

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205919Orig1s000

OTHER REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: 205919

Submission Date(s): 7/9/13

Applicant: NOVA Laboratories Limited

Product: Purixan (mercaptopurine)

Reviewer: Patricia Dinndorf

Date of Review: 4/24/14

Covered Clinical Study (Name and/or Number):

Study SC02808: Assessment of the Bioequivalence of an Oral Mercaptopurine Suspension 100mg/5mL (indicated for the treatment of Children with Acute Lymphoblastic Leukaemia) and Puri-Nethol® 50mg Tablet: A Randomised, Open-label, Single-Centre, Crossover Study in Healthy Male Volunteers, in the Fasted State

Study PXL207444: A Single Center, Single Dose, Open-Label, Randomized, Two Period Crossover Study to Assess the Bioequivalence of an Oral Mercaptopurine Suspension 100mg/5mL versus an Oral Mercaptopurine Tablet 50mg (Purinethol®) in at least 62 Healthy Male Subjects under Fasting Conditions

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

This application was a 505(b)(2) and did not rely on studies of clinical evidence of efficacy and safety. The product relied on bioequivalence to a reference product in a volunteer population. The laboratory endpoints of a bioequivalence study are unlikely to be subject to investigator bias.

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

/s/

KRISTOPHER KOLIBAB
04/24/2014

PATRICIA A DINNDORF
04/24/2014

ALBERT B DEISSEROTH
04/25/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA 205919
Product Name: Purixan

PMC Description:

(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

PMR/PMC Schedule Milestones: Prior Approval Supplement Submission: August, 2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not Applicable.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

(b) (4)

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

KRISTOPHER KOLIBAB
04/21/2014

ALI H AL HAKIM
04/21/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 205919	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Purixan Established/Proper Name: Mercaptopurine Dosage Form: Oral Suspension Strengths: 20mg/ml		
Applicant: NOVA Laboratories Limited		
Date of Receipt: July 9, 2013		
PDUFA Goal Date: May 10, 2014		Action Goal Date (if different):
RPM: Kris Kolibab, Ph.D.		
Proposed Indication(s): Purixan is indicated in pediatric, children, and adult patients for maintenance therapy of acute lymphoblastic leukemia (ALL) as part of a combination regimen.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>NDA 009053 "Purinethol"</i>	<i>FDA's previous finding of safety and effectiveness (Nonclinical, Clinical, and Quality)</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Comparative BE study reports.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Purinethol	009053	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: Purinethol

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a change in dosage form, from capsule to solution, and strength from 50mg to 20 mg/ml.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

Purinethol NDA 009053.

If “**NO**” *or* if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

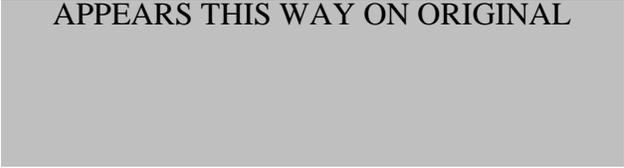
Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

APPEARS THIS WAY ON ORIGINAL



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

/s/

KRISTOPHER KOLIBAB
04/21/2014

MEMORANDUM

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

DATE: April 16, 2014

TO: John Lazor, Pharm.D.
Director
Division of Clinical Pharmacology IV
Office of Clinical Pharmacology

Ann Farrell
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EI [redacted] NDA 205919, 6 mercaptopurine
suspension ([redacted] (b)(4) 100mg/5 mL, sponsored by NOVA
Laboratories [redacted] ted Kingdom.

At the request of the Division of Clinical Pharmacology V (DCPV), Office of Clinical Pharmacology, and the Division of Hematology Products (DHP), Office of Hematology and Oncology Products (OHOP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the analytical portion of the following pharmacokinetic study:

Study Number: PXL207444
Study Title: "A Single Center, Single-Dose, Open-Label, Randomized, Two-Period Crossover Study to Assess the Bioequivalence of an Oral Mercaptopurine Suspension 100 mg/ 5mL Versus an Oral Mercaptopurine Tablet 50 mg (Purinethol®) In at Least 62 Healthy Male Subjects Under Fasting Conditions."

