CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205919Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 205919 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Purixan Established/Proper Name: Mercaptopurine Dosage Form: Oral Suspension		Applicant: NOVA Laboratories Limited Agent for Applicant (if applicable): Jennifer Spinella
RPM: Kris Kolibab, Ph.D.		Division: Division of Hematology

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 4-28-2014

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is _____	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification ised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other BURST
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

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Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval letter 4-28-2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Non-acceptability letter 9-11-2013 Acceptability letter 1-6-2014 Reviews – 9-11-2013 and 12-23-2013
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 10-28-2013 DMEPA: ☒ 10-9-2013 DMPP/PLT (DRISK): ☐ None OPDP: ☒ 4-8-2014 SEALD: ☐ None CSS: ☐ None Other: ☒ PMHS 4-8-2014
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	RPM Filing Review 10-21-2013 505(b)(2) Assessment 4-21-2014 Clearance Committee 4-2-2014 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

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• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan Designation	Pediatric Page 4-24-2014
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	April 7, 4, 2, 1, March 28, 27, 26, 25, 20, February 27, 2014; December 6, 2, September 8, August 12, 9, 8, July 24, 2013
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	3-6-2014 TCON
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1-15-2013
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 4-21-2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4-14-2014
PMR/PMC Development Templates *(indicate total number)*	☐ None 1
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	4-10-2014
• Clinical review(s) *(indicate date for each review)*	clinical review 3-25-2014 filing checklist 8-26-2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	4-25-2014
Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None

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Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ No separate review N/A
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	4-9-2014 cosigned primary review
Clinical Pharmacology review(s) *(indicate date for each review)*	primary review 4-7-2014 filing checklist 8-30-2013
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	4-17-2014
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review N/A
• Supervisory Review(s) *(indicate date for each review)*	cosigned primary review 11-13-2013
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	primary review 11-13-2013 filing checklist 8-19-2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review N/A
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	cosigned primary review 4-9-2014
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	ONDQA 4-9-2014 ONDQA checklist 8-30-2013 Biopharm 4-2-2014 Biopharm checklist 8-27-2013
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	Product quality micro 4-3-2014 Product quality micro checklist 8-26-2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	4-25-2014
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 4-4-2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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EXCLUSIVITY SUMMARY

NDA # 205919 SUPPL # HFD # 160

Trade Name Purixan

Generic Name Mercaptopurine

Applicant Name NOVA Laboratories Limited

Approval Date, If Known 4-28-2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Comparative bioequivalence study reports.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

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d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

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NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

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the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

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demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

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Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

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interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kris Kolibab, Ph.D.
Title: Regulatory Project Manager
Date: 4/29/2014

Name of Office/Division Director signing form: Edvardas Kaminskas, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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.

/s/

KRISTOPHER KOLIBAB
04/29/2014

EDVARDAS KAMINSKAS
04/29/2014

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 205919 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Hematology PDUFA Goal Date: 5/10/2014 Stamp Date: July 10, 2013

Proprietary Name: Purixan

Established/Generic Name: Mercaptopurine

Dosage Form: 20mg/mL

Applicant/Sponsor: NOVA Laboratories Limited

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Indicated in pediatric patients for maintenance therapy of acute lymphatic lymphocytic leukemia as part of a combination regimen.
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Purixan is indicated in pediatric patients for maintenance therapy of acute lymphatic lymphocytic leukemia as part of a combination regimen.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Reference ID: 3495442

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

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{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

KRISTOPHER KOLIBAB
04/24/2014

From: Agosto, Teicher
To: Michelle Taylor (mtaylor@raretx.com); Jennifer Spinella <jspinella@raretx.com> (jspinella@raretx.com)
Subject: Information Request NDA 205919
Date: Monday, April 07, 2014 1:36:00 PM

Hello Michelle,

We have the following information request. Please provide a written response by the COB Tuesday, April 8, 2014.

1. Formally update all NDA sections affected by the implementation of new gradient method (Procedure 2) such as release and stability specifications, justifications of specifications, method and validation etc. In addition, include the drug substance specification and drug substance stability protocol. The specification table should specify if it is release and /or stability specification.

In addition to formally submitting this information to your NDA, please provide me with a courtesy copy via email.

Please confirm receipt of this email.

