

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208169Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208169

SUPPL #

HFD # 180

Trade Name Xuriden

Generic Name uridine triacetate

Applicant Name Wellstat Therapeutics

Approval Date, If Known

### **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.

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:

d) Did the applicant request exclusivity?

YES  NO

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

5 years – New Chemical Entity  
7 years – orphan drug exclusivity

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?

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).

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 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 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

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



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:

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Name of person completing form: Jessica M. Benjamin  
Title: Senior Regulatory Project Manager  
Date: August 4, 2015

Name of Office/Division Director signing form: Amy Egan  
Title: Deputy Director, ODE III

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.**  
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/s/  
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JESSICA M BENJAMIN  
09/04/2015

AMY G EGAN  
09/04/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208169 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Xuriden Established/Proper Name: uridine triacetate Dosage Form: oral granules		Applicant: Wellstat Therapeutics Agent for Applicant (if applicable):
RPM: Jessica M. Benjamin		Division: DGIEP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>9/8/15</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, 505(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 revised).

<sup>3</sup> 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.

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

- |  |   |
|--|---|
| <input type="checkbox"/> Fast Track                                  | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                              | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval September 4, 2015
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included (see outgoing communication dated 8/6/15)
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included (see outgoing communication dated 8/6/15)
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included (not submitted)
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	3/3/15 2/18/15
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 4/13/15 DMEPA: <input type="checkbox"/> None 7/7/15; 6/9/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 7/17/15; 6/30/15 OPDP: <input type="checkbox"/> None 7/6/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None DPMH review under "clinical consults" dated 7/23/15
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	3/6/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) cleared 7/21/15
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC If PeRC review not necessary, explain: <u>orphan designation</u></li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	August 10, 6; July 27, 23; June 26, 15, 8; May 26, 22, 14; April 24, 16; March 23, 6; February 5, 4; January 22, 2015; April 30 and March 13, 2014
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	March 27, 2015; May 29, 2014
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 12/16/14
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 4/29/15 – copy located in outgoing communications
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 7/8/15 – copy located in outgoing communications
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)             <ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 9/4/2015
<ul style="list-style-type: none"> <li>Division Director Summary Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 9/4/2015
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 7/21/15
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input type="checkbox"/> None 2
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>❖ Clinical Reviews</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	9/4/15; 7/28/15
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	Clinical review dated 7/28/15 pages 74-75

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None DPMH 7/23/15; 5/8/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/16/15
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/5/15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 8/7/15
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/18/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page 55
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• Tertiary review ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None 9/4/15; 6/23/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )		Integrated Quality Assessment dated 6/23/15 pages 8 and 107
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )		
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )		<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/  
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JESSICA M BENJAMIN  
09/04/2015

From: [Benjamin, Jessica](#)  
To: [Bamat, Mike \(mbamat@wellstat.com\)](mailto:mbamat@wellstat.com)  
Cc: [Benjamin, Jessica](#)  
Subject: NDA 208169: PI and IFU revisions  
Date: Thursday, August 06, 2015 11:45:09 AM  
Attachments: [uridine clean PI 6Aug.docx](#)  
[uridine PI 6Aug.pdf](#)  
[uridine IFU 6Aug.pdf](#)  
[clean uridine IFU 6Aug.doc](#)

---

Hi Mike,

Please refer to NDA 208169 for Xuriden. I've attached both a clean and track changes version of our edits to the PI and IFU. If you agree to all of our revisions, please submit the updated versions as final printed labeling. We need to receive the official submission no later than Monday, August 10<sup>th</sup>.

Please let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research, FDA

301-796-3924 *office*

301-796-9904 *fax*

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/s/  
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JESSICA M BENJAMIN  
08/06/2015

**From:** [Benjamin, Jessica](#)  
**To:** [Bamat, Mike](#)  
**Cc:** [Benjamin, Jessica](#)  
**Subject:** RE: NDA 208169 - Dissolution PMC  
**Date:** Monday, July 27, 2015 10:30:07 AM

---

Hi Mike,

Please see our responses to your questions below.

*Question: If these data are satisfactory, will they fulfill the need for dissolution profiles from 5 commercial batches as specified in the PMC?*

**The fulfillment of the PMC includes demonstrating acceptable dissolution data for 5 batches of the 2g sachets and another 5 batches of the (b) (4) product. Note that the acceptability of the dissolution method also depends on providing sufficient data to support the selection of the dissolution method parameters and acceptance criteria and demonstrating the discriminating ability of the method as outlined in previous communications.**

*Question: Is it correct to assume that when the new dissolution method is successfully developed, it can be used for (b) (4) 2 g and (b) (4) sachets using (b) (4) samples from each for the dissolution testing of commercial batches for both indications?*

**Yes, the new method, once deemed acceptable, can be used (b) (4)**

*Question: And that the dissolution method and specifications (once finalized) for the 2 g and (b) (4) sachet batches would thus be harmonized?*

**Yes, the new method, once deemed acceptable, can be harmonized (b) (4)**

Please let me know if you have any further questions.

Regards,  
Jessica

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of New Drugs III  
Center for Drug Evaluation and Research, FDA  
301-796-3924 office  
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---

**From:** Bamat, Mike [mailto:mbamat@wellstat.com]  
**Sent:** Thursday, July 23, 2015 10:39 AM  
**To:** Benjamin, Jessica  
**Subject:** NDA 208169 - Dissolution PMC

Hi, Jessica

Thank you for sending the FDA reviewers' comments regarding the dissolution PMC on Monday (20 July).

We appreciate the confirmation that the use of (b) (4) samples for development and validation of the dissolution method is appropriate.

In addition, we want to be sure that we fully understand the further recommendations and are seeking confirmation of our understanding (below) or correction/clarification.

(b) (4)



Thank you again for your guidance in this area. We look forward to your responses.

Kind regards,

Mike

\*\*\*\*\*

Michael Bamat, Ph.D.  
Vice President R&D  
Wellstat Therapeutics Corporation  
930 Clopper Road  
Gaithersburg, MD 20878  
240 631-2500 ext 3205  
[mbamat@wellstat.com](mailto:mbamat@wellstat.com)

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**From:** Benjamin, Jessica [<mailto:Jessica.Benjamin@fda.hhs.gov>]  
**Sent:** Monday, July 20, 2015 11:15 AM  
**To:** Bamat, Mike  
**Cc:** Benjamin, Jessica  
**Subject:** RE: NDA 208169 - PMCs, Late Cycle minutes

Hi Mike,

Yes, this is sufficient information for the clinical PMC.

