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RESEARCH**

APPLICATION NUMBER:

205919Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS-DISCIPLINE TEAM LEADER REVIEW

Date	April 14, 2014
From	Julie M. Bullock, Pharm.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205919
Supplement#	S-000/SDN 1
Applicant	NOVA Laboratories, LTD
Date of Submission	9 July 2013
PDUFA Goal Date	5 May 2014
Proprietary Name / Established (USAN) names	PURIXAN [®] (mercaptopurine)
Dosage forms / Strength	Suspension; 20 mg/mL
Proposed Indication(s)	Component of multi-drug (b) (4) therapy of acute lymphoblastic leukemia (ALL)
Recommended Action:	Approval

1. INTRODUCTION

This review summarizes the multi-disciplinary evaluation of the information submitted by NOVA Laboratories, LTD to support a 505(b)(2) application for PURIXAN, a suspension formulation for mercaptopurine. The listed drug (LD), Purinethol (mercaptopurine) tablet was approved in 1953 (NDA 9053) as a component of multi-drug post induction therapy of acute lymphoblastic leukemia.

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

The Applicant submitted results from two clinical bioequivalence studies to support approval of the oral suspension; one with the marketed US tablet (Purinethol®, Study PXL207444) and the other using the marketed EU tablet (Puri-Nethol®, Study SC02808) as the reference drug. Study SC02808 was not reviewed for purposes of regulatory decision making due to the use of a European reference product, as well as a major formulation change in the test product (see preIND 112823 meeting minutes 12/01/11).

Study PXL20744 met the pre-defined 80-125% bounds for bioequivalence for mercaptopurine AUC(0-t) and AUC(0-∞) following administration of the test (mercaptopurine oral suspension), and reference (Purinethol tablet) products. C_{max} did not demonstrate bioequivalence; the mean ratio was 133.61%, with a 90% confidence interval between 119.98% and 148.79%. On average, the C_{max} was 30% higher following test product administration compared to reference.

Although safety analysis from single dose studies is limiting, there were no trends towards differences in adverse events following single doses of the oral suspension compared to Purinethol tablets in the reviewed bioequivalence study.

Compared to tablets, a suspension offers the advantage of more accurately delivering the desired dose, and provides flexibility in dose adjustments to children with a wide range of weights. A commercially produced suspension is more likely to provide a more consistent dose of mercaptopurine than extemporaneously compounded formulations.

In conclusion, the recommended regulatory action is approval of Purixan, a new oral suspension of mercaptopurine.

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. There is only one presentation of mercaptopurine commercially available in the US; 50 mg tablets. The daily dose of mercaptopurine ranges from 25 to 75 mg/m² depending on the treatment protocol. In most protocols the dose is titrated to maintain the absolute neutrophil count between 500 to 1500/ μ L.

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 LD (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

There are no issues that preclude approval of this application from a CMC perspective. 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 4-April-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)

I agree with Dr. Gromek-Wood's review conclusions and I also agree with the CMC post-marketing commitment delineated below in Section 13.4.

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

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical study reports are provided with this application. The Pharmacology/Toxicology reviewer, Dr. Gudi, used the information for the listed drug Purinethol for labeling of the nonclinical sections of PURIXAN.

5. CLINICAL PHARMACOLOGY/BIPHARMACEUTICS

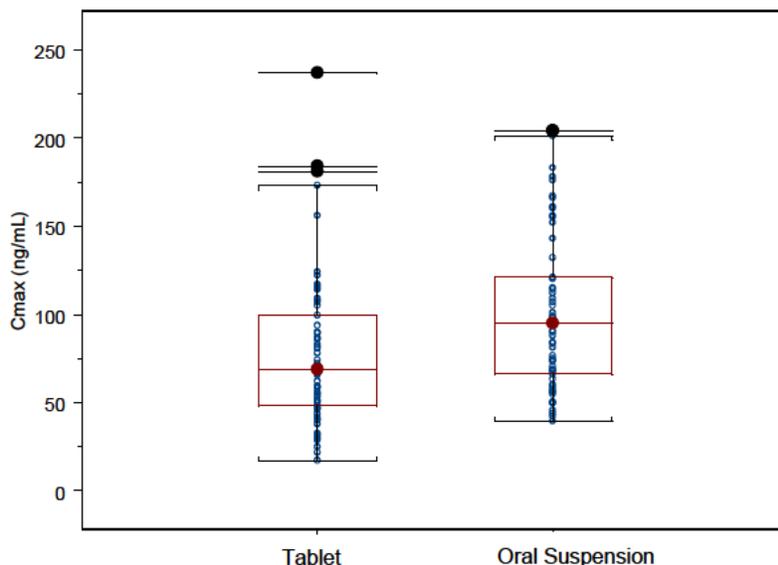
A bioequivalence study (Study PXL207444) was the only study submitted to support this 505(b)(2) application. This study was reviewed by the Office of Clinical Pharmacology reviewer Dr. Jeffrey Huang.

I agree with Dr. Huang's conclusion 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 (Table 1) are not of concern given they are within the range seen for the reference tablet product (Figure 1).