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
04/07/2014

From: Agosto, Teicher
To: "Jennifer Spinella"; Michelle Taylor (mtaylor@raretx.com)
Subject: Information Request- NDA 205919
Date: Friday, April 04, 2014 11:32:00 AM

Hello,

We have the following information request. Please provide a written response by the COB today, Friday April 4, 2014.

1. Please include new impurity method MET1350-01, Procedure 2 in the Purixan stability specification.

In addition to formally submitting this information to your NDA, please provide me with a courtesy copy via email.

Please confirm receipt of this email.

Thank you,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
04/04/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, April 02, 2014 3:36 PM
To: Jennifer Spinella (jspinella@raretx.com); Michelle Taylor (mtaylor@raretx.com)
Subject: NDA 205919 - Container and Carton Label Comments

Importance: High

Hello,

Please refer to NDA 205919.

Per the request of the review team, please provide a response to the following comments.

A. Container Label:

1. Delete the proprietary name [redacted] (b) (4)" as this name was found unacceptable.

2. Currently, the expression of the strength of the product is cumbersome and confusing. Thus, revise the strength of the product to state the drug content of the bottle, followed by concentration. See example below:
   Mercaptopurine
   Oral Suspension
   2000 mg/100 mL
   (20 mg/mL)

3. Revise the background color to a lighter color scheme. The [redacted] (b) (4) coloring on the upper half of the label decreases the legibility of the printed information; thus, making it difficult to read.

4. Revise the statement [redacted] (b) (4) to state "Each bottle contains 2000 mg/100 mL mercaptopurine (20 mg/mL)". Additionally, relocate this statement to the side panel.

5. Revise the phrase [redacted] (b) (4)" to state "100 mL per bottle" and relocate away from the strength of the product to the upper quadrant of the principle display panel.

6. Delete the [redacted] (b) (4) as this information is unnecessary and occupies space. The product already specifies that this is an "oral suspension".

7. Relocate the "Rx only" statement to the bottom of the principle display panel.

8. Decrease the prominence of the manufacturer "Nova" by decreasing the font size and relocating it to the side panel. Currently, this information is more prominent than established name of the product and distracts from important information on the principle display panel.

9. Relocate the statement "Shake vigorously before use for at least 30 seconds" to the principle display panel under the strength to increase the prominence of this statement as this is important administration information.

10. Relocate the NDC number to the principle display panel above the proprietary name to increase its prominence.

B. Carton Labeling

1. See Recommendations A.1 through A. 8 and revise the carton labeling accordingly.

Reference ID: 3482530

2. Include the strength of the product on each panel of the carton labeling after the established name of the product.

3. Include the NDC number on each panel of the carton labeling. Ensure the NDC number appears above the proprietary name of the product to ensure its prominence.

4. If feasible, include the statement “Shake vigorously before use for at least 30 seconds” on each panel as this is important administration information.

Please officially submit the responses to NDA 205919 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3482530

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/s/

KRISTOPHER KOLIBAB
04/02/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, April 01, 2014 12:56 PM
To: Michelle Taylor (mtaylor@raretx.com); Jennifer Spinella (jspinella@raretx.com)
Subject: NDA 205919 - Information Request - Package Insert

Importance: High

Hello,

Please refer to NDA 205919 and your March 31 submission regarding the package insert. Please provide a response to the following comments **as soon as possible.**

1. In section 5.3 (Immunosuppression) of the package insert, please provide basis for the original prohibition for [redacted] (b) (4) vaccine administration to patients with ALL receiving 6-MP
2. Please provide the [redacted] (b) (4) in section 4 (Contraindications) of the package insert [redacted] (b) (4)

Please confirm receipt of this message by e-mail.

Please officially submit the responses to NDA 205919 and also e-mail to me.

Please feel free to contact me if you have any questions.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3481526

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/s/

KRISTOPHER KOLIBAB
04/01/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, March 28, 2014 3:19 PM
To: Jennifer Spinella (jspinella@raretx.com); Michelle Taylor (mtaylor@raretx.com)
Subject: NDA 205919 - Quality Microbiology IR #2

Importance: High

Hello Jennifer,

Please refer to your NDA 205919.

Per the request of the product quality microbiology review team, please provide a response to the following comments by **11 am April 1, 2014 (Tuesday).**

Quality Microbiology Comments:

1. [redacted] (b) (4)

Please officially submit the responses to NDA 205919 and also e-mail to me.