FDA investigator Sam Haidar (OSI) audited the study records at (b) (4)

(b) (4) during (b) (4). The audit included a thorough review of the study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

During the audit, the FDA investigator did not observe objectionable conditions, and at the conclusion of the analytical inspection, did not issue Form FDA-483.

Conclusion:

Following the above inspection, we recommend that the analytical data from study PXL207444 are acceptable for Agency review.

Sam H. Haidar, Ph.D., R.Ph.
Pharmacologist

Final Classification:

NAI-

(b) (4)

cc:

CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Dejernet
OND/OHOP/DHP/Kolibab, Kristopher/Farrel, Ann
OTS/OCP/DCPV/Lazor/Bullock, Julie
HFC-130/ORA HQ OMPTO DMPTI MPTTPB BIMO, Keller, Anthony

Draft: SHH 4/17/2014
BE File #: 6511
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Inspections/BE Program
ECMS: Cabinets/ORA/OMPTO/BIMO/FY'14/CDER/
FACTS: 8701786

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

/s/

SAM H HAIDAR
04/17/2014

WILLIAM H TAYLOR
04/17/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: April 7, 2014 **Date Consulted:** August 28, 2013

From: Erica L. Wynn, M.D., M.P.H, Medical Officer
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Lead Medical Officer
Lynne Yao, MD, OND Associate Director
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff (PMHS)

To: OND/OHOP/Division of Hematology Products

Drug: NDA 205919 Purixan (Mercaptopurine monohydrate)
(Associated IND 112823)

Indication: Maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen.

Applicant: NOVA Laboratories, LTD

Subject: PLR Conversion as part of 505(b)(2) application for new formulation development

Materials Reviewed:

- Consult Requests dated August 28, 2013
- Approved labeling Purinethol[®] (mercaptopurine) 50-mg scored tablets dated May 27, 2011
- Annotated comparison of sponsor's proposed label with the labeling of referenced drug.
- Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling dated February 2013
- Decision/Action Items CDER Medical Policy Council Minutes dated December 4, 2013

Consult Question: "Please review the PEDS section of the package insert"

INTRODUCTION AND BACKGROUND

On July 10, 2013, NOVA Laboratories LTD submitted a 505(b)(2) application for an oral suspension containing 20mg/mL of mercaptopurine. (Note: Following rejection by DMEPA of the originally proposed trade name, (b)(4) the applicant requested the trade name Purixan. The name, Purixan, was found to be acceptable.)

Reviewer Comment: The original approval of Purinethol[®] mercaptopurine (NDA 009053) occurred on September 11, 1953 which predated PREA. Notably, the applicant has orphan designation for this drug for this indication. On August 20, 2012, Nova Laboratories Limited, received orphan designation for their mercaptopurine product for the treatment of acute lymphoblastic leukemia in pediatric patients.

A Written Request has not been issued for any mercaptopurine product and all patents and exclusivities have expired. Orbona Pharma Ltd, the sponsor of a 6-mercaptopurine liquid product, also received orphan designation on December 7, 2009, for their product for the treatment of acute lymphoblastic leukemia in the pediatric population.

Although, there are several generics in the market, the only form of mercaptopurine currently available in the United States is a 50 mg oral tablet (Purinethol[®]). According to the approved labeling for Purinethol[®] (dated May 27, 2011), mercaptopurine is an analogue of the purine bases adenine and hypoxanthine that competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRase) and is converted to thioinosinic acid (TIMP). Presently, mercaptopurine is indicated for maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia (ALL) as part of a combination regimen. The labeling also states that the “response to this agent depends upon the particular subclassification of acute lymphatic leukemia and the age of the patients (pediatric or adult).” Furthermore, the labeling states that mercaptopurine, “is not effective for prophylaxis or treatment of central nervous system leukemia,” and “is not effective in acute myelogenous leukemia, chronic lymphatic leukemia, the lymphomas (including Hodgkins Disease), or solid tumors.”

