 6-mercaptopurine (6-MP) or Purixan, under the Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and as such, relies on publically available information. The indication is “component of multi-drug (b)(4) therapy of acute lymphoblastic leukemia (ALL).”

The Risk Benefit Assessment, as formulated by Dr. Dinndorf is given below in Table 1.

Table 1: Risk Benefit Assessment

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|--|--|
| Analysis of Condition Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood with a peak incidence at the age of 3 years. | Summary of evidence: Mercaptopurine has been an integral component of ALL therapy since it was approved in 1953. Successive clinical trials have demonstrated its contribution to successful maintenance therapy and improved survival of patients with ALL. | Conclusions (implications for decision): 1. A formulation that provides more accurate dosing in a palatable form is a major contribution to ALL therapy, especially in younger patients unable to swallow pills. 2. An alternative formulation also ensures better drug availability in the event of a drug shortage. |
| Unmet Medical Need The currently available 50 mg tablet is not an ideal formulation or dosing presentation for younger children. | Summary of evidence: The formulation of a suspension 20 mg/ml is an appropriate presentation of a medicine usually administered to children less than 5 years of age at doses between 10 to 30 mg/day. | Conclusions (implications for decision): The presentation of Purixan is an appropriate formulation which is superior to the 50 mg tablet formulation available, especially for children less than 5 years of age. |
| Clinical Benefit See Unmet Medical Need | | |
| Risk Approved package in this application is a bottle of the suspension. Appropriate dosing requires the appropriate size syringe be chosen and caregiver instructed in appropriate method to measure and administer the required dose | Summary of evidence: 10 to 20 mg best delivered by a 1 ml syringe >20 mg best delivered by a 5 ml syringe Caregiver must shake bottle adequately and remove the appropriate dose, either by putting syringe in bottle and withdrawing or pouring out an aliquot and then measuring in the syringe. | Conclusions (implications for decision): An alternative dispensing presentation is a bottle with an adapter to connect the syringe used to draw up the dose. This presentation is currently in use in Europe. This presentation is superior to the bottle with syringes provided by pharmacist. |
| Risk Management | Summary of evidence: | Conclusions (implications |

| | | |
|---|--|---|
| Ensure caregivers have adequate instructions to accurately measure and administer the correct dose | | for decision): 1. Label information and a Med Guide to provide instructions for assuring the proper dose is administered. 2. Have Applicant introduce the dispensing system described above. |
| Benefit-Risk Summary and Assessment Purixan is a superior presentation of mercaptopurine for younger children. For younger children, especially those unable to swallow capsules this formulation is superior to 50 mg tablets that are broken, crushed or extemporaneously formulated. | | |

Recommendation for Regulatory Action: On the basis of the above, this reviewer recommends approval.

2. BACKGROUND: (This section was excerpted from the review of Dr. Pat Dinndorf): This is a 505(b)(2) application. Approval is based on the results of a bioequivalence study comparing the US formulation of Purinethol to the suspension, Purixan. The clinical pharmacology reviewer has evaluated the acceptability of the results of this study to support this application.

2.1 Product Information: Purixan is a 20 mg/ml oral suspension of 6-mercaptopurine monohydrate which includes inactive ingredients xanthan gum, aspartame, concentrated raspberry juice, methyl hydroxybenzoate, propyl hydroxybenzoate and water for irrigation.

2.2 Availability of Proposed Active Ingredient in the United States: The only formulation of 6 mercaptopurine currently available in the US is a 50 mg tablet (Purinethol® (mercaptopurine) tablets).

It is common practice in the US for pharmacies to compound suspensions of Purinethol. The following are directions for compounding a suspension provided by the Children's Oncology Group (COG). (DRUG INFORMATION FOR COMMERCIAL AGENTS USED BY THE CHILDREN'S ONCOLOGY GROUP; Version 6 Dated 6/19/13)

For children unable to swallow the tablets whole, a 50 mg/mL oral suspension can be compounded. The suspension is prepared by crushing 50 mercaptopurine 50 mg tablets in a mortar and adding 8.5 mL sterile water for irrigation. The mixture is triturated to form a smooth paste. Next, 16.5 mL simple syrup (pH=7) are added with continuous mixing and finally cherry syrup (pH=7.1) is added to a total volume of 50 mL. The suspension is stable in amber glass bottles at room temperature (19°C -23°C) for up to 5 weeks. The suspension should be shaken well before each use.