Please feel free to contact me if you have any questions.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3479977

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/s/

KRISTOPHER KOLIBAB
03/28/2014

From: Agosto, Teicher
To: Jennifer Spinella <jspinella@raretx.com> (jspinella@raretx.com)
Subject: NDA 205919-Information Request
Date: Thursday, March 27, 2014 10:00:00 AM

Dear Ms. Spinella,

We have reviewed your March 14, 2014 response to the FDA-recommended dissolution acceptance criterion (Q = (b) (4)) that was communicated to you via teleconference on March 6, 2014. Your capability analysis of dissolution data predicted failure rates of 25% and (b) (4) for the 20-min and (b) (4) time points, respectively. We do not consider a failure rate of 25% to be high with regard to Level 2 testing frequency. In addition, complete dissolution of batches of your product is skewed towards (b) (4) minutes. However, we believe that an acceptance criterion of Q = (b) (4) at 20 min is reasonable for your product. If you accept a recommended acceptance criterion of Q= (b) (4) at 20 min, send a revised Specifications Table to Teicher Agosto by email latest Friday, March 28, 2014; if you do not agree, please set up a conference call for Friday March 28, 2014 to further justify your new proposed dissolution acceptance criterion.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
03/27/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, March 26, 2014 4:48 PM
To: Jennifer Spinella (jspinella@raretx.com); Michelle Taylor (mtaylor@raretx.com)
Subject: NDA 205919 - Product Quality Microbiology Information Request

Importance: High

Hello Jennifer,

Please refer to your NDA 205919.

Per the request of the product quality microbiology review team, please provide a response to the following comments by **2 pm April 1, 2014 (Tuesday).**

Microbiology Comments:

1. **We refer to your 20 March 2014 submission which contained a response to our 08 September 2013 information request regarding Burkholderia cepacia complex (BCC). Please provide a revised drug product release and stability specification that includes testing for the absence of BCC according to the method described in report TRB-2014-010-01.**

2. [redacted] (b) (4)

Please officially submit the responses to NDA 205919 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3478157

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/s/

KRISTOPHER KOLIBAB
03/26/2014

From: Agosto, Teicher
To: "Jennifer Spinella"
Subject: NDA 205919- Information Request
Date: Tuesday, March 25, 2014 4:31:00 PM

Dear Ms. Spinella,

We are requesting the following information concerning your New Drug Application- NDA 205919. We request a prompt response to this IR request no later than COB Thursday, March 27, 2014.

We reviewed your amendment submitted on 20-Mar-2014 (sequence 0018), please provide the following additional information:

1. Since you will be using an isocratic HPLC method MET1227 for Assay, Identification, Related Substances (including (b) (4)) and a gradient method 1350-01 for (b) (4) and Other Related Substances, provide justifications to demonstrate that the stability data submitted in your NDA, generated with the isocratic method MET1227, still support the expiration dating period of 12 months. Otherwise, please bridge the results generated with method MET1227 (that is unable to test all the mercaptopurine impurities) and the optimized gradient method MET 1350-01.

2. Include test method for (b) (4) and Other Related Substances in the drug product specifications and provide hyperlinks in the "Analytical Procedures" directing to the specific methods. Also, update the "Justification of Specifications" section accordingly.

3. Demonstrate that the suspension vehicle peak @ (b) (4) min does not interfere with the (b) (4) peak in the method 1305-01, as the Retention Times for these peaks are very close. Therefore, include Vehicle preparation and injection in the standard method procedure along with a list of typical Retention Times and Relative Retention Times for eluted compounds accordingly.

In addition to formally submitting this information, please send me a courtesy copy via email.
Please confirm receipt of this Information Request
Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993

Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
03/25/2014

From:	Martin, Jewell
To:	"Jennifer Spinella"
Cc:	Michelle Taylor; Agosto, Teicher
Subject:	NDA 205919 - Information Request
Date:	Thursday, March 20, 2014 2:10:00 PM

Hello Jennifer,

We have the following information request. Please provide a written response by March 24, 2014.

The Purixan oral suspension is a viscous liquid. Please demonstrate that the Purixan oral suspension is filled with an overfill of (b) (4) as per USP requirements.

