

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**205919Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 205919  
Supporting document/s: 001  
Applicant's letter date: July 9, 2013  
CDER stamp date: July 14, 2013  
Product: (b) (4) Oral Suspension  
Indication: Maintenance treatment of acute lymphatic leukemia (ALL) in children  
Applicant: Nova Laboratories Ltd.,  
Martin House, Gloucester Crescent,  
Wigston, Leicester LE18 4YL,  
United Kingdom  
Review Division: Division of Hematology Oncology Toxicology  
Reviewer: Ramadevi Gudi, Ph.D.  
Supervisor/Team Leader: Haleh Saber, Ph.D.  
Division Director: John Leighton, Ph.D., DABT  
Project Manager: Kristopher Kolibab, Ph.D.

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# 1 Executive Summary

## 1.1 Introduction

NDA 205919 was submitted on July 14, 2013 as a 505(b)(2) by Rare Disease Therapeutics, Inc. on behalf of Nova Laboratories Limited for (b) (4) Oral Suspension containing 20 mg/mL mercaptopurine monohydrate. (b) (4) Oral Solution is being developed for the treatment of acute lymphoblastic leukemia (ALL) in children. The Applicant is relying on the FDA's previous findings of safety and effectiveness of the listed drug product Purinethol® (NDA009053). The oral suspension is being developed to avoid problems associated with swallowing 50 mg tablets of mercaptopurine by children.

No nonclinical study reports are provided with this application. The application contains bioequivalence data, chemistry, manufacturing and controls data.

## 1.2 Brief Discussion of Nonclinical Findings

Mercaptopurine (6-MP) is an analog of purine nucleosides, hypoxanthine and guanine. It is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl-transferase (HGPRTase) yielding thioinosinic acid (TIMP). In addition, 6-methylthioinosinate (mTIMP) is formed by the methylation of TIMP. Both TIMP and mTIMP are reported to inhibit glutamine-5-phosphoribosyl-pyrophosphate amidotransferase, an enzyme which is important in *de novo* purine synthesis. It is not known exactly which of any one or more of the biochemical effects of mercaptopurine and its metabolites are directly or predominantly responsible for cell death.

Reports of toxicology (Genetic toxicology and reproductive toxicology) studies conducted with mercaptopurine, as well as the information presented in the Purinethol label indicate effects consistent with the pharmacologic activity. Mercaptopurine is genotoxic and carcinogenic, and toxic to embryo/fetus in animals. In mice, surviving female offspring of mothers who received chronic low doses of mercaptopurine during pregnancy were found sterile, or if they became pregnant, had smaller litters and more dead fetuses as compared to control animals.

The Applicant provided potential for embryo-fetal toxicity associated with mercaptopurine treatment from the published literature<sup>1</sup>. Mercaptopurine can cause direct effects on embryo-fetal development based on the ability of 6-MP to cross the placenta during pregnancy in multiple nonclinical studies. The published nonclinical studies report that 6-MP induced embryo lethality and teratogenic effects at non-toxic dose levels for the mothers in several animal species (rats, mice, rabbits, and Syrian golden hamsters). In addition to a direct lethal effect on fetuses, mercaptopurine affected the ability of surviving female fetuses to reproduce upon reaching maturity;

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<sup>1</sup> Mosesso and Palitti 1993. The genetic toxicology of 6-mercaptopurine Mutation Research, 296, 279-294

malformations in the second and third generation of offspring were reported<sup>2,3,4</sup>. There are published human data that show embryo-fetal toxicity in women with leukemia treated with mercaptopurine<sup>5</sup>.

Mercaptopurine as a 50 mg tablet formulation (Purinethol, Teva, NDA009053) has been marketed since 1953 in United States for the treatment of ALL in pediatric and adult patients. Extensive clinical experience is available with mercaptopurine administration in children as part of chemotherapy regimen for the treatment of ALL. However, the 50 mg tablet formulation has made it difficult to give individualized doses of the drug to children according to body weight or body surface area. The desired daily doses for the treatment of ALL in childhood may range from 7.5 mg to 125 mg according to the varying body surfaces or body weights. It is reported that the hospitals used different approaches (splitting and compounding) to prepare formulations suitable for children. This has caused poor accuracy and uniformity of dosing ranging from 49 to 157% of the desired tablet. The Application for the proposed oral liquid formulation of mercaptopurine ( (b) (4) ) is to address this issue and to improve ease of administration in children.

