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APPLICATION NUMBER:

205919Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

SUBMISSION NUMBER	NDA 205919
SUBMISSION DATE	07/09/2013
SUBMISSION TYPE	505(b)(2)
BRAND NAME	PURIXAN
GENERIC NAME	Mercaptopurine (MP)
DOSAGE FORM	20 mg/mL
DOSAGE REGIMEN	1.5–2.5 mg/kg/day
INDICATION	Acute lymphatic (lymphocytic, lymphoblastic) leukemia
APPLICANT	Nova Laboratories, Ltd
OND DIVISION	Division of Hematology Products
OCP DIVISION	Division of Clinical Pharmacology V
OCP REVIEWER	Jeffrey Huang, Pharm.D.
OCP TEAM LEADER	Julie Bullock, Pharm.D.

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1. EXECUTIVE SUMMARY

Nova Laboratories, LTD submitted a 505(b)(2) application for mercaptopurine oral suspension for the treatment of acute lymphatic (lymphocytic, lymphoblastic) leukemia. The application is relying on the Agency's prior findings of safety and efficacy of the US reference drug Purinethol® (NDA 009053), approved September 1953 as a 50 mg oral tablet formulation. The proposed product is a 20 mg/mL oral suspension.

The Applicant conducted one clinical pharmacology study to assess the bioequivalence of mercaptopurine from Purinethol® tablet (US listed drug) with that of the mercaptopurine oral suspension in a healthy adult population.

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective.

1.2 POST-MARKETING REQUIREMENT AND POST-MARKETING COMMITMENT

There are no additional clinical pharmacology requested PMRs or PMCs.

Signatures

Jeffrey Huang, Pharm.D. Reviewer Division of Clinical Pharmacology V	Julie Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology V

Cc: DDOP: CSO - Kolibab; MTL - Deisseroth; MO - Dinndorf
DCP-5: Reviewer - J Huang; Deputy DD - B Booth; DD - A Rahman

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

To assess the bioequivalence (BE) of the mercaptopurine oral suspension the Applicant conducted two clinical studies with Purixan 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 listed drugs (LDs). However, due to the use of a European reference product, as well as a major formulation change in their test product, Study SC02808 could not be accepted in current the application (PIND 112823 meeting minutes 12/01/11). Thus, only the BE study PXL20744 was accepted and reviewed by the Agency.

From study PXL20744, bioequivalence was demonstrated based on the primary PK parameters AUC(0-t) and AUC(0-∞). Cmax did not demonstrate bioequivalence. There was a 30% higher mean peak concentrations seen following the Purixan oral suspension product administration. However, the range of Cmax values following Purixan administration was within range of the reference tablet Cmax values. There was no evidence that subjects with a higher Cmax (on either reference or test product) had more events or more changes in laboratory parameters.

2. CLINICAL PHARMACOLOGY FINDINGS

Study PXL207444 was conducted to compare the bioavailability of mercaptopurine from Purinethol® tablet (US LD) with that of the mercaptopurine oral suspension. A total of 70 healthy male adult volunteers were recruited and 62 completed the study. The design of the study was a conventional bioequivalence design. It was conducted as an open-label, laboratory-blind, single-dose, randomized, two-period, two-sequence, cross-over study under fasting conditions.

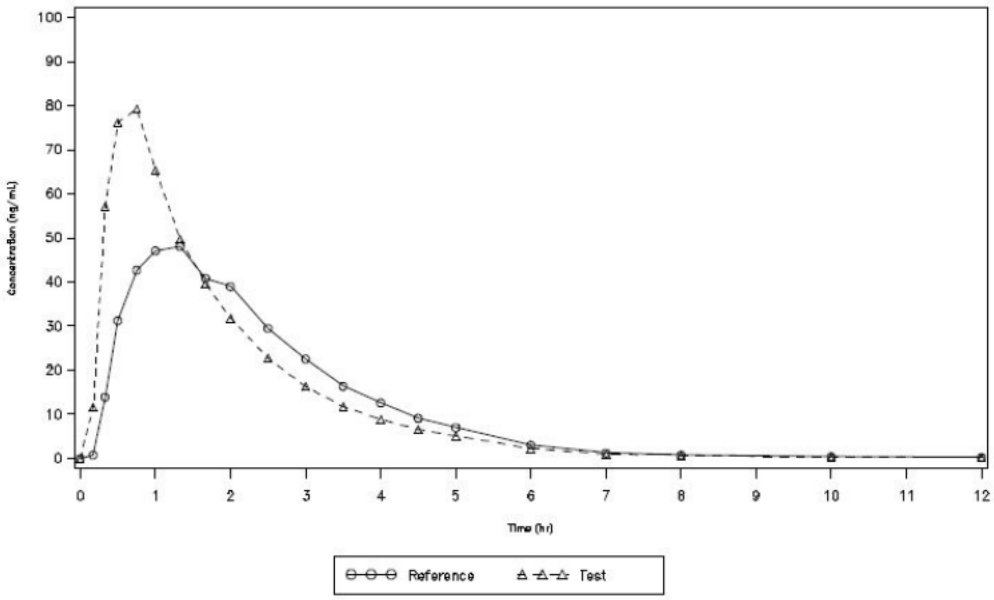
The study consisted of two treatment periods, each of which included a pharmacokinetic sampling for up to 12 hours. Treatment periods were separated by a wash-out period of at least 4 calendar days. Prior to the study, it was established that the Cmax, AUC(0-t) and AUC(0-∞) geometric mean ratio 90% confidence intervals should be contained within 80%-125%. Descriptive statistics of the pharmacokinetic parameters for mercaptopurine (MP) are presented in the table below (Table 1).