Regarding the dissolution PMC, we have the following comments:

**The use of a (b) (4) sample for the development and validation of the dissolution method is appropriate.** (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Regards,  
Jessica

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of New Drugs III  
Center for Drug Evaluation and Research, FDA  
301-796-3924 *office*  
301-796-9904 *fax*

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**From:** Bamat, Mike [<mailto:mbamat@wellstat.com>]  
**Sent:** Friday, July 17, 2015 5:09 PM  
**To:** Benjamin, Jessica  
**Subject:** RE: NDA 208169 - PMCs, Late Cycle minutes

Hi, Jessica.

We will submit the revised protocol/protocol amendment with the requested changes to FDA by or on Thursday 23 July 2015. Is this sufficient information?

I hope you have a wonderful weekend.

Kind regards,

Mike

---

**From:** Benjamin, Jessica [<mailto:Jessica.Benjamin@fda.hhs.gov>]  
**Sent:** Wednesday, July 15, 2015 2:06 PM  
**To:** Bamat, Mike  
**Cc:** Benjamin, Jessica  
**Subject:** RE: NDA 208169 - PMCs, Late Cycle minutes

Hi Mike,

We note that the current protocol for Study 401-13-001 already includes most of the assessments in the proposed clinical post-marketing commitment. However, the protocol does not include assessments of height and weight velocity and assessments of hematologic assessments are scheduled for every 6 months. Given that dosing adjustments for patients are ongoing, we recommend that the protocol be revised to specifically allow for additional assessments of both urine biomarkers (as already specified in the protocol) and hematologic indices at the discretion of the investigator (not specified in the protocol). As part of the clinical post marketing commitment, please revise the protocol for Study 401-13-001 to include the following additional assessments:

- Height velocity and weight velocity measurements at 6-month and 12-month intervals
- Additional hematologic assessments to be performed at any time at the discretion of the investigator

Please provide the proposed date for submission of the final revised PMC protocol.

Regards,  
Jessica

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of New Drugs III  
Center for Drug Evaluation and Research, FDA  
301-796-3924 *office*  
301-796-9904 *fax*

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**From:** Bamat, Mike [<mailto:mbamat@wellstat.com>]  
**Sent:** Tuesday, July 14, 2015 11:09 AM  
**To:** Benjamin, Jessica  
**Subject:** NDA 208169 - PMCs, Late Cycle minutes

Hi, Jessica.

Please find attached a courtesy copy of SN 0017 for NDA 208169, which includes Wellstat's Post-Marketing Commitments with milestone dates and our minutes from the Late-Cycle Review Meeting teleconference held on 08 July 2015. SN 0017 has been sent to our eCTD publisher and should be formally submitted to FDA later today.

Kind regards,

Mike

\*\*\*\*\*

Michael Bamat, Ph.D.  
Vice President R&D  
Wellstat Therapeutics Corporation  
930 Clopper Road  
Gaithersburg, MD 20878

240 631-2500 ext 3205

[mbamat@wellstat.com](mailto:mbamat@wellstat.com)

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JESSICA M BENJAMIN  
07/27/2015

**From:** [Benjamin, Jessica](#)  
**To:** [Bamat, Mike \(mbamat@wellstat.com\)](mailto:mbamat@wellstat.com)  
**Cc:** [Benjamin, Jessica](#)  
**Subject:** NDA 208169: labeling revisions  
**Date:** Thursday, July 23, 2015 2:56:15 PM  
**Attachments:** [NDA 208169 IFU 23 July.pdf](#)  
[NDA 208169 IFU CLEAN 23 July.doc](#)  
[NDA 208169 PI CLEAN 23 July.docx](#)  
[NDA 208169 PI 23 July.pdf](#)

---

Hi Mike,

Please refer to NDA 208169 for Xuriden. I've attached a tracked changes version of the Prescribing Information and Instructions for Use as well as a clean word version for your revisions. Please review and respond no later than close of business Tuesday, July 28<sup>th</sup>, with your proposed revisions to the PI and IFU.

Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research, FDA

301-796-3924 *office*

301-796-9904 *fax*

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JESSICA M BENJAMIN  
07/23/2015

**From:** [Benjamin, Jessica](#)  
**To:** [Bamat, Mike \(mbamat@wellstat.com\)](mailto:mbamat@wellstat.com)  
**Cc:** [Benjamin, Jessica](#)  
**Subject:** NDA 208169 - information request  
**Date:** Monday, June 15, 2015 1:16:04 PM

---

Dear Mike,

Please refer to NDA 208169 for uridine triacetate. As a result of our on-going review of this application, we have the following information request regarding your carton and container labels:

**As currently presented, the NDC number is denoted by a placeholder (XXXXX-XXXX-XX). Please submit the NDC number prior to approval ensuring the middle four digits are different between both strengths since NDC numbers are often used as an additional verification prior to drug dispensing in the pharmacy. Additionally, consider changing the last two digits of the NDC numbers to differentiate the carton and sachet packets.**

Please let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research, FDA

301-796-3924 *office*

301-796-9904 *fax*

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JESSICA M BENJAMIN  
06/15/2015



NDA 208169

## LABELING PMR/PMC DISCUSSION COMMENTS

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

We also refer to our March 6, 2015, letter in which we notified you of our target date of June 8, 2015 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On April 28, 2015, we received your April 28, 2015 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by June 15, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, call me at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Prescribing Information

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JESSICA M BENJAMIN  
06/08/2015

**From:** [Benjamin, Jessica](#)  
**To:** [Bamat, Mike \(mbamat@wellstat.com\)](mailto:mbamat@wellstat.com)  
**Cc:** [Benjamin, Jessica](#)  
**Subject:** NDA 208169 - request for information  
**Date:** Tuesday, May 26, 2015 2:29:55 PM

---

Hi Mike,

Please refer to NDA 208169 for Xuriden. As a result of our on-going review of this application, we have the following clinical pharmacology information requests:

- 1. Provide the renal function status of the four patients in the pivotal HOA trial 401.13.001. Include serum creatinine and creatinine clearance values (and associated estimation formula) for each of these patients.**
- 2. Address with rationale, whether renal and hepatic impairment are expected to affect the systemic exposure of uridine following Xuriden.**
- 3. What extrinsic factors (diet, exercise, drugs etc.) are expected to impact urinary orotic acid levels?**
- 4. Per information in the CRF, patients (b) (6) and (b) (6) did not have genetic confirmation for HOA. Address if the genetic testing for these two patients is now complete and provide the results if available. If not, clarify if the patients will be tested to confirm the diagnosis.**