It is not known exactly which one or more of the biochemical effects of mercaptopurine and its metabolites are directly or predominantly responsible for cell death. Response to the agent also depends on the particular subclassification of acute lymphatic leukemia and the age of the patient (pediatric or adult).

The labeling for the referenced drug is not in PLR format and does not contain a section 8.4 “Pediatrics”. The following information was excerpted from the “Pediatric Use” and “Dosage and Administrations” sections of the approved non-PLR labeling (dated 05/27/2011) for Purinethol[®] (available at Drugs@FDA under NDA 009053):

Pediatric Use

See **DOSAGE AND ADMINISTRATION** section.

DOSAGE AND ADMINISTRATION

Maintenance Therapy

Once a complete hematologic remission is obtained, maintenance therapy is considered essential. Maintenance doses will vary from patient to patient. The usual daily maintenance dose of PURINETHOL is 1.5 to 2.5 mg/kg/day as a single dose. It is to be emphasized that in pediatric patients with acute lymphatic leukemia in remission, superior results have been obtained when PURINETHOL has been combined with other agents (most frequently with methotrexate) for remission maintenance. PURINETHOL should rarely be relied upon as a single agent for the maintenance of remissions induced in acute leukemia.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Dosage with Concomitant Allopurinol

When allopurinol and mercaptopurine are administered concomitantly, the dose of mercaptopurine must be reduced to one third to one quarter of the usual dose to avoid severe toxicity.

Dosage in TPMT-deficient Patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established. (See **CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS** sections.)

Most patients with heterozygous TPMT deficiency tolerated recommended PURINETHOL doses, but some require dose reduction. Genotypic and phenotypic testing of TPMT status are available. (See **CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS** sections.)

Dosage in Renal and Hepatic Impairment

It is probably advisable to start with lower dosages in patients with impaired renal function, due to slower elimination of the drug and metabolites and a greater cumulative effect. Consideration should be given to reducing the dosage in patients with impaired hepatic function

OVERVIEW OF THE CURRENT SUBMISSION

The 50mg mercaptopurine (MP) tablet is the only marketed form of the drug available in the U.S. Acute Lymphatic Leukemia (ALL) is a disease that predominantly affects children. Mercaptopurine is used as a part of a combination regime for maintenance therapy. Frequent mercaptopurine dose adjustments are required due to large inter-patient variability in bioavailability and metabolic activation of mercaptopurine. According to the sponsor, "Treatment protocols have evolved over the last 60 years and necessitate that 6-MP is administered to children at doses related to their body size...the daily dose for the maintenance treatment of childhood ALL may range from 7.5mg to 125mg depending on body size." The applicant asserts that to accommodate the need for adjustable doses, pharmacists will either advise parents/carers to split the 50mg tablet or they will dispense compounded liquid mercaptopurine formulations prepared by the hospital pharmacy or compounding pharmacies. This adds to the inherent variability in pharmacokinetics observed with mercaptopurine. The need for an age appropriate mercaptopurine formulation was also highlighted at a FDA meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee. (December 15, 2009).

The clinical development program for the applicant's product focused on an assessment of the bioequivalence of the referenced drug (Purinethenol[®]) with the applicant's proposed liquid formulation. Two clinical studies assessed the bioequivalence of the oral suspension to the marketed tablet from the U.S. and E.U. in healthy adult volunteers in South Africa. The sponsor asserts that efficacy may be extrapolated from adults to pediatrics because there are no clinical or experimental data to suggest that age is likely to influence the *in vivo* performance of mercaptopurine formulations. Furthermore the product is already labeled for use in both adults and children and there is no difference in the dosing recommendations (given on a mg/m² basis) in the currently approved labeling for the product.

Reviewer Comment:

The currently labeling for mercaptopurine states that response to the agent depends on the particular subclassification of acute lymphatic leukemia and the age of the patient (pediatric or adult). Legislation on extrapolation of efficacy may be found in 21 CFR 314.55(a). "Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." However, mercaptopurine is already labeled for use in pediatrics and ALL is a disease that primarily affects the pediatric population.

