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RESEARCH**

APPLICATION NUMBER:

205919Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA #	205919
Supplement #	S-000/SDN 1
Applicant Name	NOVA Laboratories, Ltd.
Date of Submission	9 July 2013
PDUFA Goal Date	5 May 2014
Proprietary Name / Established (USAN) Name	PURIXAN Mercaptopurine
Dosage Forms / Strength	Suspension/ 20 mg/mL
Proposed Indications	Component of multi-drug (b) (4) therapy of acute lymphoblastic leukemia (ALL)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Patricia A. Dimndorf, MD, PhD/Albert B. Deisseroth, MD, PhD
Statistical Review	Kyung Y. Lee, Ph.D./Lei Nie, PhD
Pharmacology Toxicology Review	Ramadevi Gudi, PhD/Haleh Saber, PhD
CMC Review	Danuta Gromek-Woods, PhD/Janice Brown/Ali Al-Hakim, PhD
ONDQA Microbiology Review	Jessica G. Cole, PhD/Bryan Riley
Clinical Pharmacology Review	Jeffrey Huang, PharmD/Julie Bullock, PharmD
Biopharmaceutics	Okponanabofa Eradiri, PhD/Angelica Dorantes, PhD
OPDP	Lichard Lyght, PharmD
OSI	Samuel Haider
CDTL Review	Julie Bullock, PharmD
Pediatric and Maternal Health Staff	Erica L. Wynn, MD/Hari C. Sachs, MD/Lynne P. Yao, MD
OSE/DMEPRM	Kellie A. Taylor, PharmD

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPRM=Division of Medication Error Prevention and Risk Management
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Mercaptopurine (or 6-mercaptopurine, 6-MP) is one of the oldest licensed chemotherapeutic agents, approved by the FDA in 1953. In that year, investigators reported hematologic remissions in children with acute lymphoblastic leukemia (ALL). Its role over the years has changed from remission induction to maintenance therapy. 6-MP is currently available in the U.S. only as a 50 mg tablet (Purinethol® and three generic products). An oral suspension is compounded in pharmacies for children who are unable to swallow tablets. The dose of 6-MP is variable, titrated to maintain an absolute neutrophil count between 500 and 1500/ μ L. Neither 50 mg tablets nor extemporaneous formulations in pharmacies provide precise dosing.

The Sponsor, Nova Laboratories Ltd, has been manufacturing 6-MP suspensions in the EU for many years. It is marketed with a Push-in Bottle Adaptor that facilitates precise dosing. The formulation described in this 505(b)(2) NDA is a natural extension of the EU formulation, as it contains the same components.

2. Background

Mercaptopurine is a nucleoside metabolic inhibitor that is currently approved in the US for use in maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen.

Regulatory history prior to submission is detailed in the Clinical Review. Briefly, a pre-IND meeting was held on 9/8/2011, at which FDA informed the sponsor that additional toxicology studies would not be required and that additional safety data would be helpful. The Sponsor stated that this formulation has been used in the UK and Ireland over the past 10 years. No formal safety study had been done. The Sponsor was to provide justification for C_{max} outside of bioequivalence limits. A CMC meeting was held on 12/1/2011. On 8/20/2012 Orphan designation was granted for the indication “Treatment of acute lymphoblastic leukemia in pediatric patients”. On 1/18/2013 the Sponsor reported the results of a second bioequivalence study with mercaptopurine compared to US formulation of Purinethol. Again, a C_{max} outside the bioequivalence criteria was reported. FDA requested data indicating that higher C_{max} did not result in a safety signal.

The Sponsor submitted results from two clinical bioequivalence studies to support approval of the oral suspension; one with the US marketed tablet (Purinethol®, Study PXL207444) and the other using the EU marketed tablet (Puri-Nethol®, Study SC02808) as the reference drug. Based on the results of study PXL20744, the applicant is proposing a new formulation of mercaptopurine for the US market; a 20 mg/mL oral suspension. The approved labeling for the Listed Drug (Purinethol) has not been converted to Physician Labeling Rule (PLR) format,

therefore for this 505(b)(2) NDA the labeling was updated to include relevant changes for the formulation as well as updated contents to be consistent with PLR formatting.

3. CMC/Device

Drug Master File (b) (4) was reviewed by the Chemistry reviewer Dr. Gromek-Woods. The inspection of the drug substance manufacturer was completed on (b) (4) and found to be acceptable.

The Dr. Gromek-Woods review concluded that the Applicant, Nova Laboratories, Ltd., has provided sufficient information:

- to assure the identity, strength, purity, and quality of PURIXAN over the proposed shelf life (12 months) when stored as prescribed in labeling.
- adequate controls for drug substance and raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity, strength, quality, and purity of the drug product.
- The container/closure system is adequate to protect the drug product.
- Stability data assure that the product will be stable through the expiration date.

An “Acceptable” recommendation for Nova Laboratories Ltd. was issued by the Office of Compliance on 04-Apr-2014.

The proposed PURIXAN formulations contains the same components as the approved and marketed EU formulation. The active substance and excipients in the EU formulation are compliant to European Pharmacopeia compendial status, whereas in the proposed formulation they are compliant to the USP compendial status. The raspberry juice is manufactured to an in-house specification and is compliant to British Pharmacopeia (BP) 1988 specification in both the EU formulation and proposed formulation.