In addition to formally submitting this information to your NDA, please provide me with a courtesy copy via email.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov

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/s/

JEWELL D MARTIN
03/20/2014

NDA 205919

Date: March 6, 2014

TCON with Sponsor Rare Disease Therapeutics and Nova Laboratories

Purpose: To discuss IRs sent on December 6, 2013 (CMC) and March 6, 2014 (Biopharm).

FDA Attendees:
Ali Al Hakim, PhD, Branch Chief, ONDQA
Janice Brown, MS, CMC Lead, ONDQA
Danuta Gromek-Woods, PhD, CMC Reviewer, ONDQA
Vipul Dholakia, PhD, Compliance Reviewer, OMPQ
Sandra Suarez, PhD, Biopharmaceutics Team Lead, ONDQA
Okpo Eradiri, PhD, Biopharmaceutics Reviewer, ONDQA
Teicher Agosto, Pharm D., Regulatory Project Manager, ONDQA
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA

Sponsor Attendees:
Rare Disease Therapeutics:
Jennifer Spinella, MT(ASCP), RAC, VP, Regulatory Affairs and Quality Assurance, US Agent
Michelle Taylor, Sr. Director Regulatory Affairs
Milton Ellis, President
Nova Labs:
Dr. Peter White, Managing and Technical Director
Dr. Hussain Mulla, Project Lead
Dr. Neil Housley, Head of Quality Assurance
Dr. Grant Kelly, Head of Analytical Services

Meeting Discussion:

- The Agency is concerned that current isocratic method used for assay and impurities for the drug product is not able to detect and quantitate all mercaptopurine related substances. Thus, the method is not suitable. The Sponsor has agreed to provide a new assay and impurities gradient method and validation data by March 20, 2014.
- The Agency stated that the method is not very robust and lacks discriminating ability. The Agency proposed two options; the Sponsor should either develop new method or revise specifications to reflect the dissolution data for their product. The Agency recommends a specification time point of Q= (b) (4). At the moment the sponsor is proposing (b) (4), but will look at what they have and come back with another proposal.
- Sponsor will respond to Biopharm IR sent March 6, 2014, with a proposal of a tighter specification and justification taking into consideration all of the data by March 20, 2014.
- Concerning particle size-dissolution relationship, the Agency stated that (b) (4) is not discriminating enough to use in lieu of dissolution method. Sponsor accepted.

- The Agency asked if the BCC test method for the related IND planned for submission on March 31, 2014, is still on track to be submitted on time. Sponsor agreed to try to submit it by March 20, 2014.
- Sponsor asked about their shipping validation studies. Agency indicated that shipping validation studies are generally reviewed on inspection. Generally these types of studies are not submitted with the application.

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/s/

JEWELL D MARTIN
03/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205919 **INFORMATION REQUEST**

Rare Disease Therapeutics, Inc. US Agent for
Nova Laboratories Limited
Attention: Jennifer Spinella MT (ASCP), RAC
Vice President, Regulatory Affairs and Quality Assurance
9550 Cuyamaca Ste. 203
Santee, CA 92071

Dear Ms. Spinella:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) 20 mg/mL oral suspension.

We also refer to your July 10, 2013 and January 17, 2014 submissions.

We are reviewing the Quality section of your submission and we acknowledge receipt of the update to the following sections which now include dissolution data/information: 3-2-p-5-1-specifications, 3-2-p-5-2-analytical procedures, 3-2-p-5-3-validation-analytical-procedures, 3-2-p-5-4-batch-analyses and 3-2-p-5-6-justification-specifications. However, the data you have provided do not meet the requirements we explained to you during our teleconference on December 12, 2014. We request a written response by March 14, 2014, in order to continue our evaluation of your NDA.

1. The proposed dissolution specification of Q = (b) (4) is not acceptable because we are unable to verify that it is supported by the dissolution data in the Application. For example, more than (b) (4) mercaptopurine is released at (b) (4) for batch numbers 0790z001 and 0790w001. In addition, since dissolution is product specific (method and acceptance criterion), referencing the BP or USP <711> is not sufficient justification for the proposed specification. Provide the following data sets in **excel format** to permit assessment of the appropriate acceptance criterion for your product:

    a) Individual (b) (4) dissolution data (with descriptive statistics; n = 12) at release for the clinical batch, #0790y004; please include all sampling time points, i.e., at 0, 10, 20, 30, 40, 45 and 60 min.

    b) Individual (b) (4) dissolution data (with descriptive statistics) at release, at all stability time points, and in all packaging configurations for the following registration/commercial batches: 0790z001, 0790w001, 0790w002, and 0790w003. At present, only mean data at (b) (4) are presented in the NDA.