2.3 Important Safety Issues With Consideration to Related Drugs: The most common adverse events associated with treatment with 6-mercaptopurine are myelosuppression, hepatotoxicity, and mucositis. The dose of 6 mercaptopurine is usually titrated to maintain an absolute neutrophil count between 500 to 1500/ μ L.

2.4 Summary of Presubmission Regulatory Activity Related to Submission: A summary of the Regulatory History is provided in Table 2.

Table 2: Regulatory History

| Regulatory History | | |
|--------------------|---------------------------------|--|
| Date | Item | Discussion |
| 9/8/2011 | Pre- IND Meeting IND 112823 | Meeting with FDA to discuss development of 6-mercaptopurine as a commercial product <ul style="list-style-type: none"> - Additional toxicology studies not required - Discussion regarding Cmax outside of bioequivalence limits . Sponsor provided justification. FDA advised sponsor to include justification in application - FDA suggested safety data would be helpful to justify the deviation from acceptable bioequivalence. Sponsor stated formulation used in UK and Ireland over last 10 years. No formal study of safety done. FDA stated safety information should be included in application. |
| 12/1/2011 | CMC Meeting | Discussion of whether US Prinethol could be considered equivalent to EU Puri-Nethol. The formulations use different (b) (4) <ul style="list-style-type: none"> - FDA additional data comparing formulations would be required - (b) (4) - (b) (4) FDA state this would be a major formulation change. |
| 8/20/12 | Orphan Drug Designation | Nova Laboratories Limited received Orphan designation for mercaptopurine for the indication "Treatment of acute lymphoblastic leukemia in pediatric patients" |
| 1/18/2013 | Teleconference – Type B Meeting | Nova conducted a second bioequivalence study with with a 6-mercaptopurine compared to US formulation of Purinethol. <ul style="list-style-type: none"> - Discussion of Cmax outside the accepted bioequivalence criteria. - FDA stated sponsor needed to provide data supporting the conclusion higher Cmax did not result in safety signal. FDA advised sponsor on data required to support their position. |

2.5 Other Relevant Background Information: The activity of 6-mercaptopurine in ALL was first described in 1953 by Burchenal. Hematologic remission were attained in 15 of 45 children with acute leukemia treated with 6-mercaptopurine.

ALL is the most common malignancy of childhood with a peak incidence among children aged 2 to 3 years. There has been dramatic improvement in survival as a result of successive clinical trials of multiagent chemotherapy.

After initial remission induction therapy, subsequent treatment with 6-mercaptopurine has been demonstrated to be an important component of the successful treatment strategy of ALL. The backbone of maintenance therapy in most protocols includes daily oral mercaptopurine and

weekly methotrexate. The importance of 6-mercaptopurine therapy in the overall success of ALL therapy is also supported by the observation that poor compliance with oral 6-mercaptopurine is associated with an inferior outcome.

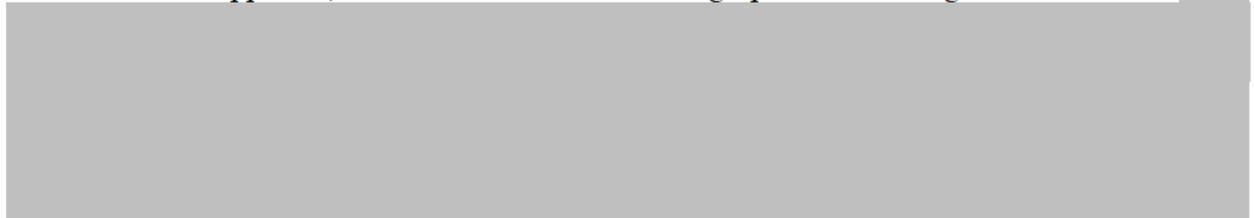
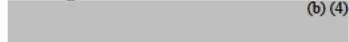
The daily dose of 6-mercaptopurine ranges from 25 to 75 mg/m² depending on the treatment protocol. In most protocols the dose is titrated to maintain the absolute neutrophil count between 500 to 1500/ μ L.