We request a response by Friday, May 29, 2015. Please let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research, FDA

301-796-3924 *office*

301-796-9904 *fax*

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JESSICA M BENJAMIN  
05/26/2015

**From:** [Benjamin, Jessica](#)  
**To:** [Bamat, Mike \(mbamat@wellstat.com\)](mailto:mbamat@wellstat.com)  
**Cc:** [Benjamin, Jessica](#)  
**Subject:** NDA 208169 - information request  
**Date:** Friday, May 22, 2015 11:50:02 AM

---

Dear Mike,

Please refer to NDA 208169 for Xuriden. As a result of our on-going review of this application, we have the following information requests:

**Please submit the following data in table format as the data become available:**

- **Any efficacy data collected during the Month 12 assessment visit**
- **Any efficacy data collected during unscheduled visits between the Month 6 and Month 12 assessment visits**

**Efficacy information should include hematologic, pharmacodynamic (urinary orotic acid and orotidine) and growth parameters (height, weight, height velocity and weight velocity). Please ensure that the growth data are also submitted as z-scores. For any patient who received a dose increase, include the rationale for the dose increase and any pre- and post-dose pharmacokinetic information, if available. The data table(s) should be appropriately linked to existing tables in the NDA.**

Please advise us of your proposed time frame for submitting this information.

Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research, FDA

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JESSICA M BENJAMIN  
05/22/2015



NDA 208169

**MID-CYCLE COMMUNICATION**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

We also refer to the teleconference between representatives of your firm and the FDA on April 29, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** April 29, 2015 from 1:00 PM to 2:00 PM

**Application Number:** NDA 208169  
**Product Name:** Xuriden (uridine triacetate)  
**Indication:** Treatment of hereditary orotic aciduria (HOA)  
**Applicant Name:** Wellstat Therapeutics Corporation

**Meeting Chair:** Joette Meyer, PhD  
**Meeting Recorder:** Jessica M. Benjamin, MPH

**FDA ATTENDEES**

Office of Drug Evaluation III

Julie Beitz, MD, Director  
Amy Egan, MD, Deputy Director  
Maria Walsh, Associate Director for Regulatory Affairs

Office of Drug Evaluation III/Division of Gastroenterology and Inborn Errors Products

Donna Griebel, MD, Director  
Dragos Roman, MD, Acting Deputy Director  
Joette Meyer, PhD, Cross Discipline Team Leader  
Anil Rajpal, MD, Clinical Team Leader  
Carla Epps, MD, Clinical Reviewer  
Sruthi King, PhD, Nonclinical Reviewer  
Sushanta Chakder, PhD, Nonclinical Team Leader  
Jessica Benjamin, MPH, Senior Regulatory Project Manager, DGIEP

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Sue Chih Lee, PhD, Clinical Pharmacology Team Leader  
Sandhya Apparaju, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Hamid Shafiei, PhD, CMC Reviewer  
Jean Tang, PhD, Chemist

Office of Biostatistics/Division of Biostatistics III

Min Min, PhD, Biostatistics Reviewer  
Yeh-Fong Chen, PhD, Biostatistics Team Leader

Office of Compliance/Office of Scientific Investigations

Susan Leibenhaut, MD, Office of Compliance

Office of Surveillance and Epidemiology

Aleksander Winiarski, Regulatory Project Manager

Kimberly Swank, PhD, Pharmacist, Division of Pharmacovigilance I

Sherly Abraham, Safety Evaluator, Division of Medical Error Prevention and Analysis

Felicia Duffy, Safety Evaluator, Division of Risk Management

Office of Medical Policy/Division of Medical Policy Programs

Shawna Hutchins, Patient Labeling Reviewer

Office of Drug Evaluation IV/ Division of Pediatric and Maternal Health

Carol Kasten, MD, Clinical Reviewer

Amy Taylor, MD, Clinical Reviewer

Tamara Johnson, MD, Acting Clinical Team Leader

Mildred Wright, Regulatory Project Manager

Eastern Research Group, Independent Assessor for PDUFA V

Patrick Zhou

Marc Goldstein

**APPLICANT ATTENDEES**

Michael Bamat, PhD, Vice President R&D

(b) (4)

Jeffrey Miller, PhD, Director Analytical R&D and Manufacturing

Rita O'Neil, PhD, Senior Director, Regulatory Project Manager

Julie Vanas, Director, Clinical Projects

Reid von Borstel, PhD, Vice President Discovery Research

Nadine Wohlstadter, President

**1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

**2.0 SIGNIFICANT ISSUES**

Nonclinical

No significant nonclinical issues have been identified to date.

Clinical Pharmacology

In vitro, uridine triacetate was found to inhibit the p-gp mediated transport of digoxin with an IC50 of 344 uM. As such, drug interaction in the gut cannot be ruled out. We are considering a post-marketing study to evaluate the p-gp inhibition potential of uridine triacetate in vivo.

Clinical

1. Dosing and administration information needs to be clarified for labeling (information request letter issued).
2. We acknowledge your proposal in labeling to include administration of XURIDEN with milk or infant formula. You have indicated that:



CMC



(b) (4)



(b) (4)



(b) (4)



(b) (4)



**3.0 INFORMATION REQUESTS**

There are no outstanding information requests at this time.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns identified at this time and there is currently no need for a REMS.

Nonclinical:

1. We remind you of your previous agreement to conduct a Segment III pre- and post-natal development study with uridine triacetate post approval. You will be issued a PMR for this study.
2. We have reviewed your waiver request for conducting a 2-year carcinogenicity study with uridine triacetate and after consulting with the CDER/ECAC, we are granting this waiver.

**5.0 ADVISORY COMMITTEE MEETING**

There are no plans at this time for an AC meeting.

**6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

The Late Cycle Meeting has been tentatively scheduled for July 8, 2015.

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/s/  
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JESSICA M BENJAMIN  
05/14/2015



NDA 208169

## INFORMATION REQUEST

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

We also refer to your April 10, 2015 submission, containing your response to the 74-day letter with regard to the dosage and administration of Xuriden.

We have the following comments, information requests, and labeling revisions. Please revise and submit the once daily dosing tables, as described below, along with the other requested information no later than May 8, 2015, in order to continue our evaluation of your NDA.