Table 1. Summary of Statistical Analyses of Plasma MP 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
$AUC_{(0-\infty)}$ *(h*ng/mL)*	62	129.3	145.5	112.5	106.9 - 118.4

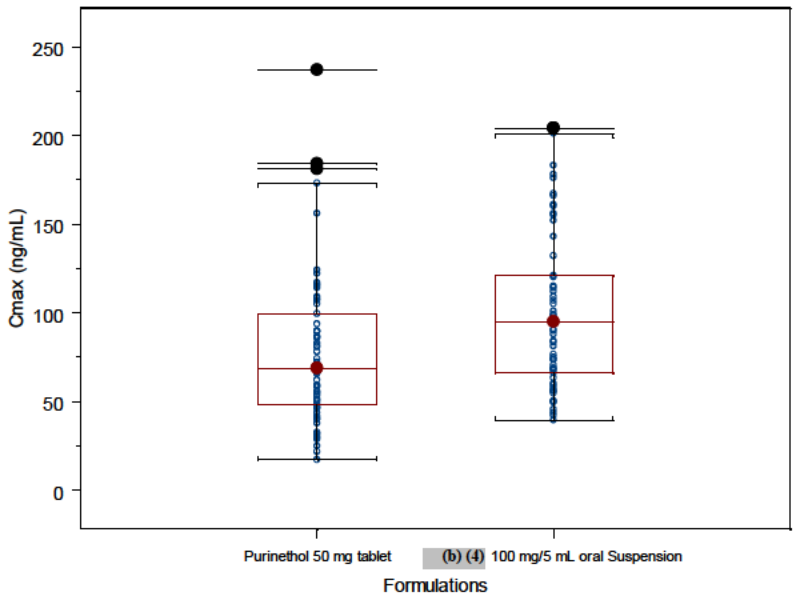
The AUC(0-t) and AUC(0-∞) were similar between the two formulations and fell within the pre-defined 80-125% bounds for bioequivalence. For Cmax, the mean ratio was 133.61%, with the 90% confidence interval between 119.98% and 148.79%. Cmax did not demonstrate bioequivalence; 30% higher mean peak concentrations were seen following test product administration (Table 1, Figure 1).

Figure 1. Graphical Representation of MP Concentrations – Arithmetic Mean (Linear Scale)



The observed range of Cmax values in subjects dosed with the tablet (n=69) was 17.1 – 237 ng/ml and oral suspension (n=63) was 39.5 – 204 ng/ml (Figure 2). The lowest and highest Cmax values were observed with the reference tablet formulation. The Cmax values observed with the suspension were contained within the range observed for the tablet formulation. Additionally, the suspension demonstrated lower variability for Cmax. This pattern is consistent with that observed in a BE study using the European comparator (Puri-Nethol® 50 mg tablet).

Figure 2. Scatterplot Purinethol® (reference, tablet) and MP (test, suspension)



Even with the increase in mean Cmax, the test suspension potentially provides more predictable systemic delivery of mercaptopurine. Current clinical practice uses varying ways of compounding Purinethol tablets for oral administration to children. This includes crushing Purinethol tablets and mixing it with ascorbic acid, simple syrup, and water in differing volumes depending on the prescribing institution. The Purixan oral suspension will limit the inherent dose-to-dose, and patient-to-patient variability compared to these various compounded formulations.