An inherited deficiency of thiopurine S-methyltransferase (TPMT), an enzyme that inactivates mercaptopurine results in altered metabolism of 6-mercaptopurine. Patients with TPMT deficiency are unable to tolerate conventional doses of 6-mercaptopurine without dose reduction.

There is only one presentation of 6-mercaptopurine commercially available in the US, 50 mg tablets. Because of the age and weight range of children with ALL, a 50 mg tablet is not ideal. Body weight dosing and dose adjustments are not easily accomplished with the 50 mg tablet. Tablets are not an ideal dosage form of medication for children less than 6 years. *Ad hoc* local formulations compounded in pharmacies are commonly used. Alternatively 50 mg tablets are split to provide children with the desired dose. Neither of these approaches provides precise dosing.

Compared to tablets, a suspension offers the advantage of more accurately delivering the desired dose to children with a wide range of weights. A suspension will allow more flexibility in adjusting the dose. A commercially produced suspension is more likely to provide a more consistent dose of 6-mercaptopurine than *ad hoc* compounded formulations.

3. CMC: Please see CMC review of Dr. Danuta Gromek-Woods for details. The review division recommended approval, but issued the following post marketing commitment: ^{(b) (4)}

 Nova will provide data from "in use" stability studies. Also included in the submission will be  ^{(b) (4)} data and revised labelling to include patient instructions.

4. NON-CLINICAL: Please see the review of Dr. Rama Gudi for details. The Non-clinical review division recommended approval.

5. CLINICAL PHARMACOLOGY: Please see the review of Dr. Jeffrey Huang for details of the bioequivalence study comparing the US formulation of Purinethol to the suspension of 6-MP (Purixan). The Clinical Pharmacology Division recommended approval.

6. EFFICACY: No new efficacy data was submitted with the application.

7. SAFETY: No new safety data was submitted with the application.

8. OTHER RELEVANT REGULATORY ISSUES: The following post marketing commitment was issued: (b) (4)



Nova will provide data from "in use" stability studies. Also included in the submission will be (b) (4) data and revised labelling to include patient instructions.

9. LABELING: The labeling is currently under negotiation.

10. RECOMMENDATION: This reviewer recommends approval.

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/s/

ALBERT B DEISSEROTH
04/10/2014

CLINICAL REVIEW

Application Type 505(b)(2)
Application Number(s) 205919
Priority or Standard Standard

Submit Date(s) 7/9/13
Received Date(s) 7/10/13
PDUFA Goal Date 5/10/14
Division / Office DHP/OHOP

Reviewer Name(s) Patricia Dinndorf
Review Completion Date 3/19/14

Established Name 6-mercaptopurine (6-MP)
(Proposed) Trade Name Purixan
Therapeutic Class Nucleoside metabolic inhibitor
Applicant NOVA Laboratories Limited

Formulation(s) Suspension 20 mg/ml
Dosing Regimen 1.5 to 2.5mg/kg/day or
(b) (4) to 75 mg/m²/day
Indication(s) Component of multi-drug (b) (4)
(b) (4) therapy of acute
lymphoblastic leukemia (ALL)
Intended Population(s) Patients with ALL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend this application 505(b)(2) application for Purixan be approved. This formulation of 6-mercaptopurine will improve the ability to reliably provide the appropriate dose of this essential medication to children with acute lymphoblastic leukemia (ALL).