### 1.3 Recommendations

#### 1.3.1 Approvability

From a Pharmacology/Toxicology perspective, the approval of mercaptopurine ( (b) (4) ) is recommended.

#### 1.3.3 Labeling

The nonclinical information in the listed drug, Purinethol, will be used for labeling of the nonclinical sections of (b) (4). Additional changes may be implemented in accordance with Physician Labeling Rule (PLR) formatting<sup>6</sup>.

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<sup>2</sup> Reimers et al 1980. Bi-Generational Effects of 6-Mercaptopurine on Reproduction in Mice

<sup>3</sup> Thiersch 1954. The effect of 6-mercaptopurine on the rat fetus and on reproduction of the rat. Annals of the New York Academy of Sciences, 60: 220-227

<sup>4</sup> Reimers and Sluss 1978. 6-Mercaptopurine Treatment of Pregnant Mice: Effects on Second and Third Generations, Science 201, 65-67

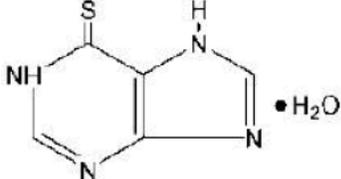
<sup>5</sup> Polifka and Friedman 2002. Teratogen Update: Azathioprine and 6-Mercaptopurine TERATOLOGY 65:240-261.

<sup>6</sup>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf>

## 2 Drug Information

### 2.1 Drug

CAS Registry Number	50-44-2
Generic Name	Mercaptopurine
Code Name	(b) (4)
Other Code Names	(o) (4)
Chemical Name	1,7-dihydro-6H-purine-6-thione monohydrate (6-mercaptopurine monohydrate)
Molecular Formula/ Relative Molecular Mass	C <sub>5</sub> H <sub>4</sub> N <sub>4</sub> S, H <sub>2</sub> O/ 170.2
Structure or Biochemical Description	 <p>6-mercaptopurine is an analog of the purine base hypoxanthine.</p>
Pharmacologic class	A nucleoside metabolic inhibitor

### 2.2 Relevant NDAs

NDA 009053 PURINETHOL by TEVA Pharmaceuticals Ltd.

### 2.3 Drug Formulation

The drug product composition, per nominal 5 mL dose is given in the Table below excerpted from the Applicant's NDA.

Component	Function	Formula (mg Unless Specified)			Quality Standard
		Per 1mL Dose	Per 5mL Dose	Per 100mL	
Mercaptopurine <sup>1</sup>	Active	20.0	100.0	2000	USP
Xanthan Gum	(b) (4)	(b) (4)			USP
Aspartame	(b) (4)	(b) (4)			USP
Concentrated Raspberry Juice <sup>2</sup> <ul style="list-style-type: none"> <li>Juice of the raspberry <i>Rubus idaeus</i> L.</li> <li>Sucrose (b) (4)</li> </ul>	(b) (4)	(b) (4)			In house specification <sup>4</sup>
Methyl para-hydroxybenzoate	(b) (4)	(b) (4)			USP
Propyl para-hydroxybenzoate	(b) (4)	(b) (4)			USP
Water <sup>3</sup>	(b) (4)	(b) (4)			USP

<sup>1</sup> The U.S Pharmacopoeia defines mercaptopurine as mercaptopurine monohydrate. The formulation contains 20mg mercaptopurine monohydrate (20mg mercaptopurine USP) per mL.

<sup>2</sup> (b) (4)

<sup>3</sup> Complies with the USP monograph for 'sterile purified water'

<sup>4</sup> Complies with British Pharmacopoeia 1988

## 2.4 Comments on Novel Excipients

The table below shows the concentration, the function and the characteristics influencing the drug product for each excipient (excerpted from Applicants NDA).

Component	% w/v	Function	Characteristics Influencing Drug Product Performance
Xanthan Gum		(b) (4)	(b) (4)
Concentrated Raspberry Juice			
Aspartame			
Methyl para-hydroxybenzoate			
Propyl para-hydroxybenzoate			
Water†			

\* % v/v

† Complies with the USP monograph for Sterile Purified water

The inactive ingredients used in the formulation can be found in other FDA approved drug products at comparable or higher exposure levels.