**You provided a copy of the “Digital Weighing Spoon - Instructions for Use”, which was provided to patients in the clinical trial. These instructions describe how to use the weighing spoon, but do not include the instructions given to individual patients/caregivers as to what dosage they should be administering in grams. Did the clinician/investigator calculate the actual dose in grams for the patient? What instructions were given on rounding actual doses?**

**Did the patients give any feedback as to whether or not they liked using the digital spoon or describe any limitations of using the device to measure the recommended dose? Any positive or negative comments related to administration and/or dosing would be helpful.**

**Thank you for providing dosing tables based on body weight for the Dosage and Administration section of labeling.**

(b) (4)

**Therefore, we ask that you only include dosing tables for once daily dosing in labeling (i.e., Table 1).**

The first column in the once daily dosing tables (Table 1) contains body weight in (b) (4), followed by (b) (4) in column two. Labeling instructions for weight-based dosing should be based on kilogram body weight; (b) (4).

The third column of Table 1 provides the (b) (4) dose in (b) (4). The labeling also provides the instruction to “measure the dose using...a (b) (6) accurate to at least 0.1 gram.” (b) (4)

(b) (4)

(b) (4)

Please provide a maximum total daily dose, your rationale for selecting this dose, and revise the tables to cap the dose for patients whose weight exceed a selected cut-off.

Finally, you have chosen (b) (4) patients in the clinical trial received a maximum of 120 mg/kg per day. We wish to ensure that the maximum recommended dose in labeling is supported by safety information in patients with HOA, which can include use of other formulations of uridine as described in the literature. Please provide information on the maximum mg/kg daily dose of uridine in the literature and how that dose compares to a dose of (b) (4) mg/kg per day of uridine triacetate.

If you have any questions, please contact Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
04/24/2015



NDA 208169

## INFORMATION REQUEST

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated January 8, 2015, received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

We are reviewing the clinical pharmacology section of your application and have the following information requests. We request a written response no later than April 22, 2015, in order to continue our evaluation of your NDA.

With regard to the assay method as described in (b) (4)  
Protocol Manual: Orotic acid/Orotidine Determination By Electrospray tandem mass spectrometry," provide the following information:

1. **Submit the assay validation report. Such a report should include validation parameters such as sensitivity, selectivity, precision, accuracy, dilution integrity, etc. Please refer to the draft bioanalytical method validation guidance (2013) at the following location:**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>
2. **For the pivotal HOA trial 001, provide the in-study assay report. Such a report should include the performance results for the calibration and QC samples. In addition, clarify whether your analytical runs included any QC samples with known/spiked orotic acid concentrations (other than the high and low tolerance limit controls specified in the protocol).**

**Your label proposes the use of urinary orotic acid as one of the criteria for dose adjustment. Please address the following:**

- 1. What is the basis of your proposed normal reference range for urinary orotic acid and orotidine? Submit any relevant in-house or literature information justifying reference ranges for the various pediatric age groups.**
- 2. What are the threshold values for urinary orotic acid that would prompt a dose adjustment in the clinical setting?**
- 3. In the clinical setting, do you anticipate that patient samples for assessment of urinary orotic acid will be sent to a centralized laboratory and if so, would this be the same facility that was employed during the pivotal HOA trial 001 ( (b) (4) )?**

If you have any questions, please contact Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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BRIAN K STRONGIN  
04/16/2015

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** March 26, 2015  
**Application Number:** NDA 208169  
**Product Name:** Xuriden (uridine triacetate)  
**Sponsor/Applicant Name:** Wellstat Therapeutics Corporation  
**Subject:** Filing Communication: Clarification of Information Requests

### **FDA Participants:**

Julie Beitz, M.D., Director, ODE III  
Amy Egan, M.D., Deputy Director, ODE III  
Dragos Roman, M.D., Acting Deputy, DGIEP  
Joette Meyer, Pharm.D., Associate Director for Labeling, DGIEP  
Anil Rajpal, M.D., Medical Team Leader, DGIEP  
Sherly Abraham, R.Ph., Safety Evaluator, DMEPA  
Kendra Worthy, Pharm.D., Team Leader, DMEPA  
Shawna Hutchins, MPH, BSN, RN, Senior Patient Labeling Reviewer, DMPP  
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer  
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader  
Amy Taylor, M.D., Clinical Reviewer, DPMH  
Marie Kowblansky, Ph.D., CMC Team Lead  
Maureen Dewey, M.P.H., Senior Regulatory Project Manager, DGIEP

### **Applicant Participants:**

#### Wellstat Therapeutics Corporation

Michael Bamat, Ph.D., VP R&D  
Joan Helton, Quality Assurance  
Jeffrey Miller, Ph.D., Director Analytical R&D and Manufacturing  
Rita O'Neil, Ph.D., Senior Director, Regulatory Project Management  
Julie Vanas, Director, Clinical Projects  
Reid von Borstel, Ph.D., VP Discovery Research  
Nadine Wohlstadter, President

### **1.0 BACKGROUND:**

On January 8, 2015, Wellstat submitted NDA 208169 for Xuriden (uridine triacetate) oral granules indicated for treatment of hereditary orotic aciduria (HOA).

On March 8, 2015, the Agency completed a filing review and determined that the application was sufficiently complete to permit a substantive review. The review classification for this application is **Priority**. While conducting the filing review, new requests for information were communicated to the sponsor in a filing communication dated March 23, 2015 (74 Day Letter).

On March 25, 2015, the sponsor submitted a request for clarification of 4 areas of discussion in advance of the teleconference.

## 2.0 DISCUSSION:

FDA Items from the 74 Day letter are shown in *italics*, the sponsor's question are shown in **bold**. FDA Responses are shown in **bold** and underlined.

### Clinical

*FDA Item #3. Please provide with the 120-Day Safety Update the latest available data regarding dose regimen(s) and efficacy assessments in the extension phase of Study 401.13.001. Efficacy information should include hematologic, pharmacodynamic (urinary orotic acid and orotidine) and growth parameters (height, weight, height velocity and weight velocity). Please ensure that the growth data are submitted also as Z scores. For any patient who received a dose increase, please include any pre- and post-dose pharmacokinetic information, if available.*

#### Wellstat Preliminary Response:

The 120-Day Safety Update will contain the requested information. Wellstat proposes the following:

- i. With 4 total patients, only 3 of whom have had visits since the NDA submission, we propose to provide the 120-day update as a narrative which will incorporate any new efficacy data, including hematology, urinary orotic acid and orotidine, growth data (weight, height and the corresponding growth curves and Z-scores), as well as safety data (any AEs).
- ii. We will provide details of Patient (b) (6)'s dose increase, including the rationale for the increase, and data from the patient's extension visit which became available after the original NDA submission. There are no additional PK data for this patient.
- iii. The pre- and post-dose-increase pharmacokinetic information for both patients at Site 02 was already provided in the CSR body for Study 401.13.001 (Figure 11.5 (Page 52), Figure 11-6 (Page 60) and Section 11.5 (Page 65)) provided in Section 5.3.5.1 of the NDA (SN0003).
- iv. We propose to provide the 120-day update as an addendum ("append") to CSR 401.13.001 in Section 5.3.5.1 of the NDA.