1.2 Risk Benefit Assessment

Table 1: Risk Benefit Assessment

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|--|--|--|
| Analysis of Condition Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood with a peak incidence at the age of 3 years. | Summary of evidence: Mercaptopurine has been an integral component of ALL therapy since it was approved in 1953. Successive clinical trials have demonstrated its contribution to successful maintenance therapy and improved survival of patients with ALL. | Conclusions (implications for decision): 1. A formulation that provides more accurate dosing in a palatable form is a major contribution to ALL therapy, especially in younger patients unable to swallow pills. 2. An alternative formulation also ensures better drug availability in the event of a drug shortage. |
| Unmet Medical Need The currently available 50 mg tablet is not an ideal formulation or dosing presentation for younger children. | Summary of evidence: The formulation of a suspension 20 mg/ml is an appropriate presentation of a medicine usually administered to children less than 5 years of age at doses between 10 to 30 mg/day. | Conclusions (implications for decision): The presentation of Purixan is an appropriate formulation which is superior to the 50 mg tablet formulation available, especially for children less than 5 years of age. |
| Clinical Benefit See Unmet Medical Need | | |
| Risk Approved package in this application is a bottle of the suspension. Appropriate dosing requires the appropriate size syringe be chosen and caregiver instructed in appropriate method to measure and administer the required dose | Summary of evidence: 10 to 20 mg best delivered by a 1 ml syringe >20 mg best delivered by a 5 ml syringe Caregiver must shake bottle adequately and remove the appropriate dose, either by putting syringe in bottle and withdrawing or pouring out an aliquot and then measuring in the syringe. | Conclusions (implications for decision): An alternative dispensing presentation is a bottle with an adapter to connect the syringe used to draw up the dose. This presentation is currently in use in Europe. This presentation is superior to the bottle with syringes provided by pharmacist. |

| | | |
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| Risk Management Ensure caregivers have adequate instructions to accurately measure and administer the correct dose | Summary of evidence: | Conclusions (implications for decision): 1. Label information and a Med Guide to provide instructions for assuring the proper dose is administered. 2. Have Applicant introduce the dispensing system described above. |
| Benefit-Risk Summary and Assessment | | |
| Purixan is a superior presentation of mercaptopurine for younger children. For younger children, especially those unable to swallow capsules this formulation is superior to 50 mg tablets that are broken, crushed or extemporaneously formulated. | | |

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- Label information
- Medication Guide
- Introduction of the presentation currently use in Europe

1.4 Recommendations for Postmarket Requirements and Commitments

CMC will provide a PMR that will [REDACTED] (b) (4)

2 Introduction and Regulatory Background

This is a 505(b)(2) application. Approval is based on the results of a bioequivalence study comparing the US formulation of Purinethol to the suspension, Purixan. The clinical pharmacology reviewer has evaluated the acceptability of the results of this study to support this application.

2.1 Product Information

Purixan 20 mg/ml oral suspension

Purixan is a suspension of 6-mercaptopurine monohydrate which includes inactive ingredients xanthan gum, aspartame, concentrated raspberry juice, methyl hydroxybenzoate, propyl hydroxybenzoate and water for irrigation.

2.3 Availability of Proposed Active Ingredient in the United States

The only formulation of 6 mercaptopurine currently available in the US is a 50 mg tablet (Purinethol® (mercaptopurine) tablets).

It is common practice in the US for pharmacies to compound suspensions of Purinethol. The following are directions for compounding a suspension provided by the Children's Oncology Group (COG). (DRUG INFORMATION FOR COMMERCIAL AGENTS USED BY THE CHILDREN'S ONCOLOGY GROUP; Version 6 Dated 6/19/13)

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2.4 Important Safety Issues With Consideration to Related Drugs

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of the Regulatory History is provided in Table 2.

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| Regulatory History | | |
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| 8/20/12 | Orphan Drug Designation | Nova Laboratories Limited received Orphan designation for mercaptopurine for the indication "Treatment of acute lymphoblastic leukemia in pediatric patients" |
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2.6 Other Relevant Background Information

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ALL is the most common malignancy of childhood with a peak incidence among children aged 2 to 3 years. There has been dramatic improvement in survival as a result of successive clinical trials of multiagent chemotherapy.