Please submit the complete multi-point (0, 10, 20, 40, 30, 45 and 60 min) dissolution profiles in both graphical and tabulated excel formats;

c) On the basis of the complete multipoint dissolution profile data sets and the selection of the sampling time point when Q (b) (4) dissolution occurs, provide your proposal for the dissolution acceptance criterion of your product.

2. Although you have selected an Official dissolution method for release and stability testing, the NDA does not contain data supporting the adequacy and discriminating power of the selected method for your specific product. Other than the dissolution medium, other factors (such as paddle speed) have not been investigated to demonstrate optimum conditions for the test. Note that a slower paddle speed may be necessary to confer discriminating power to the method; provide these experimental data.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
02/27/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, December 06, 2013 9:57 AM
To: Jennifer Spinella (jspinella@raretx.com)
Cc: Michelle Taylor (mtaylor@raretx.com)
Subject: NDA 205919 - CMC Defiencies - Response by January 15, 2014

Importance: High

Hello,

Please refer to your NDA 205919 dated July 10, 2013.

Per the request of the CMC review team, please provide a response to the following requests for information **by January 15, 2014.**

NDA deficiencies:

DRUG SUBSTANCE

1) ***Although the drug substance is referenced in the DMF, submit the following drug substance information to the NDA:***
   - ***Nomenclature***
   - ***Description***
   - ***Molecular Structure***
   - ***Molecular Weight***
   - ***Molecular Formula***
   - ***Drug Substance Specification***
   - ***Stability Protocol and Stability Commitment including retest date***

DRUG PRODUCT

2) ***Justify the acceptance criterion of NLT (b) (4) mg/mL for aspartame. Submit aspartame impurity profile and actual impurity levels on stability.***

3) ***Revise headings to Test, Acceptance Criteria, and Analytical Procedure. The "Mercaptopurine Content by HPLC" should be revised to "Assay". The acceptance criterion should be revised from (b) (4) mg/mL to XX-XX% of label claim.***

4) ***As per ICH Q6A, include a test for identification of mercaptopurine in your drug product specification.***

5) ***Please justify the following discrepancies between the release specification and stability test results in section 3.2.P.8.3:***
   - ***pH: (b) (4) vs. (b) (4)***
   - ***(b) (4): (b) (4) w/w vs. (b) (4) w/w***
   - ***Dissolution: (b) (4) vs. Q > (b) (4)***

Reference ID: 3418256

6) Labeling states that "The bottle should be shaken vigorously for at least 30 seconds to ensure the oral suspension is well mixed"; therefore, as described in ICH Q6A, include a test for redispersibility in drug product specification.

7) Submit results of in-use stability testing of the mercaptopurine suspension in presence of (b) (4) for the (b) (4) suspension. Additionally, provide safety evaluation for a (b) (4) as per Guidance for Industry "Container Closure System for Packaging Human Drugs and Biologics".

8) Demonstrate that your isocratic HPLC Method for the Determination of Mercaptopurine and Related Substances in Mercaptopurine 100mg/5mL Oral Suspension, MET1227, is capable to detect and quantify all mercaptopurine degradants. Additionally, provide data for mass balance of "stressed" samples.

9) Please provide a sample of the drug product suspension along with a (b) (4)

Please officially submit the responses to NDA 205919 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
12/06/2013

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, December 02, 2013 12:15 PM
To: Jennifer Spinella (jspinella@raretx.com)
Cc: Michelle Taylor (mtaylor@raretx.com)
Subject: NDA 205919 - Quality Microbiology Information Request

Importance: High

Hello,

Please refer to your NDA 205919 dated July 10, 2013.

Per the request of the Quality Microbiology review team, please provide a response to the following requests for information **by January 15, 2014.**

1. We refer to your stability study results for the [redacted] (b) (4) effectiveness test [redacted] (b) (4). Several batches (0790w001, 0790w002, 0790w003) failed to meet the acceptance criteria at either 6 or 12 months during stability. Please submit a summary of the failed test results and indicate whether the failed tests would have met the [redacted] (b) (4).