The applicant performed two clinical trials. The first trial (Trial PXL207444) was conducted using the referenced product marketed in the U.S. and entitled, "A Single Center, Single Dose, Open-Label, Randomized, Two Period Crossover Study to Assess the Bioequivalence of an Oral Mercaptopurine Suspension 100mg/5mL versus an Oral Mercaptopurine Tablet 50mg (Purinethol®) in at least 62 Healthy Male Subjects under Fasting Conditions." The study was conducted as an open-label, laboratory-blind, single-dose, randomized, two-period, two-sequence, cross-over study under fasting conditions. There were two treatment periods, each of which included a pharmacokinetic profile period up to 12 hours. Treatment periods were separated by a wash-out period of at least 4 calendar days. Data from the study revealed that the applicant's product and the referenced drug were bioequivalent with respect to AUC. The 90% confidence intervals for the AUC parameters were within the pre-defined bioequivalence limits of 80% to 125%. The mean ratio (90% confidence intervals) of C_{max} was 133.61% (119.98% - 148.79%); outside the conventional acceptance limits of 80-125%. The rate of absorption of 6-MP was significantly higher for test product with the confidence interval for C_{max} excluding unity and T_{max} occurring significantly earlier (p value <0.0001). However, there were no new safety signals in this trial.

The second trial (Trial SC02808) was conducted using the referenced product marketed in the EU and entitled, "Assessment of the Bioequivalence of an Oral Mercaptopurine Suspension 100mg/5mL (indicated for the treatment of Children with Acute Lymphoblastic Leukaemia) and Puri-Nethol® 50mg Tablet: A Randomised, Open-label, Single-Centre, Crossover Study in Healthy Male Volunteers, in the Fasted State." According to the applicant, "There were 2 study periods. In each period, volunteers were given a single dose of mercaptopurine (test and reference product) and blood samples were taken over 12 hours after administration. Doses were separated by a washout period of at least 72 hours. The primary parameters for pharmacokinetic evaluation were C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ and the acceptance range for these parameters was 80% - 125%." This trial demonstrated that the applicant's mercaptopurine suspension was bioequivalent to the Puri-Nethol® tablet marketed in the EU with respect to AUC. The trial also showed that mercaptopurine is more rapidly absorbed from the suspension than from the tablet formulation and the mean C_{max} was approximately 40% higher than that seen for the tablet. Although conventional acceptance limits for bioequivalence were not met, there were no new safety signals.

Reviewer Comment:

PMHS defers comment on the acceptability of the results of the bioequivalence trial to Clinical Pharmacology. Mercaptopurine has now been used clinically for 60 years and the labeling already states that there is a wide range of inter-individual variability in exposures that is dependent on a number of factors including (but not limited to) patient age and staging of disease. Although the available data are limited, the medical literature does not appear to suggest that the C_{max} of mercaptopurine is correlated to efficacy or safety.^{1,2}

PEDIATRIC USE LABELING

The “Pediatric Use” subsection should clearly describe what is known and unknown about the use of the drug in pediatric patients, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products, like mercaptopurine, with approved pediatric indications, pediatric use information should be placed in the specific sections throughout the labeling as warranted (see Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling).

Reviewer Comment

PMHS reviewed the proposed PLR labeling submitted by the applicant. Revisions to the proposed labeling are recommended to strengthen or clarify the presentation of information related to pediatric patients. Because there were no pediatric trials conducted with this product, the Division would have to include a statement stating that approval of this product was not based on adequate and well-controlled studies performed in pediatric patients using this drug. However, because the referenced product is already approved for use in pediatrics and adults, available information related to the efficacy and the safety of the referenced drug may be gathered from the original approval letter (NDA application), medical literature, and/or post-marketing databases and included in section 8.4 of the labeling. All other pediatric information in the non-PLR version of the old labeling may be placed throughout the PLR labeling of this product. The applicant has proposed the following for Section 8.4 Pediatrics:

8.4 Pediatric Use

(b) (4)