**Question: Are these proposals acceptable to the Division?**

#### FDA Response:

**In general, this proposal is acceptable.**

**Regarding Sponsor's response # i, FDA asked for clarification as to why data will be submitted for only 3 out of 4 patients enrolled in the clinical trial. The sponsor stated that the fourth patient's visit took place in (b) (6), which was prior to the NDA submission. This patient is scheduled to be seen every 6 months; therefore the next visit will be in (b) (6) FDA requested that the sponsor submit any**

**intermediate data points for this patient, should such data be available. The sponsor agreed to submit the requested data and any additional data when available.**

**FDA requested that the sponsor submit the data also in table format and that it should be appropriately linked to existing tables in the NDA. The sponsor agreed.**

**FDA Item #6:** Please provide a summary analysis of the case reports published in the literature describing the results of uridine treatment in patients with hereditary orotic aciduria (HOA). This summary should describe uridine's effect on the efficacy parameters studied in the respective case reports with emphasis on the efficacy endpoints evaluated in your clinical program (see #3 above). Please include any information on pharmacodynamic responses (see #3 above). In addition, provide a summary of any literature data that defines the safe and effective uridine dose(s) in patients with HOA, the time to pharmacodynamic and clinical response, as well as the time course of pharmacodynamic and clinical deterioration that is associated with discontinuation of uridine treatment in patients with HOA. Please note that depending on the adequacy of such data we may consider including relevant information in Section 14 (Clinical Studies) of your proposed label.

**Wellstat Preliminary Response:**

**Wellstat proposes to provide tables and written summaries capturing the presenting symptoms in all known HOA patients, the magnitudes and rates of responses to uridine replacement therapy, and the doses of uridine required or used. Emphasis will be on hematologic and pharmacodynamics data, mirroring the clinical study endpoints, but non-hematologic issues will be included to capture information about the full range of known presenting symptoms among HOA patients. The reported cases where uridine replacement has been temporarily discontinued or reduced have been identified, providing information about clinical and pharmacodynamic relapse when uridine replacement is inadequate.**

**Wellstat proposes to provide this information as an Addendum to Module 2.5 (Clinical Overview).**

**Question: Is this proposal acceptable to the Division?**

**FDA Response:**

**FDA provided background on the reason for the information request. Specifically, FDA requested that the sponsor submit the published data relied on for uridine dose selection and for establishing the "effective" uridine dose. The sponsor agreed.**

**Dosage and Administration of Uridine Triacetate**

***FDA Item #7: The Xuriden prescribing information (PI) states the proposed starting dosage is 60 mg/kg/day*** (b) (4)



The (PI) also states the prescribed dose of Xuriden should be accurately measured using a scale or (b) (4).

FDA comment:

For the purposes of commercialization, it is not realistic to expect that all patients/caregivers have access to a scale (b) (4) to measure out an accurate dose.

Please address the following:

a. Include weight-based dosing charts in the PI covering the dosage range of 60 to (b) (4) mg/kg/day. We note that patients in the clinical trial received the total daily dose once daily and (b) (4)

(b) (4)

(b) (4)

c. The proposed dosing charts should convert the recommended mg/kg/day dosage into a dose that can be accurately measured from the available 2 gram (b) (4) packets and should minimize the variability, as much as possible, between the dosage to be administered and the weight-based recommended dosage.

d. Provide data on selected measuring device(s) that deliver a reproducible amount of granules. The recommended dosage may need to be rounded to the nearest dosage that can be accurately measured by the selected device(s) and should utilize increments that are understood by patients/caregivers (i.e., 1/4 teaspoon, 1/2 teaspoon, etc.).

It may be more appropriate to construct your dosing tables based on the amount of granules that can be measured using fractions of a teaspoon or (b) (4). See #11 under the subheading of Chemistry, Manufacturing and Controls.

Wellstat Preliminary Response:

Dosing tables and teaspoons:

**Wellstat will provide weight-based dosing charts in the PI based on the instruction and guidance provided by the Division.** (b) (4)

(b) (4)

(b) (4)

Wellstat agrees that it is more appropriate – generally more accurate – to create the dosing tables based on teaspoons of uridine triacetate (b) (4)

In light of the safety profile of uridine triacetate, the dosing tables will be constructed to remove any potential for under-dosing at each prescribed mg/kg dosage.

*Scales and (b) (4):*

With regard patient/caregiver access to a scale or (b) (4), Wellstat is providing several documents (please see attached PDF file) that suggest accurate, simple and inexpensive versions are available through consumer channels. If feasible for patients/caregivers, these metering devices would provide the most accurate doses for patients and may even be easier to use than other alternatives.

Question: Would the Division be willing to consider or comment on this possibility?

**FDA Response:**

**No, we are unable to comment at this time on the use of metering devices, such as a scale or (b) (4) FDA inquired about the type of teaspoon used to determine a 'level teaspoon' of Xuriden weighs approximately (b) (4) grams. The sponsor used a (b) (4), but agreed that a standardized device should be used.**

**The sponsor was willing to do further investigation to determine what options for teaspoon-type measuring devices were commercially available.**

**Chemistry, Manufacturing and Controls**

*FDA Item #10: Since milk/infant formula or (b) (4) may be a preferred vehicle for administering the drug for some patients, please provide in-use stability data for the drug product in milk/infant formula and in (b) (4). Also, please provide solubility data for your product in these administration vehicles.*

**Wellstat Preliminary Response:**

**Stability: As the Division pointed out in Comment #8, the PI states that Xuriden can be administered (b) (4) or mixed with foods such as applesauce, yogurt or pudding. If mixed in food, ingest the entire dose (b) (4) of mixing and studies with**

(b) (4)

(b) (4)

The soft foods in which stability was tested had a pH of 3.6 (applesauce), 7.0 (pudding) and 4.2 (yogurt), and (b) (4) All of these matrices are aqueous in nature.

Milk has a pH of 6.4 to 6.7 and the pH of infant formula generally ranges from 4.8 to 6.5. The stability of Xuriden in milk-based products has been established (yogurt and pudding).