Please officially submit the responses to NDA 205919 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3415476

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/s/

KRISTOPHER KOLIBAB
12/02/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 205919
IND 112823

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Nova Laboratories Limited
c/o Rare Disease Therapeutics, Inc.
9550 Cuyamaca Street
Suite 203
Santee, CA 92071

ATTENTION: Jennifer Spinella, MT (ASCP), RAC
Vice President, Regulatory Affairs & Quality Assurance

Dear Ms. Spinella:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act; and to your New Drug Application (NDA) dated July 9, 2013, received July 10, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mercaptopurine Oral Suspension, 20 mg/mL.

We also refer to your March 14, 2013, IND correspondence, received March 15, 2013; and to your July 30, 2013, NDA correspondence, received July 31, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

We note that our conclusions regarding unacceptability of the name (b) (4) differ from the external study conclusions conducted by (b) (4). The external study did not identify the name (b) (4) as potential source of confusion.

We note that you have proposed an alternate proprietary name in your submissions dated March 14, 2013, and July 30, 2013, to your IND and NDA, respectively. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kristopher Kolibab at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205919

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

NOVA Laboratories Limited
Attention: Jennifer Spinella
Vice President, Regulatory Affairs & Quality Assurance
9550 Cuyamaca Street, Suite 203
Santee, CA 92071

Dear Jennifer Spinella:

Please refer to your New Drug Application (NDA) dated July 9, 2013, received July 10, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (Mercaptopurine).

We also refer to your amendments dated July 30, 2013 and August 8, 14, 16, 26, and 27, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 10, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 12, 2014.

During our filing review of your application, we identified the following potential review issues:

Quality Microbiology:

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of

many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

    a. If you propose to omit release testing for BCC you should provide a risk assessment and description of the control methods used to insure that BCC does not contaminate the raw materials or drug product during manufacture. The waiving of release testing for BCC, if proposed, would likely require testing of incoming components at risk for contamination with BCC.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. (b) (4)

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EDVARDAS KAMINSKAS
09/08/2013

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, August 12, 2013 2:07 PM
To: Jennifer Spinella (jspinella@raretx.com); Michelle Taylor (mtaylor@raretx.com)
Subject: NDA 205919 - Information Request

Hi Jennifer,
Please see the information request below.

In order to review the requested data and information in this review cycle, please submit your responses before October 31, 2013.

"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 (b) (4) dissolution occurs."

Reference ID: 3356066

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3356066

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/s/

KRISTOPHER KOLIBAB
08/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205919 **INFORMATION REQUEST**

Rare Disease Therapeutics, Inc. US Agent for
Nova Laboratories Limited
Attention: Jennifer Spinella MT (ASCP), RAC
Vice President, Regulatory Affairs and Quality Assurance
9550 Cuyamaca Ste. 203
Santee, CA 92071

Dear Ms. Spinella:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) 20 mg/mL oral suspension.

We also refer to your July 10, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 16, 2013, in order to continue our evaluation of your NDA.

1. Provide a summary table showing the differences (manufacturing process, container closure, etc.) between batch 0790z001 and batches 0790w001, 0790w002 and 0790w003 used to support the shelf life.
2. Clarify why stability data was not included for lots 790y003 and 0790y004.
3. Is the (b) (4) with the drug product since information was not included in the NDA?
4. If the (b) (4) is included with the drug product, submit 5 samples (without drug product) of the vial, closure and (b) (4)

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
08/09/2013

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, August 08, 2013 2:28 PM
To: Jennifer Spinella; Linda Martinez
Cc: Ali Ibrahim, Ebla; Kolibab, Kristopher
Subject: NDA 205919 - Information Request

Hello Jennifer,
Please identify where the following are located in the submission.

- A benefit-risk analysis for the product
- Narrative summaries for dropouts in trial INV298

Please e-mail me this information by August 14 (Wednesday).

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Reference ID: 3354764

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/s/

KRISTOPHER KOLIBAB
08/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205919

NDA ACKNOWLEDGMENT

NOVA Laboratories Limited
Attention: Jennifer Spinella
Vice President, Regulatory Affairs & Quality Assurance
9550 Cuyamaca Street, Suite 203
Santee, CA 92071

Dear Jennifer Spinella:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (Mercaptopurine) Oral Suspension, 20 mg/mL

Date of Application: July 9, 2013

Date of Receipt: July 10, 2013

Our Reference Number: NDA 205919

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 8, 2013 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ebla Ali Ibrahim, M.S.
Lead Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EBLA ALI IBRAHIM
07/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 112823

MEETING MINUTES

(b) (4)

Dear Mr. Adams:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Mercaptopurine Monohydrate.