PMHS proposes the following language be included in Section 8.4. for the Division’s consideration:

8.4 Pediatric Use:

The safety and effectiveness of mercaptopurine for the treatment of ALL in pediatric patients have not been established in adequate and well-controlled studies. The evidence for efficacy of mercaptopurine is derived from the published literature. In 45 pediatric patients ages 2 to 12 years of age with ALL, 15 children (33 %) developed clinical and hematologic remission (defined as less than 30% of stem cells plus lymphocytes in the differential nucleated cell count of a bone marrow aspirate). The initial starting dose of mercaptopurine in most patients was 2.5mg/Kg/day calculated to the nearest 25 mg. The dose was continued for 4 weeks, then increased to 5mg/Kg/day if there was no clinical improvement or direct evidence of leukocyte suppression. The most common toxicities were related to the bone marrow suppressive effects of the drug. Other adverse events included oral mucositis, nausea, vomiting, and anorexia.

Response to mercaptopurine is dependent upon the particular sub-classification of the acute leukemia and the age of the patient. Treatment protocols for acute lymphoblastic leukemia are based on a range of prognostic factors, therefore therapy is individualized and based upon risk.

PMHS attended the Division’s mid-cycle meeting and actively participated in labeling meetings which commenced on January 22, 2014, and concluded in April, 2014. Preliminary revisions for additional language were sent via email to the Division on March 26, 2014. Final labeling is subject to negotiations with the applicant and may not fully reflect changes suggested above. Reference should be made to the final approved labeling in DARRTS, which is appended to the decision letter issued by the Division.

REFERENCES

¹ Balis FM, Holcenberg JS, Poplack DG et al. "Pharmacokinetics and Pharmacodynamics of Oral Methotrexate and Mercaptopurine in Children With Lower Risk Acute Lymphoblastic Leukaemia: A Joint Children's Cancer Group and Pediatric Oncology Branch Study." *Blood* 1998; 92: 3569-3577.

² Hayder S., Björk, O and Lafloie P. "The Course of Biological parameters and 6-Mercaptopurine Pharmacokinetics during Maintenance Treatment of Children with Acute Lymphoblastic Leukaemia." *Acta Paediatr ica*.1990; 79: 832-837.

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

/s/

ERICA WYNN
04/07/2014

LYNNE P YAO
04/08/2014

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

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

Memorandum

Date: April 8, 2014

To: Kristopher Kolibab – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Ph.D, Team Leader, OPDP

Subject: OPDP comments on draft Prescribing Information (PI) for Purixan (mercaptopurine) oral suspension

This consult is in response to DHP's October 9, 2013 request for OPDP review of the draft Purixan Prescribing Information. OPDP comments are based on the proposed draft marked-up labeling revised by the review division and received by OPDP on April 2, 2014.

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

Section	Statement from draft	Comment
Highlights-Warnings and Precautions "Hepatotoxicity"	<ul style="list-style-type: none">Monitor transaminases and bilirubin	Consider revising this statement to include monitoring of alkaline phosphatase to be more consistent with 5.2
Highlights-Adverse Reactions	<ul style="list-style-type: none">The most common adverse reaction (> 20% of patients) is myelosuppression including anemia, neutropenia, and thrombocytopenia. Less common (5-20% of patients) adverse	Consider revising this section to be more consistent with the list found in 6.1; "Adverse reactions occurring 5 to 20 % include anorexia, nausea, vomiting, diarrhea, malaise, and rash. Rare adverse reactions occurring < 5 % include urticaria,