Table 1. Summary of Statistical Analyses of Plasma 6-mercaptopurine Pharmacokinetic Parameters, Study PXL207444

Parameter (unit)	n	Purinethol® Mean (Reference product)	Mercaptopurine Mean (Test Product)	Mean Ratio % (Test / Reference)	90% Confidence Interval of Ratio
Cmax (ng/mL)	62	69.5	93.8	133.6	120 - 148.8
AUC(0-t) (h*ng/mL)	62	128.1	144.4	112.7	107 - 118.7
AUC(0-∞) (h*ng/mL)	62	129.3	145.5	112.5	106.9 - 118.4

Figure 1. Individual Cmax values following tablet and oral suspension administration



I agree with Dr. Huang's conclusion that the submitted bioequivalence trial is adequate to support approval of PURIXAN oral suspension. For more details on the PK analysis and study design of study PXL207444 see Dr. Huang's review.

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 following dissolution method and acceptance criterion for Mercaptopurine Oral Suspension have been agreed upon with the Applicant:

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
II/50 rpm	0.1M HCl, 37 °C	900 mL	Q = (b) (4) at 20 min

6. CLINICAL MICROBIOLOGY

Not applicable.

7. CLINICAL/STATISTICAL- EFFICACY

No clinical efficacy studies were conducted for this application. Dr. Dinndorf's assessment of risk benefit is below in Section 13.2.

8. SAFETY

No clinical efficacy studies were conducted for this application. The Clinical Pharmacology Reviewer, Dr. Huang, reviewed the safety information from the submitted PK study and found no substantial differences between the formulations with regard to related AEs or serious AEs (Table 2). Also, there was no evidence that subjects with a higher C_{max} (on either reference or test product) had more adverse events or more changes in laboratory parameters. I agree with Dr. Huang's conclusion about the safety of this product demonstrated in the PK study.

Table 2. Summary of All Adverse Events Reported (Safety Population)

Variable	INVESTIGATIONAL MEDICINAL PRODUCT	
	Reference product	Test product
	N (%)	N (%)
Total number (%) of subjects with:		
TEAEs	12 (17.4)	3 (4.8)
Serious TEAEs	0 (0.0)	0 (0.0)
TEAEs leading to withdrawal	3 (4.3)	1 (1.6)
TEAEs leading to death	0 (0.00)	0 (0.0)
Total number (%) of:		
TEAEs	17 (24.6)	3 (4.8)
Serious TEAEs	0 (0.0)	0 (0.0)
TEAEs leading to withdrawal	3 (4.3)	1 (1.6)
TEAEs leading to death	0 (0.0)	0 (0.0)

9. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not needed for this supplement.

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 product use in pediatric patients. A Pediatric and Maternal Health consult was submitted for them to review the Pediatric section of the label.

11. OTHER RELEVANT REGULATORY ISSUES

There are no relevant regulatory or patent issues of concern for this supplement. Office of Surveillance and Epidemiology (OSE) reviewed the proprietary name reviewed on 11-Sept-13 and found the name "(b) (4)" unacceptable. Sponsor re-submitted a new proprietary name, PURIXAN, on and it was accepted on 6-Jan-2014

Division of Scientific Investigations (DSI) audit was not considered necessary for this application since there were no clinical efficacy or safety studies submitted. The BE study PXL20744 was conducted at a single site at the "(b) (4)".

Since a single BE study was submitted for approval the Office of Scientific Investigations (OSI; Sam Haider) inspection was conducted for the bioanalytics of study PLX207444. There were no deficiencies observed and Form FDA-483 was not issued.

12. 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; Richard Lyght 8-Apr-2014), the Division of Medication Error Prevention and Analysis (DMEPA; Yelena Maslov), the Pediatric and Maternal Health Staff (PMHS; Erica Wynn 8-Apr-2014), and Safety Endpoint and Labeling Division (SEALD).

The review team has recommended changes to all sections of the sponsors proposed labeling. The review team's revisions should be incorporated into the final label.

13. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

13.1. Recommended Regulatory Action

I concur with the assessments made by the review team and recommend this application for PURIXAN, an oral suspension of mercaptopurine, be approved. This formulation of mercaptopurine will improve the ability to reliably provide the appropriate dose of this essential medication to children with acute lymphoblastic leukemia. The labeling revisions recommended by the review team should be incorporated into the final label.

13.2. Risk-Benefit Assessment

I agree with Dr. Dinndorf's risk benefit assessment conclusions below:

- a formulation that provides more accurate dosing in a palatable form is a major contribution to ALL therapy, especially in younger patients unable to swallow pills
- an alternative formulation also ensures better drug availability in the event of a drug shortage.
- The presentation of PURIXAN is an appropriate formulation which is superior to the 50 mg tablet formulation available, especially for children less than 5 years of age.

13.3. Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable

13.4. Recommendation for other Postmarketing Requirements and Commitments

The CMC reviewer has proposed the following PMC:

Cross Discipline Team Leader Review

(b) (4)

(b) (4)

13.5. Recommended Comments to Applicant

Not applicable

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/s/

JULIE M BULLOCK
04/14/2014