After initial remission induction therapy, subsequent treatment with 6-mercaptopurine has been demonstrated to be an important component of the successful treatment strategy of ALL (MRC 1986; Dolan 1989). The backbone of maintenance therapy in most protocols includes daily oral mercaptopurine and weekly methotrexate. The

importance of 6-mercaptopurine therapy in the overall success of ALL therapy is also supported by the observation that poor compliance with oral 6-mercaptopurine is associated with an inferior outcome (Bhatia 2012).

The daily dose of 6-mercaptopurine ranges from 25 to 75 mg/m² depending on the treatment protocol. In most protocols the dose is titrated to maintain the absolute neutrophil count between 500 to 1500/ μ L.

An inherited deficiency of thiopurine S-methyltransferase (TPMT), an enzyme that inactivates mercaptopurine results in altered metabolism of 6-mercaptopurine. Patients with TPMT deficiency are unable to tolerate conventional doses of 6-mercaptopurine without dose reduction (Relling 1999; Anderson1998).

There is only one presentation of 6-mercaptopurine commercially available in the US, 50 mg tablets. Because of the age and weight range of children with ALL, a 50 mg tablet is not ideal. Body weight dosing and dose adjustments are not easily accomplished with the 50 mg tablet. Tablets are not an ideal dosage form of medication for children less than 6 years. *Ad hoc* local formulations compounded in pharmacies are commonly used. Alternatively 50 mg tablets are split to provide children with the desired dose. Neither of these approaches provides precise dosing.

Compared to tablets, a suspension offers the advantage of more accurately delivering the desired dose to children with a wide range of weights. A suspension will allow more flexibility in adjusting the dose. A commercially produced suspension is more likely to provide a more consistent dose of 6-mercaptopurine than *ad hoc* compounded formulations.

9 Appendices

9.1 Literature Review/References

Andersen JB, Szumlanski C, Weinshilboum RM, Schmiegelow K., 1998, Pharmacokinetics, dose adjustments, and 6-mercaptopurine/methotrexate drug interactions in two patients with thiopurine methyltransferase deficiency, *Acta Paediatr*, 87:108-111.

Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, et al., 2012, Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group, *J Clin Oncol*, 30:2094-2101.

Burchenal, JH, Murphy, ML, Ellison, RR, Sykes, TC, Tan, TC, et al., 1953, Clinical Evaluation of a New Antimetabolite, 6-Mercaptopurine, in the Treatment of Leukemia and Allied Diseases, *Blood*, 8:965-999.

Dolan G, Lilleyman JS, Richards SM., 1989, Prognostic importance of myelosuppression during maintenance treatment of lymphoblastic leukaemia, *Arch Dis Child*, 64:1231-1234.

MRC:Report to the Council by the Working Party on Leukaemia in Childhood, 1986, Improvement in Treatment for Children with Acute Lymphoblastic Leukaemia. The Medical Research Council UKALL Trials, 1972-1984, *Lancet* , 327:408-410.

Relling MV, Hancock ML, Rivera GK, Sandlund JT, Ribeiro RC, et al., 1999, Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus, *J Natl Cancer Inst*, 91:2001-2008.

9.2 Labeling Recommendations

The label is being converted to the PLR format.

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/s/

PATRICIA A DINNDORF
03/25/2014

ALBERT B DEISSEROTH
03/25/2014

Patricia Dinndorf
 CLINICAL FILING CHECKLIST FOR NDA 205919
 8/26/13

| | Content Parameter | Yes | No | NA | Comment |
|----------------------|---|-----|----|----|---|
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | | | x | |
| 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 | | No deaths or serious AEs, No narrative for dropouts. CRFs for the 4 subjects who dropped out due to AE were included. This is adequate. |
| 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 | |

Patricia Dinndorf
 CLINICAL FILING CHECKLIST FOR NDA 205919
 8/26/13

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|---------------------------------|
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | | | x | Not required Orphan designation |
| 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? Yes



8/26/13

 Reviewing Medical Officer

 Date

Reviewed with Dr. Deisseroth 8/13/13

 Clinical Team Leader

 Date

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/s/

PATRICIA A DINNDORF
08/26/2013

ALBERT B DEISSEROTH
08/26/2013