Therefore, Wellstat proposes that the existing stability data for Xuriden are supportive of its stability in milk, infant formula and (b) (4) and that, therefore, no additional stability studies in milk or (b) (4) are required.

**Question: Is this acceptable to the Agency?**

**FDA Response:**

**FDA agreed with sponsor's proposal that stability studies in milk are not needed.**

*FDA, Item #10 (continued)*

**Solubility:** As shown in Table 1, uridine triacetate can be classified as slightly soluble to sparing soluble in aqueous systems at neutral pH and ambient temperature. Similar solubility would be expected in milk or infant formula.

v. **Table 1: Solubility Estimates of Uridine Triacetate at 20 °C in Solvent/Aqueous Mixtures and (b) (4)**

---

Solvent	Solubility range (mg/mL)	USP Solubility Category
(b) (4)		

**FDA Response:**

**Because the aqueous solubility of the product in (b) (4) is low, FDA reiterated that the sponsor must provide solubility data in milk. The sponsor agreed.**

**3.0 ACTION ITEMS:**

Sponsor plans to submit revised labeling by April 6, 2015 and responses to information requests outlined in 74 Day letter by April 12, 2015. The proposed time frame is acceptable to the Agency.

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MAUREEN D DEWEY  
03/27/2015



NDA 208169

**FILING COMMUNICATION -  
NO FILING REVIEW ISSUES IDENTIFIED**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated January 8, 2015, received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

This application is subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

The planned date for our internal mid-cycle review meeting is April 13, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Clinical Pharmacology

1. The food-effect PK study PN401.07.002 was conducted using a granule formulation that differs in composition from the proposed commercial formulation. Please comment on the applicability of the food effect PK study findings to the new formulation.
2. Despite receiving comparable or higher total daily doses, patients (b) (6) and (b) (6) in study site (b) (4) had lower systemic exposure of uridine after the starting dose of ~60 mg/kg/day, compared to patients in site (b) (4). Please comment on the likely cause(s) for this lower exposure. Also address whether instructions for accurate weighing of the dose (granules) across the two study sites were standardized.

### Clinical

3. Please provide with the 120-Day Safety Update the latest available data regarding dose regimen(s) and efficacy assessments in the extension phase of Study 401.13.001. Efficacy information should include hematologic, pharmacodynamic (urinary orotic acid and orotidine) and growth parameters (height, weight, height velocity and weight velocity). Please ensure that the growth data are submitted also as Z scores. For any patient who received a dose increase, please include any pre- and post-dose pharmacokinetic information, if available.
4. Please provide a rationale for the (b) (4) daily dosing regimen described in the label.
5. Please provide the dosing instructions given to patients/caregivers in the clinical trials on how to measure and administer the prescribed dose, including information on the measuring device(s) used for individual patients.
6. Please provide a summary analysis of the case reports published in the literature describing the results of uridine treatment in patients with hereditary orotic aciduria (HOA). This summary should describe uridine's effect on the efficacy parameters studied in the respective case reports with emphasis on the efficacy endpoints evaluated in your clinical program (see #3 above). Please include any information on pharmacodynamic responses (see #3 above). In addition, provide a summary of any literature data that defines the safe and effective uridine dose(s) in patients with HOA, the time to pharmacodynamic and clinical response, as well as the time course of pharmacodynamic and clinical deterioration that is associated with discontinuation of uridine treatment in patients with HOA. Please note that depending on the adequacy of such data we may consider including relevant information in Section 14 (Clinical Studies) of your proposed label.

### Dosage and Administration of Uridine Triacetate

7. The Xuriden prescribing information (PI) states the proposed starting dosage is 60 mg/kg/day (b) (4) with dose escalation to a maximum of (b) (4) mg/kg/day. (b) (4)

The (PI) also states the prescribed dose of Xuriden should be accurately measured using a scale or (b) (6). New unopened packet(s) are to be used for each dose and the unused granules from an opened packet are to be discarded.

#### FDA comment:

For the purposes of commercialization, it is not realistic to expect that all patients/caregivers have access to a scale or (b) (4) e to measure out an accurate dose.

Please address the following:

- a. Include weight-based dosing charts in the PI covering the dosage range of 60 to (b) (4) mg/kg/day. We note that patients in the clinical trial received the total daily dose once daily and (b) (4)

(b) (4)

- c. The proposed dosing charts should convert the recommended mg/kg/day dosage into a dose that can be accurately measured from the available 2 gram and/or <sup>(b) (4)</sup> packets and should minimize the variability, as much as possible, between the dosage to be administered and the weight-based recommended dosage.
- d. Provide data on selected measuring device(s) that deliver a reproducible amount of granules. The recommended dosage may need to be rounded to the nearest dosage that can be accurately measured by the selected device(s) and should utilize increments that are understood by patients/caregivers (i.e., ¼ teaspoon, ½ teaspoon, etc.).

(b) (4)

(b) (4)

8. The PI also states that Xuriden can be administered (b) (4) mixed with foods such as applesauce, yogurt or pudding. If mixed in food, ingest the entire dose (b) (4) of mixing. (b) (4)

FDA Comment:

You have provided data on the stability of Xuriden in various foods mentioned in labeling. However, it may be desirable for some patients to be able to mix the granules with liquids (e.g., milk). See Comment #10 under the subheading of Chemistry, Manufacturing and Controls.

Chemistry, Manufacturing and Controls

(b) (4)

10. Since milk/infant formula or water may be a preferred vehicle for administering the drug for some patients, please provide in-use stability data for the drug product in milk/infant formula and in (b) (4). Also, please provide solubility data for your product in these administration vehicles.
11. Provide information on the weight of uridine triacetate in 1 teaspoon or other standard unit of measurement that you plan to recommend for administration of this product. The information should include data to demonstrate dose reproducibility when administered with your proposed dosing device.

Biopharmaceutics

12. Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

- a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e.*, *selection of the 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. We recommend use of at least twelve samples per testing variable. (b) (4)

(b) (4) Provide dissolution method development report pertaining to your method of choice.

- b. 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).

(b) (4)

(b) (4)

14. Provide dissolution profiles (graphical and tabulated form) as a function of drug substance particle size.

(b) (4)

16. Provide the dissolution profile of clinical batch (Lot W017891) that was used in the clinical efficacy study.

17. Provide justification with supporting data to bridge the to-be-marketed formulation used in the efficacy study and the early formulation used in the clinical pharmacology studies. Note that major manufacturing/formulation changes need to be supported with BA/BE data.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified labeling issues and are communicating these issues in the attached draft labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 6, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **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 none of these criteria apply to your application, you are exempt from this requirement

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DRAGOS G ROMAN

03/23/2015

Signing for Dr. Donna Griebel



NDA 208169

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research & Development  
930 Clopper Road  
Gaithersburg, MD 20878  
Fax: (301) 519-7020

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Uridine Triacetate, oral granules (b) (4).