We also refer to the teleconference between representatives of your firm and the FDA on January 15, 2013. The purpose of the meeting was to discuss your proposed 505 (b)(2) NDA application.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mara Miller, Regulatory Project Manager at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 15, 2013 11:00 AM- 12:00 PM EST
Meeting Location: White Oak Building #22, Room 2201, via Teleconference

Application Number: 112823
Product Name: Mercaptopurine monohydrate
Indication: ALL in pediatrics
Sponsor/Applicant Name: Nova Laboratories, Ltd

Meeting Chair: Kathy Robie Suh, M.D., Ph.D.
Meeting Recorder: Mara Miller, M.A.

FDA ATTENDEES

Division of Hematology Products
Ann Farrell, M.D., Division Director
Kathy Robie Suh, M.D., Ph.D., Clinical Team Lead
Andrew Dmytrijuk, M.D., Clinical Reviewer
Ebla Ali Ibrahim, M.S., Regulatory Project Manager
Mara Miller, M.A., Regulatory Project Manager

Office of Clinical Pharmacology
Julie Bullock, Pharm.D., Team Lead
Bahru Habtemariam, Pharm.D., Reviewer

Office of New Drug Quality Assessment
Janice Brown, M.S., Team Lead

Office of Hematology and Oncology Products
Gregory Reaman, M.D., Associate Director

Division of Medical Error Prevention
Yelena Maslov, Pharm.D., Team Lead
Kevin Wright, Pharm.D., Reviewer

Office of Business Informatics
Jared Lantzy, Regulatory Information Specialist

SPONSOR ATTENDEES

Nova Laboratories Limited
Dr. Peter White, Managing and Technical Director
Dr. Hussain Mulla, Project Lead

Rare Disease Therapeutics, Inc.
Milton Ellis, President
Jennifer Spinella, Vice President, Regulatory Affairs & Quality Assurance
Jude McNally, Vice President, Medical Science Liaison

(b) (4)

1.0 BACKGROUND

Nova Laboratories are developing [redacted] (b) (4) for the treatment of acute lymphoblastic leukemia (ALL). Nova Laboratories Ltd has submitted and was granted an Orphan Designation in the US for mercaptopurine oral suspension (trade name [redacted] (b) (4) for treatment of acute lymphoblastic leukemia (ALL) in pediatric patients. (Designation request# 12-3735, approval letter dated 20 Aug 2012).

Nova Laboratories Ltd and [redacted] (b) (4) met with members of the Division on September 8, 2011, and December 2, 2011 by teleconference to discuss clinical and CMC aspects of an IND application. Following those meetings Nova Laboratories decided to conduct a further bioequivalence study comparing [redacted] (b) (4) to the US formulation of the reference product Purinethol 50mg tablet (TEVA) and are now planning to submit a NDA application.

2. DISCUSSION

QUESTION 1a

Does the Agency agree with the proposed raw and derived datasets and that no other Reviewer dataset is needed?

- All data needed to generate case report tabulations (CRT)s will be provided in .xpt files. CRTs will not be provided for the tables, listings, and figures.

- The sponsor agrees to provide character mapping for numerical variables (describing categorical data) in the derived datasets. All programs used to generate the derived datasets will be included, but the intermediate files will not be required.

FDA Response:

The content and structure of the data submitted is a review issue.

The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. The submission should support analyses datasets to tabulations datasets traceability. Each study submitted should be complete and evaluated on its own merits.

Submit datasets based on the *Study Data Specifications* version published at the time of submission (currently 2.0). In general, datasets are accepted that comply, within a reasonable timeframe, with previous versions of the *Study Data Specifications* and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

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Studies should be maintained independently in the SEND datasets, SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*).

Discussion

No discussion occurred.

QUESTION 1b

Nova plan to use (b) (4) an established eCTD vendor in the US, to create and submit the eCTD. Since (b) (4) has extensive experience, does the Agency require the sponsor to submit a sample eCTD or Standardized Data Sample to the FDA?