The EU formulation is marketed as a Push-in Bottle Adaptor (PIBA) which includes 1 mL and 5 mL oral dispensing syringes. The US formulation is filled into 100 mL amber type III glass bottle with child resistant cap. This is a standard packaging format for an oral suspension. The pharmacist will be responsible for providing an appropriate syringe with the PURIXAN product at the point-of-service. The US formulation bottle will not contain a PIBA.

It was decided by the review team that the EU packaging is superior to the US packaging since it contains the PIBA and the syringes are provided in the box of the EU product; this was conveyed to the Applicant on 11-March-2014. (b) (4)

Dr. Jessica Cole from ONDQA Product Quality Microbiology reviewed the supplement and found the microbial limits specification for PURIXAN to be acceptable (review dated 4/3/2014).

The chemistry reviewer concluded that there are no issues that preclude approval of this application from a CMC perspective.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

N/A. No nonclinical study reports are provided with this application. The pharmacology/toxicology reviewer used the information for the listed drug Purinethol for labeling of the nonclinical sections of PURIXAN.

5. Clinical Pharmacology/Biopharmaceutics

A bioequivalence study (Study PXL207444) was the only study submitted to support this 505(b)(2) application. This study was reviewed by the Office of Clinical Pharmacology reviewer Dr. Jeffrey Huang, who concluded that the AUC(0-t) and AUC(0-∞) were similar between the two formulations and fell within the pre-defined 80-125% bounds for bioequivalence. Although, Cmax did not demonstrate bioequivalence, the 30% higher mean peak concentrations were seen following test product administration are not of concern given they are within the range seen for the reference tablet product.

The Biopharmaceutics reviewer (Dr. Eradiri) found the dissolution method proposed by the applicant to be acceptable. The setting of the dissolution acceptance criteria were based on capability analyses of release and stability dissolution data for 7 manufactured batches, including the clinical batch. The dissolution method and acceptance criterion for Mercaptopurine Oral Suspension have been agreed upon with the Applicant.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

No clinical efficacy studies were conducted for this application. Risk/benefit analysis by the clinical reviewer is described below.

8. Safety

No clinical safety studies were conducted for this application. The safety information from the submitted PK study showed no substantial differences between the formulations with regard to related adverse events. There was no evidence that subjects with a higher C_{max} (on either the reference or the test product) had more adverse events or more changes in laboratory parameters.

9. Advisory Committee Meeting

An Advisory Committee meeting was not needed for this application.

10. Pediatrics

Although this formulation will be used primarily in pediatric patients, no pediatric data was submitted for this application. Bioequivalence in adults supports the use of this product in pediatric patients. A Pediatric and Maternal Health Staff assisted in PLR conversion of the label.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations inspection was conducted for the bioanalytics of study PLX207444. This study was conducted at a single site at the (b) (4). There were no deficiencies observed and Form FDA-483 was not issued. A Division of Scientific Investigations audit was not considered necessary for this application since there were no clinical efficacy or safety studies submitted.

Office of Prescription Drug Promotion provided comments for the Product Label.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The Office of Surveillance and Epidemiology found a new proprietary name proposed by the Sponsor, PURIXAN, acceptable.
- Physician labeling: The approved package insert (label) for the LD (Purinethol) has not been converted to Physician Labeling Rule (PLR) format, therefore the labeling was updated to include relevant changes for the formulation and administration as well as updated contents to be consistent with PLR formatting.

The package insert (label) and medication guide have been reviewed by the clinical, clinical pharmacology, and non-clinical reviewers, as well as by the Office of Prescription Drug Promotion (OPDP), the Division of Medication Error Prevention and Analysis (DMEPA), the Pediatric and Maternal Health Staff (PMHS), and Safety Endpoint and Labeling Division (SEALD).

The review team has recommended changes to all sections of the Sponsor's proposed labeling. The review team's revisions were incorporated into the final label, and accepted by the Sponsor.

- Carton and immediate container labels: Revised. Revisions were accepted by the Sponsor.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment. PURIXAN is a superior presentation of mercaptopurine for younger children. For younger children, especially those unable to swallow capsules, this formulation is superior to 50 mg tablets that are broken, crushed, or extemporaneously formulated. A formulation that provides more accurate dosing in a palatable form is a major contribution to acute lymphoblastic leukemia therapy. An alternative dispensing presentation (as marketed in EU) is a bottle with an adapter to connect the syringe used to draw up the dose. This presentation is superior to the bottle with syringes provided by the pharmacist. An alternative formulation also ensures better drug availability in the event of a drug shortage.
- Recommendation for Postmarketing Risk Management Activities
None.
- Recommendation for other Postmarketing Study Commitments

PMC 2148-1 Submit a Prior Approval Supplement

(b) (4)

[Redacted]

Nova

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

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The timetable you submitted on March 26, 2014 states that you will provide this information according to the following schedule:

PMC Schedule Milestones:

Prior Approval Supplement Submission: August, 2014

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/s/

EDVARDAS KAMINSKAS
04/21/2014