We will be performing methods validation studies on Uridine Triacetate, oral granules (b) (4) as described in NDA 208169.

In order to perform the necessary testing, we request the following sample materials and equipments:



Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
645 S. Newstead Ave.  
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael E. Hadwiger, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL E HADWIGER

03/16/2015

MVP Sample request



NDA 208169

**PRIORITY REVIEW DESIGNATION**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated January 8, 2015, received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate), oral granules.

We also refer to your submissions dated January 21, 23, and February 12, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 8, 2015.

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 requirement/commitment requests by June 8, 2015.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before March 23, 2015.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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RICHARD W ISHIHARA  
03/06/2015  
Signing for Donna Griebel.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 208169

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Wellstat Therapeutics Corporation  
930 Clopper Road  
Gaithersburg, MD 20878

ATTENTION: Michael K. Bamat  
Vice President, Research & Development

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) dated and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uridine Triacetate Oral Granules, 2 gram, (b) (4)

We also refer to your correspondence, dated and received January 21, 2015, requesting review of your proposed proprietary name, Xuriden.

We have completed our review of the proposed proprietary name, Xuriden and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your January 21, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796 5295. For any other information regarding this application, contact Maureen Dewey, Regulatory Project Manager in the Office of New Drugs, at (301) 796 0845.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy 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/  
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TODD D BRIDGES  
03/03/2015

**From:** [Dewey, Maureen](#)  
**To:** [Bamat, Mike](#)  
**Cc:** [Dewey, Maureen](#)  
**Subject:** NDA 208169 Information Request 2  
**Date:** Thursday, February 05, 2015 5:21:00 PM

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Mr. Bamat:

Thank you for your message. Please submit the information outlined in your email dated February 5, 2015 promptly as an amendment to the NDA. In the cover letter, please include an explanation and description of the error.

Please respond to the additional request for information:

1. In 14.8 Listing DEM\_L1: Disease Information, the dosing units for uridine for Patient (b) (6) are teaspoons. Please provide the daily uridine dose in mg or grams for this patient.
2. Please provide any available growth data (height, weight, head circumference) obtained from birth to 36 months for the four patients, including z-scores for each growth parameter.
3. It is unclear why the selected primary efficacy endpoint for Patient (b) (6) is white blood cell count since all white blood cell count values submitted for this patient were within normal limits and low white blood cell counts were not listed in the patient's medical history (14.9 Listing MSH\_L1: Medical History at Baseline). Please provide any available historical clinical documentation of low white blood cell counts for Patient (b) (6)

If you have any questions, please contact me, at (301) 796-0845.

Regards,

**Maureen Dewey, MPH**

Senior Regulatory Project Manager | DGIEP | ODE III | OND | CDER | FDA | 301.796.0845 | FAX 301.796.9904  
[maureen.dewey@fda.hhs.gov](mailto:maureen.dewey@fda.hhs.gov)

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/s/  
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MAUREEN D DEWEY  
02/05/2015

**From:** [Dewey, Maureen](#)  
**To:** [mbamat@wellstat.com](mailto:mbamat@wellstat.com)  
**Cc:** [Dewey, Maureen](#)  
**Subject:** NDA 208169 Information Request  
**Date:** Wednesday, February 04, 2015 1:16:29 PM

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Mr. Bamat,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate granules.

We are reviewing the clinical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please submit any available historical white blood count values for Patient (b) (6), including any values obtained prior to the patient being diagnosed with hereditary orotic aciduria.

If you have any questions, please contact me, at (301) 796-0845.

Regards,

**Maureen Dewey, MPH**

Senior Regulatory Project Manager | DGIEP | ODE III | OND | CDER | FDA | 301.796.0845 | FAX 301.796.9904  
[maureen.dewey@fda.hhs.gov](mailto:maureen.dewey@fda.hhs.gov)

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/s/  
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MAUREEN D DEWEY  
02/04/2015



NDA 208169

**NDA ACKNOWLEDGMENT**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Dr. Bamat:

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

Name of Drug Product: uridine triacetate granules 2g, (b) (4)

Date of Application: January 8, 2015

Date of Receipt: January 8, 2015

Our Reference Number: NDA 208169

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 March 9, 2015, 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 Gastroenterology and Inborn Errors 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](mailto: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 me, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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MAUREEN D DEWEY  
01/22/2015



IND 118931

**MEETING MINUTES**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, PhD  
Vice President, Research & Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2014. The purpose of the meeting was to discuss the clinical and nonclinical data for an upcoming NDA submission.

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

If you have any questions, call me at (301) 796-2302.

Sincerely,

*{See appended electronic signature page}*

Kevin B Bugin, MS, RAC  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** December 16, 2014, from 3:00 to 4:00 PM, EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903

**Application Number:** IND 118931  
**Product Name:** uridine triacetate  
**Indication:** uridine replacement therapy in [REDACTED] (b) (4) with orotic aciduria  
**Sponsor/Applicant Name:** Wellstat Therapeutics Corporation

**Meeting Chairperson:** Anil Rajpal  
**Meeting Recorder:** Kevin Bugin

**Attendees:**

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Acting Associate Director of Rare Disease, Office of New Drugs - Immediate Office (OND-IO)  
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)  
Dragos Roman Acting Deputy Director, DGIEP  
Anil Rajpal, M.D., Medical Team Leader, DGIEP  
Carla Epps, M.D., Medical Reviewer, DGIEP  
Sushanta Chakder, Ph.D., Pharmacology Team Leader, DGIEP  
Sruthi King, Ph.D., Pharmacology Reviewer, DGIEP  
Kevin Bugin, M.S., R.A.C., Sr. Regulatory Project Manager, DGIEP  
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)  
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, OCP  
James Bona, M.D., Medical Officer, Office of Orphan Products Development  
Robert Pratt, PharmD, Risk Evaluator, Division of Risk Management, Office of Safety and Epidemiology  
Yeh-Fong Chen, PhD, Statistics Team Leader, Office of Biostatistics, Division of Biostatistics III  
Susan Liebenhaut, MD, Medical Officer, Office of Scientific Investigations  
Patrick Jo, Eastern Research Group, PDUFA V Independent Assessor

