

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205919Orig1s000**

**CHEMISTRY REVIEW(S)**



**NDA 205 919**

**PURIXAN**

**Nova Laboratories Limited**

**Danuta Gromek-Woods, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment 1  
Branch 2**

**CMC REVIEW OF NDA 205 919  
For the Division of Hematology Products (DHP)**

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## Chemistry Review Data Sheet

1. **NDA: 205 919**
2. **REVIEW #: 1**
3. **REVIEW DATE: 01-Apr-2014**
4. **REVIEWER: Danuta Gromek-Woods, Ph.D.**

### 7. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
meeting-minutes-jan-18-2013	18-Jan-2014

### 7. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Description</u>
Original NDA	10-Jul-2013	
Amendment Sequence 0006	27-Aug-2013	Response to IR dated 09-Aug-2013 (clarification on primary stability data to support the shelf life of PURIXAN)
Amendment Sequence 0014	17-Jan-2014	Response to IR dated 6-Dec-2013
Amendment Sequence 0015	31-Jan-2014	Response to IR dated 6-Dec-2013 (impurity analytical method)
Amendment Sequence 0018	20-Mar-2014	Response to IR dated 6-Dec-2013 (new gradient impurity analytical method)
Amendment Sequence 0020	24-Mar-2014	Response to IR dated 20-Mar-2014 (overfill of <sup>(b)</sup> <sub>(4)</sub> )
Amendment Sequence 0021	26-Mar-2014	PMC
Amendment Sequence 0022	26-Mar-2014	Resubmission of the impurity analytical method
Amendment Sequence 0023	27-Mar-2014	Response to IR dated 25-Mar-2014 (suitability of the impurity analytical method)
Amendment Sequence 0024	31-Mar-2014	Labeling

Chemistry Review Data Sheet

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Description</u>
Amendment Sequence 0024	01-Apr-2014	Specification, Justification of specifications

**7. NAME & ADDRESS OF APPLICANT:**

Name:	Nova Laboratories Limited
Address:	Martin House, Gloucester Crescent, Wigston, Leicester, England, LE18 4YL
Representative:	Jennifer Spinella, MT (ASCP), RAC, Vice President Regulatory Affairs & Quality Assurance Rare Disease Therapeutics, Inc. U.S. Agent for Nova Laboratories Limited
Telephone:	619-328-5370

**8. DRUG PRODUCT NAME/CODE/TYPE:**

**PURIXAN oral suspension.**

Proprietary Name: PURIXAN ®

Non-Proprietary Name (USAN): Mercaptopurine oral suspension

**9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)**

**10. PHARMACOL. CATEGORY:** Maintenance treatment of acute lymphoblastic leukaemia (ALL) in children

**11. DOSAGE FORM:** Oral Suspension 20 mg/mL

**12. STRENGTH/POTENCY:** 2000 mg/100mL (20 mg/mL)  
mercaptopurine

**13. ROUTE OF ADMINISTRATION:** Oral

**14. Rx/OTC DISPENSED:**  Rx  OTC

## Chemistry Review Data Sheet

**15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product – Form Completed

Not a SPOTS product

**15b. NANOTECHNOLOGY PRODUCT TRACKING:**

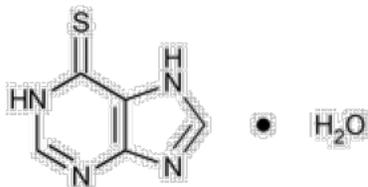
NANO product – Form Completed (See Appendix A.4)

Not a NANO product

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

**Chemical Name:** 1,7-dihydro-6H-purine-6-thione monohydrate

**Structural Formula:**



**Molecular formula:** C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>S·H<sub>2</sub>O

**Molecular weight:** 170.20 as a monohydrate

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	24-Mar-2014	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**18. STATUS**

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Quality Microbiology	Recommended for Approval	03-Apr-2014	Jessica Cole, Ph.D.
EES	Acceptable	04-Apr-2014	Vipul Dholakia, Ph.D.
Methods Validation	NA		
Labeling	Under Review Team discussion		
Biopharmaceutics	Recommended for Approval	02-Apr-2014	Okpo Eradiri, Ph.D.
Toxicology/Clinical	Recommended for Approval	13-Nov-2013/ 25-Mar-2014	Ramadevi Gudi, Ph.D., Non-clinical Reviewer/ Particia A. Dinndorf, MD, Clinical Reviewer
EA	NA		
Radiopharmaceutical	NA		

**19. ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**20. EES INFORMATION**

Drug Substance			
Function	Site Information	FEI/CFN#	Status
Drug substance (6-mercaptopurine) manufacture, release tester, stability tester	(b) (4)	(b) (4)	Acceptable
Drug Product			
Function	Site Information	FEI/CFN#	Status
Finished dosage form manufacturer, release tester, stability tester	Martin House, Gloucester Crescent, Wigston, Leicester, England, LE18 4YL	3000323524	Acceptable

# Chemistry Review for NDA 205 919

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels/labeling have required information. An "Acceptable" recommendation for Nova Laboratories was issued by the Office of Compliance on 04-Apr-2014. From a CMC perspective, this NDA is recommended for "Approval".