	<p>reactions include elevated transaminases, elevated bilirubin, intestinal ulceration, nausea, vomiting, anorexia, diarrhea and rashes (6.1).</p>	<p>hyperuricemia, oral lesions, elevated transaminases, hyperbilirubinemia, hyperpigmentation, pancreatitis.”</p>
Highlights—Drug Interaction	<ul style="list-style-type: none"> Allopurinol: (b) (4) (7.1) 	<p>Consider revising this interaction to include the following statement from 5.1, “Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity.”</p>
Highlights--Dosing and Administration	<ul style="list-style-type: none"> Use (b) (4) (2.1) 	<p>Consider adding periodic monitoring of platelet count to be more consistent with 2.1</p>
Highlights--Warnings & Precautions		<p>We note that the “Treatment Related Malignancies” (section 5.5) and “Laboratory Tests” (section 5.6) are omitted from the Highlights. Consider including these Warnings and Precautions.</p>
1. INDICATIONS AND USAGE	<ul style="list-style-type: none"> PURIXAN (mercaptopurine) is indicated for the treatment of patients with acute lymphoblastic leukemia as part of a combination regimen. 	<p>We note that the indication statement in the “Highlights” section restricts Purixan’s use to maintenance therapy and dosing guidelines are only provided for maintenance therapy administration in section 2.1, while section 1.1 gives a more general indication. We suggest editing the label to ensure that there is agreement between the indications presented in these sections and the corresponding dosing parameters.</p>

8.6 Renal Impairment	Starting at the low end of the PURIXAN dosing range, or increasing the dosing interval to 36-48 hours can be considered in patients with baseline renal impairment.	We suggest adding this language to the Dosing and Administration section of the label as well. This is important information for prescribers and promotional "dosing cards" are created by excerpting language from this section of the label. Without including this important guidance in section 2, prescribers will not see this language in the sponsor's promotional dosing cards.
8.7 Hepatic Impairment	In patients with baseline hepatic impairment, starting at the low end of the PURIXAN dose range should be considered and patients should be monitored for toxicity.	We suggest adding this language to the Dosing and Administration section of the label as well. Please see our rationale in the comment above related to Renal Impairment.
17. PATIENT COUNSELING INFORMATION		<p>We suggest adding a statement to section 17 to account for Purixan's WARNING regarding Immunosuppression and live virus vaccines. Suggested language may read:</p> <p><u>Immunization:</u></p> <p>Advise patients that response to all vaccines may be diminished while receiving treatment with PURIXAN and there is a risk of infection with live virus vaccines."</p>

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

/s/

RICHARD A LYGHT
04/08/2014

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 205919

Application Type: New NDA

Name of Drug: (b) (4)/Mercaptopurine 20mg/mL

Applicant: Nova Laboratories Ltd

Submission Date: July 9, 2013

Receipt Date: July 10, 2013

1.0 Regulatory History and Applicant's Main Proposals

This NDA for (b) (4) was submitted on July 9, 2013. (b) (4) is indicated in pediatric patients for maintenance therapy of acute lymphatic leukemia as part of a combination regimen.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the 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).

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI was conveyed to the applicant in the 74-day letter. The applicant was asked to correct these deficiencies and resubmit the PI in Word format by September 25, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

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:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: (b) (4)

Product Title

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

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: (b) (4)

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- YES** 12. All text must be **bolded**.
Comment:
- NO** 13. Must have a centered 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**”).
Comment: *WARNING needs to be centered.*
- NO** 14. Must always have the verbatim statement “**See full prescribing information for complete boxed warning.**” centered immediately beneath the heading.
Comment: *The above verbatim statement needs to be added.*
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “**See full prescribing information for complete boxed warning.**”)
Comment:
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. 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

- N/A** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. 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: www.raretx.com – this website is a general link to the company

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

NO

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *The boxed warning title is missing.*

YES

32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES

33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES

34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES

35. 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)

GENERAL FORMAT

YES

36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES

37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

Selected Requirements of Prescribing Information (SRPI)

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: *References should be listed as heading 15 and not at the bottom of the table of contents.*

- NO** 39. 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 patient labeling must appear at the end of the PI upon approval.

Comment: *17.1 “Information for Patients” section needs to be deleted. It must appear at the end of the PI upon approval.*

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. 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

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. 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**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is 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 clinical practice.”