From a safety perspective, this study did not demonstrate any 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 Cmax (on either reference or test product) had more adverse events or more changes in laboratory parameters. Additionally, as was seen in Figure 2, the highest individual Cmax values were observed with the tablet formulation. Concerns about the possibility of increased toxicity as a consequence of a higher average Cmax (33%) seen with the oral suspension may be diminished knowing that in this study, as well as the European comparator study, higher individual Cmax values were seen in the tablet formulation.

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 towithdrawal	3 (4.3)	1 (1.6)
TEAEs leading to death	0 (0.0)	0 (0.0)

In summary, the bioequivalence study PXL207444 demonstrates that the tablet and oral suspension products are bioequivalent with respect to AUC, but a higher average Cmax is observed with the oral suspension. However, this Cmax finding is not considered to be clinically significant, as AUC correlates with cytotoxicity and myelotoxicity rather than a short-lived higher Cmax peak. Furthermore, the range of Cmax values observed with the oral suspension falls within the range observed for the tablet. Lastly, no substantial differences in related AEs or serious AEs were seen between the two formulations.

3 GENERAL ATTRIBUTES

3.1 GENERAL BIOPHARMACEUTICS

The proposed formulation is an oral suspension containing mercaptopurine at strength of 20 mg/mL, compared to the 50 mg tablet reference product. A mercaptopurine product approved in Europe was also used in a previous BE study (SC02808). However, only the PK results of

Study PXL207444 comparing the proposed oral suspension with the US reference product was discussed in Section 2 above.

Table 3. Description and Composition of the Proposed Drug Product (Mercaptopurine, Oral Suspension)

Component	Function	Formula (mg Unless Specified)			Quality Standard
		Per 1mL Dose	Per 5mL Dose	Per 100mL	
Mercaptopurine[1]	Active	20.0	100.0	2000	USP
Xanthan Gum	[redacted]			(b) (4)	USP
Aspartame					USP
Concentrated Raspberry Juice[2] • Juice of the raspberry *Rubus idaeus* L. • Sucrose added to (b) (4)					In house specification[4]
Methyl para-hydroxybenzoate					USP
Propyl para-hydroxybenzoate					USP
Water[3]					USP

[1] The U.S Pharmacopoeia defines mercaptopurine as mercaptopurine monohydrate. The formulation contains 20mg mercaptopurine monohydrate (20mg mercaptopurine USP) per mL.
[2] (b) (4)
[3] Complies with the USP monograph for 'sterile purified water'
[4] Complies with British Pharmacopoeia 1988

Reference Product
Name: Purinethol®: USA marketed product; Active ingredient: mercaptopurine
Formulation: Tablet, Strength: 50 mg
Manufacturer: (b) (4) Batch No.: A78637A, Expiry Date: 31 October 2013

3.2 ANALYTICAL

3.2.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

6-mercaptopurine was the primary active moiety assessed in the plasma of patients in the clinical study. An analytical method (VAL 205/01) was developed and validated for the quantification of 6-mercaptopurine in human plasma over the range of 0.250 - 128 ng/ml. The sponsor states the method validation had met the acceptance criteria as stipulated in the standard operating procedures of the (b) (4) They state that the analytical method is suitable for the quantification of 6-mercaptopurine in human plasma samples over a concentration range of 0.250 - 128 ng/ml. Samples with concentration levels above the ULOQ (up to 204 ng/ml) may be analyzed by applying a maximum of a 2-fold dilution.

3.2.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The method demonstrates suitable accuracy, precision, and linearity (0.250 ng/mL to 128 ng/mL, up to 204 ng/mL with 2-fold dilution) for the assessment of 6-mercaptopurine from PK samples in humans. This linear range of the standard curve adequately meets the needs for clinical studies.

3.2.3 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The lower limits of quantification (LLOQ) and the upper limits of quantification (ULOQ) for 6-mercaptopurine were 0.250 ng/mL and 128 ng/mL, respectively.

3.2.4 What are the accuracy, precision and selectivity at these limits?

The accuracy, precision, and selectivity parameters for the determination of mercaptopurine are summarized in the table below (Table 4).