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

During teleconference dated 11-Mar-2014, FDA requested a Post-Marketing Commitment to submit a Prior Approval Supplement (b) (4)

In response to FDA requirement, in a letter dated 26-Mar-2014, (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".

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

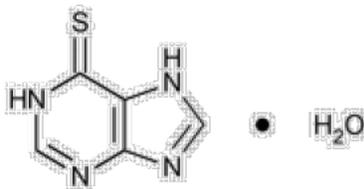
This 505(b)(2) application relies on the FDA's finding of safety and effectiveness of the listed drug, Purinethol (mercaptapurine) tablets, 50 mg marketed by Teva Pharmaceuticals, Inc. under approved NDA 009 053.

## Executive Summary Section

PURIXAN (mercaptopurine) oral suspension is supplied for oral administration and contains 2000 mg/100 mL (20 mg/mL) of mercaptopurine. The suspension also contains the following inactive ingredients: xanthan gum, aspartame, concentrated raspberry juice, sucrose, methyl parahydroxybenzoate, propyl parahydroxybenzoate and purified water. PURIXAN is a pink to brown viscous suspension.

Mercaptopurine is a well-established active substance which has been marketed for several decades in the US in a tablet formulation. The innovator product is Purinethol (Teva), and three additional generic products (Roxane, Prometheus Laboratories, and Mylan) are available in the US. The drug substance supplier was chosen on the basis of their ability to supply material which conforms to both the EU and US Pharmacopeia standards.

Mercaptopurine, a nucleoside metabolic inhibitor, known chemically as 1,7-dihydro-6H-purine-6-thione monohydrate, is an analogue of the purine bases adenine and hypoxanthine. Mercaptopurine is a yellow, odorless or practically odorless, crystalline powder with a molecular formula of  $C_5H_4N_4S \cdot H_2O$  and a molecular weight of 170.20 as a monohydrate. The structural formula is:



The suspension also contains the following inactive ingredients: xanthan gum, aspartame, concentrated raspberry juice, sucrose, methyl parahydroxybenzoate, propyl parahydroxybenzoate and purified water.

Nova Laboratories Ltd currently has a licence for the manufacture and sale of an oral suspension formulation containing 20mg/mL mercaptopurine in the EU, which was developed using expertise from many years manufacturing mercaptopurine suspensions. The formulation described in this NDA is a natural extension of the EU formulation, as it contains the same components; 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.

**B. Description of How the Drug Product is Intended to be Used**

PURIXAN oral suspension is intended for oral administration.

**Basis for Approvability or Not-Approval Recommendation**

Adequate controls for drug substance and raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity,

### Executive Summary Section

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. Based on provided stability data, 12 months of expiration dating period is granted. Labeling has been under discussion. An “Acceptable” recommendation for Nova Laboratories was issued by the Office of Compliance on 04-Apr-2014.

Therefore, NDA 205 919 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.

This NDA is recommended for “Approval” from the CMC perspective.

84 Pages Have Been Withheld In Full As b4 (CCI/TS)  
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DANUTA E GROMEK-WOODS  
04/09/2014

ALI H AL HAKIM  
04/09/2014

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>NDA Number:</b>	<b>Supplement Number and Type:</b>	<b>Established/Proper Name:</b>
205919	NA	Mercaptopurine Oral Suspension
<b>Applicant:</b>	<b>Letter Date:</b>	<b>Stamp Date:</b>
Nova Laboratories Limited	07/09/2013	07/10/2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>		X	<p>A information request was sent to the sponsor asking who performs the release and stability testing for both drug substance and drug product. Applicant satisfactorily responded on 8/26/2013.</p>
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced DMF No. (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced DMF No. (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced DMF No. (b) (4)
15.	Does the section contain controls for the DS?	X		Referenced DMF No. (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Referenced DMF No. (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
28.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

<b>I. Labeling</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
33.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
34.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA
35.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		X	

*{See appended electronic signature page}*

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Janice Brown, Branch II/DNDQA1/ONDQA

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*{See appended electronic signature page}*

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Ali Al-Hakim, Ph.D. /DNDQA1/ONDQA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE T BROWN  
08/30/2013

ALI H AL HAKIM  
08/30/2013