FDA Response:

Samples for eCTD or standardized data are not required before submitting eCTD applications.

Discussion

No discussion occurred.

QUESTION 2a

Does the FDA agree that above discussion provides the necessary justification in the absence of bioequivalence of C_{max} for the two formulations to support registration of the product as a 505(b)(2) application?

FDA Response:

No. The issue is that when using the suspension formulation, the starting dose will result in up to 50% higher Cmax than the reference tablet formulation. You have not provided adequate evidence that this higher Cmax will not result in unacceptably high rate of adverse events. We reiterate our previous suggestion that to address the potential safety concerns, you will need to provide data or references to support the claim that AUC correlates with cytotoxic effect and principal toxic effects. Population dose-response or concentration-response data acquired over a range of doses may be sufficient to demonstrate that the increase in plasma levels would not be accompanied by additional risk.

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Discussion

The Sponsor stated that mercaptopurine tablet has been marketed in Europe for 60 years and their suspension has been marketed for 10 years, and there have been no new safety signals as a result of formulation. They believe that efficacy and toxicity are related to the AUC. Furthermore, they asserted that in the US it is accepted that pharmacy compounding is widely used in clinical practice. They described some of the information they have that supports their contentions. The Agency responded that the Sponsor should compile all the available literature and other information that they have and submit it for review. In addition, if the Sponsor has access to information about pharmacy compounded formulations that are commonly used in the US it would be very helpful to have detailed information (pharmacokinetics and safety) submitted.

If what the Sponsor submits is not sufficient, the Agency would be open to having another meeting to discuss a clinical trial design.

QUESTION 2b

Does the FDA agree that the higher average C_{max} observed with the oral suspension does not raise additional safety concerns in real-life clinical practice and no additional safety study is required in order to file for registration of the product?

FDA Response:

Please see response to Question #2a. This will be a review issue.

Discussion

No discussion occurred.

QUESTION 3a

As the only formal clinically related data being presented are results from the two bioequivalence studies, will formal Integrated Summaries of Efficacy and Integrated Safety be required?

FDA Response:

Yes, formal ISE and ISS summaries are necessary.

Discussion

The Sponsor requested clarification. The Agency responded that integrated summaries will be needed both for efficacy and safety. The Sponsor should determine the appropriate merging for the efficacy data for different formulations. Full study reports (including data sets) for all

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of the individual clinical studies should be included in the clinical data section of the application.

QUESTION 3b

If so, can the two studies be summarised in the respective sections of 2.5 and 2.7, in order to meet this requirement, and the detailed results presented with the study reports in Module 5.3.1, rather than combining the results in a detailed comprehensive Integrated Summaries in Module 5.3.5.3.?

FDA Response:

Please see response to Question #3a.

Discussion

No discussion occurred.

Additional FDA Comments:

Comments from DMEPA:

1. Placing two different syringes (i.e., oral dosing devices) in a single package can lead to the use of the wrong syringe, which can further lead to wrong dosing errors. As a result, we recommend the Sponsor does not include dosing devices with the suspension and let the pharmacist choose commercially available syringe based on the dose of the medication for a particular patient. However, if the Sponsor intends to keep the dosing devices, we request the Sponsor to conduct Human Factors Usability Study of the dosing devices to ensure that the patients can measure out the dose correctly using the correct syringe or combination of syringes if needed. The study should be conducted well in advance of the NDA PDUFA date to ensure the Agency has enough time to review the study results. We also recommend the Sponsor submit study protocol prior to conducting the study to the Agency for review and concurrence. Use can refer to the following guidances regarding Human Factors Usability Study:
    1. CDRH guidance for industry and FDA Premarket and Design Control Reviewers, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, July 18, 2000
    2. CDRH draft guidance for industry and Food and Drug Administration staff on *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, June 22, 2011.
    3. CDER draft guidance for the industry *Safety Considerations for Product Designs to Minimize Medication Errors, December, 2012.*

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2. If you intend to have a proprietary name (e.g., (b) (4), please submit a proprietary name request in accordance with the following guidance:
   CDER guidance for the industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names*, February, 2010.

Discussion

The Sponsor stated they will not supply the syringes with the product. The Agency had no further comments.

General Comments

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)). We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2)

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Reference ID: 3503207

application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Discussion

No discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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/s/

KATHY M ROBIE SUH
01/18/2013