Table 4. Summary of Method Validation for the Determination of Mercaptopurine and Related Substances by Diode Array Detection

Parameter	Acceptance Criteria	Results and Commentary
Specificity (mercaptopurine)	(b) (4)	Criteria were met
Linearity (mercaptopurine)		$R^2 = 0.998$
Accuracy (mercaptopurine)		All accuracy data met the acceptance limit of % recovery to be within the range 98.0-102.0%. There was no trend in recovery values evident over the three spiked levels. The mean of all 9 recovery values was 99.9%, which was within the acceptance limit of 98.0-102.0%.
Precision (mercaptopurine)		%RSD = 0.19
Repeatability (mercaptopurine)		%RSD = 0.7
Intermediate precision (mercaptopurine)		0.8% and 1.2% for each set of analyses
Range (mercaptopurine)		Suitable for the assay of mercaptopurine over the range 80-120% of the nominal concentration
(b) (4)		

3.2.5 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

Long-term stability of 6-mercaptopurine in human plasma (anticoagulant K3EDTA) was assessed by assaying previously prepared stability samples, QC H and QC B (prepared on 05 October 2012), after storage at approximately -70 °C in polypropylene tubes for a period of 69 days. The samples were assayed on 13 December 2012. The concentrations of the stability samples were calculated against a calibration curve consisting of calibration standards prepared on 13 December 2012. Stability is indicated for the analyte if the measured concentrations are within 15 % of the nominal concentrations. For the high nominal concentration (102 ng/mL) and the low concentration (0.637 ng/ml), the %CV and %Bias for the analytes were reported to be within 15%. The sponsor concludes that 6-mercaptopurine is stable in human plasma, collected on K3EDTA, when stored in polypropylene tubes at -70°C for at least 69 days.

Stability for the analyte is indicated over 3 freeze-thaw cycles. Plasma samples spiked with 6-mercaptopurine at high and low concentrations were prepared on 05 October 2012 and stored frozen at approximately -70ºC, for at least 24 hours. The samples were allowed to thaw unassisted at room temperature, and then refrozen for a minimum period of 12 hours. After three such freeze-thaw cycles, the samples were assayed on 08 October 2012 with a set of freshly prepared calibration standards. The results met the required acceptance criteria.

Short-term stability for the analyte is indicated for 13 hours and 34 minutes. Samples of plasma spiked with 6-mercaptopurine at high and low concentrations were prepared on 05 October 2012. After being kept at room temperature for 13 hours and 34 minutes, the samples were assayed on 08 October 2012 with a set of freshly prepared calibration standards. The results meet the required acceptance criteria.

On-instrument/post-preparative stability is assessed over a period which mimics the expected duration that a batch will remain on-instrument. The results meet the required acceptance criteria. On-instrument/post-preparative stability of the analyte is indicated for 71.5 hours.

3.2.6 What is the QC sample plan?

Quality control samples were prepared gravimetrically in plasma (anticoagulant K3EDTA) on 05 October 2012 (according to SOP BL01/BA). (b) (4)

[redacted]

3.3 OFFICE OF SCIENTIFIC INVESTIGATION INSPECTION

Office of Scientific Investigation has been consulted to inspect the clinical study and bioanalytical sites in (b) (4) that was responsible for the bioequivalence study PXL207444. Results of the OSI inspection are pending at the time of composing this clinical pharmacology review. At this time, no deficiencies were observed and Form FDA-483 was not issued. Any significant finding by OSI that may affect the outcome of study results may result in a revised clinical pharmacology review.

4 APPENDIXES

The current label for Purinethol is not in the Physician Labeling Rule (PLR) format. Therefore, the PLR label for Purixan was updated to make clinical pharmacology sections relevant for today's health care providers. The following Appendixes delineate the resources and corresponding data considered to update labeling for TPMT-deficient patients (Appendix 4.1), and patients with renal (Appendix 4.2) or hepatic (Appendix 4.3) impairment.

4.1 Dosage in TPMT-deficient Patients

PLR language proposed by FDA for Section 2.2:
Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe mercaptopurine toxicity from conventional doses of mercaptopurine and generally require dose reduction. Testing for TPMT gene polymorphism should be considered in patients who experience severe bone marrow toxicities [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)*]. Homozygous deficient patients may require up to a 90% dosage reduction (10% of the standard PURIXAN dose). Most patients with heterozygous TPMT deficiency tolerated recommended mercaptopurine doses, but some require dose reduction based on toxicities.

Micromedex

Based on pediatric data for the treatment of acute lymphoblastic leukemia (ALL), a 90% dosage reduction (10% of the standard dose) can be considered among individuals with TPMT-deficiency

- *Evans WE, Hon YY, Bomgaars L, et al: Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. J Clin Oncol 2001; 19(8):2293-2301.*
- *Andersen JB, Szumlanski C, Weinshilboum RM, et al: Pharmacokinetics, dose adjustments, and 6-mercaptopurine/methotrexate drug interactions in two patients with thiopurine methyltransferase deficiency. Acta Paediatr 1998; 87(1):108-111.*
- *Lennard L, Gibson BES, Nicole T, et al: Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukemia. Arch Dis Child 1993; 69:577-579.*

Lexi-Comp

Patients with homozygous TPMT deficiency: Substantial dosage reduction required; however, optimal initial dosage not established. Some clinicians recommend a reduction to 10% of the usual dosage with further adjustments based on occurrence of myelotoxicity.