Comment: *The above verbatim statement or appropriate modification is missing.*

- N/A** 47. When postmarketing adverse reaction data is 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:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *There is no reference to any FDA-approved patient labeling, the type of patient labeling, and none of the above verbatim statements were included at the beginning of section 17.*

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

/s/

KRISTOPHER KOLIBAB
10/28/2013

EBLA ALI IBRAHIM
10/28/2013

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 # 205919 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Mercaptopurine Dosage Form: Oral Suspension Strengths: 20mg/mL		
Applicant: NOVA Laboratories Limited Agent for Applicant (if applicable): Jennifer Spinella		
Date of Application: 7/9/2013 Date of Receipt: 7/10/2013 Date clock started after UN: N/A		
PDUFA Goal Date: 5/10/2014	Action Goal Date (if different):	
Filing Date: 9/8/2013	Date of Filing Meeting: 8/22/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): (b) (4) is indicated in pediatric patients for maintenance therapy of acute lymphatic lymphocytic leukemia as part of a combination regimen.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 112823				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, 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</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> If yes, explain in comment column.		X		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>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.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>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)].</p>		<p>X</p>																		
<p>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)]?</p> <p><i>If you answered yes to any of the above 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</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

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)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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).	X			
Index: Does the submission contain an accurate comprehensive index?		X		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>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), 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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
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)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>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].</i> <i>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...”</i>	X			
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? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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</i>		X		Peds Page

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Under the IND
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL		X		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X			Needs the format in the FPI section
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?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) 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)	X			SEALD

4

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

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): January 15, 2013	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 22, 2013

BLA/NDA/Supp #: 205919

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Mercaptopurine

DOSAGE FORM/STRENGTH: Oral suspension, 20mg/mL

APPLICANT: NOVA Laboratories Limited

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (b) (4) is indicated in pediatric patients for maintenance therapy of acute lymphatic lymphocytic leukemia as part of a combination regimen.

BACKGROUND: NOVA Laboratories submitted a 505 (b)(2) application, NDA 205919, on July 9, 2013 and received on July 10, 2013. The proprietary name, (b) (4) was requested under the PIND 112823.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kris Kolibab	Y
	CPMS/TL:	Ebla Ali Ibrahim	Y
Cross-Discipline Team Leader (CDTL)	Julie Bullock		Y
Clinical	Reviewer:	Pat Dinndorf	Y
	TL:	Al Deisseroth	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Jeffrey Huang	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Kyung Lee	N
	TL:	Lei Nie	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Rama Gudi	Y
	TL:	Haleh Saber	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Danuta Gromek-Woods	N
	TL:	Ali Al Hakim	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Bob Pratt	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Okpo Eradiri (ONDQA – Biopharmaceutics) TL: Angelica Dorantes		N
Other attendees	Tracy Salaam - OSE/DPV II		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <p>Comments: CMC Reviewer to review</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • 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? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Kris Kolibab</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 12/5/2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

KRISTOPHER KOLIBAB
10/21/2013

EBLA ALI IBRAHIM
10/21/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 9, 2013

Reviewer: Yelena Maslov, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Mercaptopurine Oral Suspension, 20 mg/mL

Application Type/Number: NDA 205919

Applicant/sponsor: Nova Laboratories, Ltd.

OSE RCM #: 2013-1748

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	INTRODUCTION	1
1.2	Regulatory History	1
1.3	Product Information.....	1
2	METHODS AND MATERIALS REVIEWED	1
2.1	Labels and Labeling	1
3	CONCLUSIONS	2
4	RECOMMENDATIONS.....	2
	Appendices.....	5

1 INTRODUCTION

This review evaluates the proposed container label, carton, prescriber information labeling, and packaging for Mercaptopurine Oral Suspension, NDA 205919 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted NDA 205919, for Mercaptopurine Oral Suspension on July 10, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 10, 2013 NDA submission.

- Active Ingredient: Mercaptopurine Oral Suspension
- Indication of Use: for maintenance therapy of acute lymphatic leukemia as part of combination regimen
- Route of Administration: Oral
- Dosage Form: Oral Suspension
- Strength: 2 g/100 mL (20 mg/mL)
- Dose and Frequency: 1.5 mg/kg/day to 2.5 mg/kg/day as a single dose
- How Supplied: Amber glass bottle containing 2 g/100 mL
- Storage: 15⁰ to 25⁰C (59⁰ to 77⁰F) in a dry place.
- Container and Closure System: Amber glass bottle with (b) (4) cap/ (b) (4) oral dosing syringe is inserted into the neck of the bottle and the original cap is released.