### Xanthan gum

Xanthan gum (CAS No. 11138-66-2. E415) is a commonly used component in pharmaceutical products. Several FDA approved drugs have higher amounts of xanthan gum present<sup>7</sup> (For example, Children's Advil® Allergy Sinus Suspension/Children Dimetapp® Allergy and Sinus, Ibuprofen Children's Oral Suspension, Children's Tylenol Pus Multi-Symptom Cold, Children's mucus relief multi-symptom cold, Acetaminophen Oral Suspension, etc.). In addition xanthan gum has been extensively tested in animals and accepted as a food additive in USA (FDA 21 CFR 172.6<sup>8, 9, 10</sup>.)

### Aspartame

Aspartame is a food additive used as a low-calorie sweetener in variety of beverages and foods. It is a dipeptide ester composed of phenylalanine and aspartic acid. Several FDA approved drugs have comparable or higher amounts of Aspartame<sup>11</sup> (for example, Children's Chewable Acetaminophen, Children's Allegra Allergy, Children's Mucinex

<sup>7</sup> <http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm>

<sup>8</sup> <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=172.695>

<sup>9</sup> <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>

<sup>10</sup> <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>

<sup>11</sup> <http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm>

Mini-Melts Cough). In addition, the FDA has assigned aspartame an acceptable daily intake (ADI) of 50 mg/kg bodyweight<sup>12, 13, 14</sup>.

#### Methyl-hydroxybenzoate and propyl para-hydroxybenzoate

The proposed oral mercaptopurine suspension contains (b) (4) % w/v methyl-hydroxybenzoate (other nonproprietary names: methylparaben, methyl para-hydroxybenzoate) and (b) (4) % w/v propyl hydroxybenzoate (other nonproprietary names: propylparaben, propyl para-hydroxybenzoate) as (b) (4)

Several FDA approved drugs have comparable or higher amounts of methyl-hydroxybenzoate and propyl para-hydroxybenzoate commonly known as parabens (for example, Gentamicin Injection USP, Children's Cetirizine Hydrochloride Children's mucus relief multi-symptom cold, and Children's Silapap).

Gentamicin Injection USP (Pediatric – Preservative), NDA 062356:

Each mL contains: 40 mg gentamicin, (b) (4) mg methylparaben, (b) (4) mg propylparaben. The dose in children is 6-7.5 mg/kg/day (up to 150 mg/day for a 20 kg child). The volume of administration will be 3.75 mL of gentamicin ((b) (4) mg of methylparaben and (b) (4) mg of propylparaben)

Based on a mercaptopurine dose of 2.5 mg/kg, the total dose of methyl-hydroxybenzoate and propyl para-hydroxybenzoate would be (b) (4) mg/kg (methyl-hydroxybenzoate (b) (4) mg/kg and propyl-hydroxybenzoate (b) (4) mg/kg) for a 20 kg pediatric patient.

The proposed amounts of methyl ((b) (4) %) and propyl ((b) (4) %)-hydroxybenzoate in the oral mercaptopurine suspension are acceptable from a Pharmacology/Toxicology perspective.

## 2.5 Comments on Impurities/Degradants of Concern

(b) (4): Forced degradation studies of 6-MP under exposure to acidic, alkaline and oxidative conditions resulted in one of the degradation products identified as (b) (4). The drug product specification indicates the level of (b) (4) at  $\leq$  (b) (4) w/w with respect to mercaptopurine peak.

According to the label, the dose of (b) (4) is 1.5 to 2.5 mg/kg/day. This will be up to 50 mg/day for a 20 kg pediatric subject. The proposed specification for (b) (4) at

<sup>12</sup> Final Rule Food Additives Permitted for Direct Addition to Food for Human Consumption; Aspartame. 21 CFR Part 172 (June 28, 1996)

<sup>13</sup> Tschanz C, Butchko HH, Stargel WW, Kotsonis FN. The Clinical Evaluation of a Food Additive; Assessment of Aspartame. 1996.

<sup>14</sup> EFSA 2006. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission related to a new long-term carcinogenicity study on aspartame, The EFSA Journal (2006) 356, 1-44

NMT (b) (4) is acceptable; this level is below the 0.5% qualification threshold described in ICH Q3B(R2) for drugs administered at 10-100 mg/day.

## 2.6 Proposed Clinical Population and Dosing Regimen

(b) (4) is a nucleoside metabolite inhibitor indicated for pediatric patients for maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen. The usual daily maintenance dose of (b) (4) is 1.5 to 2.5 mg/kg/day as a single dose. The oral suspension contains 20 mg mercaptopurine in 1 mL.

## 3 Studies Submitted

### 3.1 Studies Reviewed

No new nonclinical studies were submitted.

### 3.2 Studies Not Reviewed

Not applicable.