Patients with heterozygous TPMT deficiency: Usual dosages generally tolerated, but dosage reduction may be required.

NCCN Guidelines

Testing for TPMT gene polymorphism should be considered in patients receiving mercaptopurine as part of maintenance therapy, particularly those who experience severe bone marrow toxicities.

4.2 Patients with Renal Impairment

PLR language proposed by FDA for Section 8.6:
No formal clinical or pharmacokinetic studies have been conducted in patients with 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. Subsequent PURIXAN doses should be adjusted based on efficacy and toxicity [*see Dosage and Administration (2.1) and Warnings and Precautions (5.1)*]

Lexi-Comp

No specific dosage adjustment is provided. The following adjustments have been used by some clinicians:

- CrCl <50 mL/minute/1.73 m^2: Administer every 48 hours
- Hemodialysis: Administer every 48 hours
- Continuous ambulatory peritoneal dialysis (CAPD): Administer every 48 hours
- Continuous renal replacement therapy (CRRT): Administer every 48 hours

Aronoff GR, Bennett WM, Berns JS, et al, Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 173.

Facts and Comparisons

Start with lower dosages.

Adults:

Mercaptopurine Dosage Adjustment for Renal Dysfunction in Adults	
Renal function	**Recommended dosage interval**
CrCl[a] < 50 mL/min	Every 48 h
Hemodialysis, continuous ambulatory peritoneal dialysis, or continuous renal replacement therapy	Every 48 h

Aronoff GR, Bennet WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. Philadelphia, PA: American College of Physicians; 2007:173.

Dialysis:

Conventional hemodialysis is minimally effective (25% to 49%) in removing mercaptopurine.

4.3 Hepatic Impairment

PLR language proposed by FDA for Section 8.7:
No formal clinical or pharmacokinetic studies have been conducted in patients with hepatic impairment. Mercaptopurine is hepatotoxic. 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 [see Warnings and Precautions (5.1, 5.2)]

Lexi-Comp

No specific dosage adjustment is provided. Discontinue therapy if deterioration of liver function tests, jaundice, hepatomegaly, anorexia with tenderness in the right hypochondrion, or other evidence of toxic hepatitis or biliary stasis occurs, until exact etiology determined.

Facts and Comparisons

Consider reducing the dosage.

NCCN Guidelines

Dosing: Adjustments should be made as needed at signs of increased toxicity (myelosuppression and/or hepatotoxicity).

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/s/

JEFFREY HUANG
04/07/2014

JULIE M BULLOCK
04/09/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205919	**Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DHP		
Applicant:	Nova Labs Ltd	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	(b) (4) Suspension	**Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D.	
Generic Name:	Mercaptopurine	**Date Assigned:**	7/23/2013
Indication	For pediatric use in the treatment of acute lymphoblastic leukemia (ALL) as part of a combination regimen.	**Date of Review:**	4/2/2014
Formulation/ Strength	Suspension; 20 mg/mL		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of Informal/Formal Consult**	**Primary Review due in DARRTS**
July 10, 2013.	July 10, 2013.	April 5, 2014.

Type of Submission:	505 (b)(2) Application
Key review points:	- Dissolution method and acceptance criterion

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS:

The Applicant seeks approval for an oral suspension of mercaptopurine for use in children for the maintenance treatment of acute lymphocytic leukemia (ALL) as part of a combination regimen. The drug (6-Mercaptopurine, 6-MP) is a prodrug that gets activated via hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and several enzymes to form 6-thioguanine nucleotides (6-TGNs). The cytotoxicity of mercaptopurine is due, in part, to the incorporation of 6-TGN into DNA resulting in abnormal DNA-protein interactions that interfere with the function of DNA polymerases, ligases and endonucleases. The absorption of an oral dose of 6-MP variable and incomplete, averaging about 50 % of the dose administered.

6-mercaptopurine is a yellow crystalline powder that is practically insoluble in aqueous solvents; however, it is slightly soluble in alcohol. The drug is soluble in solutions of alkali hydroxides and has pKa values of 7.8 and 11.2. The to-be-marketed product is a 20 mg/mL oral suspension of mercaptopurine.

The Biopharmaceutics review of the NDA will focus on:

1. Adequacy of the dissolution method; and
2. Acceptability of proposed dissolution acceptance criteria.
3. Evaluation of relationship between dissolution and Particle Size Distribution.