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted July 10, 2013 (Appendix A)
- Carton Labeling submitted July 10, 2013 (Appendix B)
- Insert Labeling submitted July 10, 2013 (no image)
- Any additional materials when applicable

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to enhance clarity, readability, and prominence of the important information to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA/ANDA/supplement:

I. Comments to the Applicant

A. Container Label:

1. Delete the proprietary name (b) (4) as this name was found unacceptable.
2. Currently, the expression of the strength of the product is cumbersome and confusing. Thus, revise the strength of the product to state the drug content of the bottle, followed by concentration. See example below:

Mercaptopurine
Oral Suspension
2 g/100 mL
(20 mg/mL)

3. Revise the background color to a lighter color scheme. The (b) (4) coloring on the upper half of the label decreases the legibility of the printed information; thus, making it difficult to read.
4. Revise the statement “(b) (4)” to state “Each mL contains 20 mg mercaptopurine”. Additionally, relocate this statement to the side panel.
5. Revise the phrase “(b) (4)” to state “100 mL per bottle” and relocate away from the strength of the product to the upper quadrant of the principle display panel.
6. Delete the (b) (4) as this information is unnecessary and occupies space. The product already specifies that this is an “oral suspension”.
7. Relocate the “Rx only” statement to the bottom of the principle display panel.
8. Decrease the prominence of the manufacturer “Nova” by decreasing the font size and relocating it to the side panel. Currently, this information is more prominent than established name of the product and distracts from important information on the principle display panel.

9. Relocate the statement “Shake vigorously before use for at least 30 seconds” to the principle display panel under the strength to increase the prominence of this statement as this is important administration information.
10. Relocate the NDC number to the principle display panel above the proprietary name to increase its prominence.

B. Carton Labeling

1. See Recommendations A.1 through A. 8 and revise the carton labeling accordingly.
2. Include the strength of the product on each panel of the carton labeling after the established name of the product.
3. Include the NDC number on each panel of the carton labeling. Ensure the NDC number appears above the proprietary name of the product to ensure its prominence.
4. If feasible, include the statement “Shake vigorously before use for at least 30 seconds” on each panel as this is important administration information.

II. Comments to the Division

Prescriber Information Labeling

1. Highlights of Prescribing Information and Full Prescribing Information
 - i. Delete the proprietary name “(b) (4)” from the labeling as this name was found unacceptable.
 - ii. Include space between numerical values of the strength and doses and the units of use throughout labeling (i.e., 1.5 mg/kg/day, 2.5 mg/kg/day or 20 mg/mL, etc.).
2. Dosage and Administration, Section 2 Full Prescriber Information and Highlights of Prescribing Information

Include the statement “Shake bottle vigorously for at least 30 seconds to ensure the oral suspension is well mixed” in the Dosage and Administration Section on a separate line immediately before the second paragraph that start with (b) (4)”
3. Dosage Form and Strengths, Section 3 Full Prescriber Information and Highlights of Prescribing Information

Revise this Section to state “Each bottle of oral suspension contains 2 g/100 mL (20 mg/mL) of mercaptopurine”.
4. How Supplied, Section 16 Full Prescriber Information

ii) Revise the statement “ [REDACTED] (b) (4)
[REDACTED]
[REDACTED] to state “It is supplied in amber-colored multi-dose bottle containing 2 g/100 mL (20 mg/mL) of mercaptopurine”.

iii) Revise the instructions regarding shaking of the bottle for at least 30 seconds to use the active verb (i.e., “Shake bottle vigorously for at least 30 seconds to ensure the oral suspension is well mixed”). Additionally, place this statement under the NDC # statement.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

1 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/

YELENA L MASLOV
10/09/2013