### 3.3 Previous Reviews Referenced

Not applicable.

## 4 Pharmacology

No pharmacology studies were submitted.

A review of the published literature concerning mercaptopurine shows that mercaptopurine is a chemical analog of the physiologic purine nucleosides, adenine and hypoxanthine. It is a pharmacologically inactive prodrug and uptake into cells is via the nucleoside transporter, where it is subject to anabolic reactions, catalyzed by several enzymes, to eventually form thioguanine nucleotides (TGNs), and catabolic reactions to form metabolites that are predominantly inactive<sup>15, 16</sup>. The cytotoxicity of mercaptopurine arises as a result of the incorporation of TGNs into DNA<sup>17, 18</sup> and inhibitors of phosphoribosyl pyrophosphate (PRPP) amidotransferase, an enzyme which

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<sup>15</sup> Elion G.B. 1989. The Purine Path to Chemotherapy. Bioscience Reports, Vol. 9, 509-529.

<sup>16</sup> Krynetski 1995. Methylation of Mercaptopurine, Thioguanine, and Their Nucleotide Metabolites by Heterologously Expressed Human Thiopurine S-Methyltransferase. MOLECULAR PHARMACOLOGY, 47:1141-1147.

<sup>17</sup> Yi-He Ling et al, 1992. Consequences of 6-Thioguanine Incorporation into DNA on Polymerase Ligase and Endonuclease Reactions. Molecular Pharmacology, 42:802-807

<sup>18</sup> Coulthard and Hogarth 2005. The thiopurines: An update. Investigational New Drugs 23: 523-532.

is important in de novo purine synthesis<sup>19,20</sup>. The anti-tumor effects of mercaptopurine has been shown *in vitro* and *in vivo* test systems<sup>21,22,23,24</sup>.

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<sup>19</sup> Tay B.S. et al 1968. Inhibition of phosphoribosyl pyrophosphate amidotransferase from Ehrlich ascites-tumor cells by thiopurine nucleotides.

<sup>20</sup> Shi RZ et al 1998. Metabolic effects of thiopurine derivatives against human CCRF-CEM leukaemia cells. The International Journal of Biochemistry & Cell Biology 30 885-895.

<sup>21</sup> Tidd and Paterson 1974. A Biochemical Mechanism for the Delayed Cytotoxic Reaction of 6-Mercaptopurine. Cancer Research 34, 738-746

<sup>22</sup> Adamson et al 1994. The Cytotoxicity of Thioguanine vs. Mercaptopurine in Acute Lymphoblastic Leukemia. Leukemia Research Vol. 18, 805-810.

<sup>23</sup> Clarke DA, Philips FS, Sternberg SS et al. 6-Mercaptopurine: Effects in mouse sarcoma 180 and in normal animals. Cancer Res 1953; 13(8): 593-604.

<sup>24</sup> Philips et al 1954. The toxic effects of 6-mercaptopurine and related compounds. Annals of New York Academy of Sciences

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/s/  
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RAMADEVI GUDI  
11/13/2013

HALEH SABER  
11/13/2013

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

**NDA Number: 205919**

**Applicant: Nova Laboratories  
Limited**

**Stamp Date: July 14, 2013**

**Drug Name:** (b) (4)

**NDA Type: 505(b)(2)**

On **initial** overview of the NDA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		The Applicant is relying on the FDA's previous findings of safety and effectiveness for an FDA approved product mercaptopurine product Purinethol® NDA 009053. No formal pharmacology/toxicology studies are submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		Not applicable. The Applicant is relying on the FDA's previous findings of safety and effectiveness for an FDA approved product mercaptopurine product Purinethol® NDA 009053. No formal pharmacology/toxicology studies are submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable; Separate toxicology studies were not conducted with this drug.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable; Separate toxicology studies were not conducted with this drug.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		Not applicable. The Applicant is relying on the FDA's previous findings of safety and effectiveness for an FDA approved product mercaptopurine product (Purinethol®, NDA 009053). No formal pharmacology/toxicology studies are submitted.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Labeling is comparable to Purinethol®.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		No known impurity issues at this time. This will be addressed in the review.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA is not fileable from the pharmacology/toxicology 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.

Ramadevi Gudi, Ph.D.  
Reviewing Pharmacologist

August 19, 2013  
Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA**

Haleh Saber, Ph.D.

Team Leader/Supervisor

Date

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RAMADEVI GUDI  
08/19/2013

HALEH SABER  
08/19/2013