1) Dissolution Method
The following dissolution method proposed by the Applicant for Mercaptopurine Oral Suspension is deemed acceptable:

USP Apparatus/RPM	Medium/Temperature	Volume
II/50 rpm	0.1M HCl at 37 ˚C	900 mL

The discriminating ability of the method was demonstrated by the sensitivity of the method to the drug substance particle size.

2) Dissolution Acceptance Criterion
The Applicant has agreed to the following recommended acceptance criterion.

$$Q = {}^{(b)}_{(4)}\% \text{ at } 20 \text{ min}$$

3) Relationship between dissolution and Particle Size Distribution
The data submitted by the Applicant are inadequate for evaluation of the quantitative relationship between particle size distribution and dissolution rate.

II) RECOMMENDATION

The ONDQA/Biopharmaceutics team has reviewed NDA 205919 and its amendments submitted on Feb 26, 2014, March 14, 2014 and April 1, 2014. 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

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.

From the Biopharmaceutics perspective, NDA 205919 for Mercaptopurine Suspension, 20 mg/mL, is recommended for APPROVAL.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Drug Substance

Mercaptopurine monohydrate (6-mercaptopurine) is a yellow crystalline powder that is practically insoluble in aqueous solvents; however, it is slightly soluble in alcohol. The drug is soluble in solutions of alkali hydroxides and has pKa values of 7.8 and 11.2. The to-be-marketed product is a 20 mg/mL oral suspension of mercaptopurine. The solubility of mercaptopurine between (b) (4) was determined and is summarized in Table 1.

Table 1: Summary of pH-Solubility Data for Mercaptopurine

(b) (4)

The Applicant chose 0.1M HCl as the dissolution medium to sustain sink conditions throughout testing.

Drug Product

The to-be-marketed product is a 20 mg/mL oral suspension of mercaptopurine for use by children diagnosed with ALL. The Applicant plans to package the suspension in a 100-mL amber glass bottle with a (b) (4) screw cap. The quantitative composition of a 5-mL dose is presented in Table 2.

Table 2: Quantitative Composition of Mercaptopurine Suspension, 20 mg/mL

Component	Function	Formula (mg Unless Specified)			Quality Standard
		Per 1mL Dose	Per 5mL Dose	Per 100mL	
Mercaptopurine[1]	Active	20.0	100.0	2000	USP
Xanthan Gum	[redacted]			(b) (4)	USP
Aspartame					USP
Concentrated Raspberry Juice[2] • Juice of the raspberry *Rubus idaeus* L. • Sucrose added to (b) (4)					In house specification[4]
Methyl para-hydroxybenzoate					USP
Propyl para-hydroxybenzoate					USP
Water[3]					USP

2. *What is the BCS classification of the drug substance?*

No data are included in the submission with regards to BCS.

B) DISSOLUTION INFORMATION

B.1 DISSOLUTION METHOD

3. *What is the proposed dissolution method?*

Apparatus:	USP 2 (Paddle)
Medium:	0.1M HCl
Volume:	900 mL
Temperature:	37 ˚C
Rotation speed:	50 rpm
Product amount:	5 mL of 20 mg/mL suspension (100 mg mercaptopurine)
Test Duration:	(b) (4)
Analysis:	(b) (4)

4. ***What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?***

Based on the pH-solubility data in Table 1, the Applicant selected 0.1M HCl as the dissolution medium to sustain sink conditions throughout testing. No other dissolution test parameters were evaluated experimentally but the Applicant considered the selected equipment and parameters to be appropriate.

5. ***What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?***

A summary of the analytical method validation is presented in Table 2.

Table 2: Analytical Method Validation Summary

Parameter	Acceptance limit (b) (4)	Results and Commentary
Specificity		0.5%
Accuracy		Recovery at 70%: 99.3%, 99.7%, 100.2% Recovery at 90%: 98.9, 98.7, 98.7 Recovery at 110%: 98.7, 98.7, 98.4
Linearity		$R^2 = 0.9998$
Linearity		y-residuals showed no significant bias in the regression line by visual assessment
Method repeatability		% RSD = 2.3%
Intermediate precision		% RSD = 3.7%
Range		Acceptable linearity, accuracy and precision from 70% to 110% of label claim

6. **What data are available to support the discriminating power of the method?** ***Is the proposed dissolution method biorelavant? What data are available to support this claim?***

The Applicant has provided data to demonstrate reduction in cumulative percent mercaptopurine dissolved at (b) (4) (b) (4). No other critical process or manufacturing parameters were investigated to demonstrate discriminating ability of the proposed method. Since the proposed dosage form is a suspension, demonstration of sensitivity of the dissolution method to particle size is deemed

acceptable for investigation of discriminating power. The Applicant does not make a claim that the method is biorelevant.

7. Is the proposed method acceptable? If not, what are the deficiencies?

The dissolution method is acceptable, provided the Applicant agrees to tighten the proposed acceptance criterion.

B.2 ACCEPTANCE CRITERION

8. What is the proposed dissolution acceptance criterion?

The Applicant's initial proposed dissolution acceptance criterion was:

Q > (b) (4)

Following a teleconference on March 6, 2014 with the Quality Review Team, the Applicant updated the proposed dissolution acceptance criterion on March 18, 2014 as follows:

Q = (b) (4)

9. What data are available to support this criterion?

Official compendia (USP and BP) were initially cited as justification for the proposed criterion of Q = (b) (4). The dissolution data for the clinical batch at the start, middle and end (b) (4), as summarized in Table 3, was submitted by the Applicant on February 26, 2014.

Table 3: Summary of In-Vitro Dissolution Data of Mercaptopurine Suspension, Lot # 0790v004 (Clinical lot)

(b) (4)

The data demonstrate the rapid dissolution of the product, with (b) (4) being released in (b) (4). In the March 6, 2014 teleconference with the Applicant, the Biopharmaceutics review team recommended an acceptance criterion of Q = (b) (4); the Applicant revised it to Q = (b) (4) in their March 14, 2014 amendment. The Applicant reviewed release and stability dissolution data for 7 batches, including the clinical batch, and submitted the results of capability analyses in support of their revised proposed acceptance criterion (\\cdsesub1\evsprod\nda205919\0017\m1\us\12-cover-letters\27-feb-2014-ir-0017.pdf).

Figure 1: Dissolution Profiles of Clinical and Registration Batches of Mercaptopurine Suspension, 20 mg/mL.

The Applicant's capability analysis predicted a failure rate of 25% based on Q = (b) (4) at 20 min and (b) (4). The Applicant contends that an acceptance criterion of Q = (b) (4) is supported by their analyses.

10. Is the acceptance criterion adequate? If not, what is the recommended criterion?

The Biopharmaceutics Review team informed the Applicant in an IR (dated March 27, 2014 in DARRTS) that a predicted failure rate of 25% is acceptable for Level 2 testing. The Applicant confirmed their agreement with the revised recommended dissolution acceptance criterion on April 1, 2014. The recommended dissolution acceptance criterion to be implemented for the proposed Mercaptopurine Oral Suspension is therefore:

Q = (b) (4) at 20 min

11. Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?

Yes, the acceptance criterion is based on clinical and registration batches.

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/s/

OKPONANABOFA ERADIRI
04/02/2014

ANGELICA DORANTES
04/02/2014

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA 205919

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

This NDA is based on the use of (b) (4) (mercaptopurine monohydrate), a liquid formulation of the approved mercaptopurine, indicated for the treatment of ALL in children. The sponsor is seeking marketing approval using the 505(b)(2) pathway. To support the NDA application, the sponsor submitted results of two bioequivalence studies as well as chemistry, manufacturing and controls data to support the use of (b) (4) The two studies presented in this summary aimed to compare and determine the PK and bioequivalence of a new 100 mg/5 mL 6-MP oral suspension (test product) and the 50 mg tablet formulations (reference products).

Due to formulation changes, two bioequivalence studies were submitted in this application. Both studies (PXL207444 and SC02808) were open label, randomized, two-way, two-period, single dose crossover bioequivalence studies in healthy adult male volunteers (n=70 [PXL207444] and n=62 [SC02808]) under fasting conditions.

Study SC02808 used a non-US approved 6-MP reference formulation while Study PXL207444 used the US approved 6-MP tablet. The formulation of (b) (4) differed slightly between the two studies. The to-be-marketed formulation of (b) (4) was used in study PXL207444.

	Information		Information
NDA/BLA Number	NDA 205919	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Mercaptopurine monohydrate
Medical Division	DHP	**Drug Class**	Immunosuppressive
OCP Reviewer	Jeffrey Huang, Pharm.D.	**Indication(s)**	Pediatric patients for maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia
OCP Team Leader	Julie Bullock, Pharm.D.	**Dosage Form**	Oral suspension
Pharmacometrics Reviewer		**Dosing Regimen**	1.5-2.5mg/kg/day single dose
Date of Submission	07/09/2013	**Route of Administration**	Oral
Estimated Due Date of OCP Review	TBD	**Sponsor**	Nova Laboratories Limited
Medical Division Due Date	TBD	**Priority Classification**	Standard
PDUFA Due Date	**May 10, 2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments, If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	2		
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	X			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA 205919

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		2		PXL207444; SC02808
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		
Other Comments				

	Comments
QBR (key issues to be considered)	Bioequivalence
Other comments or information not included above	

On **initial** review of the NDA/BLA application for filing:

NDA 205919 mercaptopurine monohydrate ((b) (4))

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA 205919

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA 205919

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___YES____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Jeffrey Huang, Pharm.D. Date
Reviewing Clinical Pharmacologist

Julie Bullock, Pharm.D. Date
Team Leader

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/s/

JEFFREY HUANG
08/29/2013

JULIE M BULLOCK
08/30/2013

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

NDA Number	205,919
Receipt Date	7/10/2013
Associated IND	112,823
Product name, generic of active(s)	Mercaptopurine Oral Suspension
Dosage form and strengths	20 mg/mL
Indication	Maintenance treatment of Acute Lymphoblastic Leukemia (ALL) as part of a combination regimen in children.
Applicant	Nova Laboratories
Clinical Division	DHP
Type of Submission	505(b)(2) New Drug Application
Biopharmaceutics Reviewer	Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader	Sandra Suarez, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

SUBMISSION

The Applicant seeks approval for an oral suspension of mercaptopurine for use in children for the maintenance treatment of acute lymphocytic leukemia (ALL) as part of a combination regimen. The drug (6-Mercaptopurine, 6-MP) is a prodrug that gets activated via hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and several enzymes to form 6-thioguanine nucleotides (6-TGNs). The cytotoxicity of mercaptopurine is due, in part, to the incorporation of 6-TGN into DNA resulting in abnormal DNA-protein interactions that interfere with the function of DNA polymerases, ligases and endonucleases. The absorption of an oral dose of 6-MP variable and incomplete, averaging about 50 % of the dose administered.

6-mercaptopurine is a yellow crystalline powder that is practically insoluble in aqueous solvents; however, it is slightly soluble in alcohol. The drug is soluble in solutions of alkali hydroxides and has pKa values of 7.8 and 11.2. The to-be-marketed product is a 20 mg/mL oral suspension of mercaptopurine.

The Biopharmaceutics review of the NDA will focus on:

1. Adequacy of the dissolution method; and
2. Acceptability of proposed dissolution acceptance criteria.

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. **INITIAL** OVERVIEW OF THE APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the dissolution test part of the DP specifications?		X	Recommendation will be made for development and inclusion of dissolution as a release test in the 74-day letter.
2.	Does the application contain the dissolution method development report?		X	Recommendation will be made for this report to be requested in the 74-day letter.
3.	Is there a validation package for the analytical method and dissolution methodology?		X	See 1 & 2 above.
4.	Does the application include a biowaiver request?			N/A
5.	Is there information provided to support the biowaiver request?			N/A
6.	Is there information provided to assess dose dumping in the presence of alcohol?		X	The product is an IR formulation.
7.	Is discriminating power of the dissolution test demonstrated?		X	See 1 & 2 above.
8.	Does the application include an IVIVC model?		X	N/A
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	N/A
10.	Is information on mixing the product with foods or liquids included?		X	N/A
11.	Is there any in *vivo* BA or BE information in the submission?	X		BA studies will be reviewed by OCP.
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
12.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		The NDA is fileable from a Biopharmaceutics perspective.
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
14.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Please see comments below.

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

FILING COMMENTS TO BE SENT TO THE APPLICANT

According to 21 CFR 314.50, every drug product application must include the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, and acceptance criterion relating to, dissolution rate. Therefore, conduct dissolution testing of your proposed drug product using an adequate dissolution method. The proposed dissolution method should be supported by the following information/data:

1. **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution method development report should include the following information:

   a. Aqueous solubility data for the drug substance over the physiologic pH range;

   b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc*.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

   c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);

   d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the proposed (target) product and test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables);

   e. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

   a. Normally, the dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value). However, we are willing to accept dissolution data from stability batches and other batches not tested in clinical trials which are being manufactured in the same conditions as those for the clinical batches for setting the dissolution acceptance criterion.

   b. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

   c. For immediate release products, the selection of the specification time point should

be where Q=80 % dissolution occurs.

In order to review the requested data and information in this review cycle, it will need to be submitted no later than October 31, 2013.

{See appended electronic signature page}
Okpo Eradiri, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Sandra Suarez, Ph.D. Date
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

OKPONANABOFA ERADIRI
08/27/2013

SANDRA SUAREZ
08/27/2013