**Sponsor Attendees:**

Michael Bamat, PhD, Vice President, Research & Development, Wellstat  
Mark DeSiato, Vice President Global Regulatory Affairs, AstraZeneca  
Joan Helton, Quality Assurance, Wellstat  
Rita O'Neil, Ph.D., Senior Director, Regulatory Project Management, Wellstat  
Julie Vanas, Director, Clinical Project Management, Wellstat  
Reid von Borstel, PhD, Vice President, Discovery Research, Wellstat  
Nadine Wohlstadter, President, Wellstat

## 1.0 BACKGROUND

On October 20, 2014, the Sponsor requested a Type B, Pre-NDA meeting with the Division to discuss the filing of a New Drug Application for uridine triacetate, specifically the clinical and nonclinical data to be submitted. The clinical and nonclinical Pre-NDA meeting was scheduled to occur on December 16, 2014. A Pre-NDA, CMC-Only meeting was also requested on October 15, 2014, and preliminary comments were sent on December 05, 2014. The CMC-Only meeting was not held as the Sponsor indicated preliminary comments were sufficient. The Pre-NDA meeting took place as scheduled, on December 16, 2014.

## 2.0 DISCUSSION

### IND 118931 Pre-NDA Questions

*Question 1. Does FDA concur that the battery of nonclinical safety studies conducted with uridine triacetate is adequate to support filing and review of the NDA, and fulfills all agreements made with the Division?*

#### FDA Response:

**Yes, we agree that the battery of nonclinical safety studies you have conducted or propose to conduct with uridine triacetate is adequate to support filing of the NDA.**

*Wellstat Preliminary Response:* Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.

*Question 2. Does FDA have any comments to Wellstat's plan for addressing the carcinogenic potential of uridine triacetate to support its use as replacement uridine therapy in HOA patients?*

#### FDA Response:

**Your proposal appears to be reasonable. However, we will need to review the carcinogenicity risk assessment for uridine triacetate that you plan to submit in the NDA and discuss the matter internally before making any comments on the requirement of carcinogenicity studies with your product for the indication of HOA.**

*Wellstat Preliminary Response:* Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.

*Question 3. Based on the data provided in the meeting briefing packet, and considering the previous agreements made with the Division, does FDA agree that the efficacy data with uridine triacetate in patients with HOA, as assessed by the stability of the response (clinical endpoint relative to the disease) to oral uridine after switching from oral uridine to oral uridine triacetate are adequate to support the NDA submission?*

**FDA Response:**

**The adequacy of the efficacy data will be determined upon review of the application. We recommend that you also submit longitudinal historical data on growth (height and weight) for each patient including their age in months, pre- and post-initiation of uridine and any available efficacy data (including height and weight) obtained during the extension phase of the trial. Also, submit longitudinal historical data regarding CBC indices pre- and post-uridine for each patient and include transfusion history over time.**

**You should also submit a summary of published case studies on HOA patients treated with uridine (include the copies of the publications). Submit a rationale for the duration of the study to detect a change in MCV.**

***Wellstat  
Preliminary  
Response:***

*Wellstat can include longitudinal historical data on growth (height and weight) for each patient, including their age, pre- and post-initiation of uridine in the Clinical Study Report (CSR).*

*Attached to this document in Appendix 1 are preliminary longitudinal body weight (BW) graphs for each of the four patients, including pre-uridine, during uridine treatment, and during the 6-week Main Study with uridine triacetate. The BW is also included in the graph for the 1 patient (b) (6) assessed thus far during the Treatment Extension.*

*The historical BW and height data were recently collected and are not monitored. We propose to include these data in the body of the CSR.*

*BW and height data during the Treatment Extension were also recently collected and are not yet monitored. We also propose to include these in the body of the CSR in the original NDA. Will this approach be acceptable? Should there be any changes after the monitoring has occurred, we will notify you no later than the 120-day safety update report.*

*Wellstat collected historical CBC data during the study and will submit these longitudinal historical data regarding CBC indices for each patient in the CSR. There were no documented transfusions.*

*Wellstat will also provide a summary of published case studies on HOA patients treated with uridine along with copies of the publications in the NDA. We propose we submit the summary in Module 2.5 (Clinical Overview) with links to the publications in Module 5.4 (References). A summary table of published cases is provided as Appendix 2 to this document for the Agency's review. Is a table like this with links to the available publications or reports on each patient a sufficient summary?*

*There is no published literature or experience beyond Pts (b) (6) and (b) (6) that we are aware of with regard to MCV changes in HOA patients in whom hemoglobin is within the normal range (not "anemic"). Thus far, MCV has remained stable in Pts (b) (6) and (b) (6). Therefore, it is*

*very difficult to provide a rationale for when changes could be expected to occur. Wellstat will continue to monitor and report MCV throughout the Treatment Extension.*

**Discussion:**

***The Agency indicated that it is acceptable to submit the unmonitored data for body weight, PK and CBC in the body of the CSR in the original NDA, but the Sponsor should clearly denote monitored vs. unmonitored data. It was noted that the laboratory data have been through formal QC/QA processes for the respective lab. The Sponsor clarified that “unmonitored” refers to the fact that a Clinical Research Associate has not source verified the data in some cases.***

***The Agency requested that the Sponsor provide the height and weight data on the CDC growth charts. In addition, such data should be provided as z-scores. The Sponsor agrees to include these data in the body of the CSR. A description of methodology for the collection of height and weight data should be provided.***

***The Sponsor’s proposal for summarizing published case studies, with hyperlinks to the references in Module 5.4, and submitting the summaries in Module 2.5 is acceptable.***

***The Agency asked that any dose adjustment should be accompanied by a description of the investigator’s rationale for adjusting the dose. Such information should be included in the body of the CSR.***

***The Agency recommended that the Sponsor provide any information on PD changes (such as MCV for patients while on drug) including PD information that can be collected and summarized from published case reports. In addition, the Sponsor was asked to consult experts in the field of hematology and provide general information on the time course for changes expected to occur in peripheral blood indices (such as MCV) related to the correction of the various causes of megaloblastic anemia/macrocytosis.***

***Question 4. Data for plasma uridine and for orotic acid and orotidine in urine from patients enrolled in the Main Study of Protocol 401.13.001 are provided in this meeting briefing packet. These data confirm exposure to uridine in plasma and stability of orotic acid and orotidine levels in urine after the patients were switched from oral uridine to oral uridine triacetate.***

*Does FDA concur?*

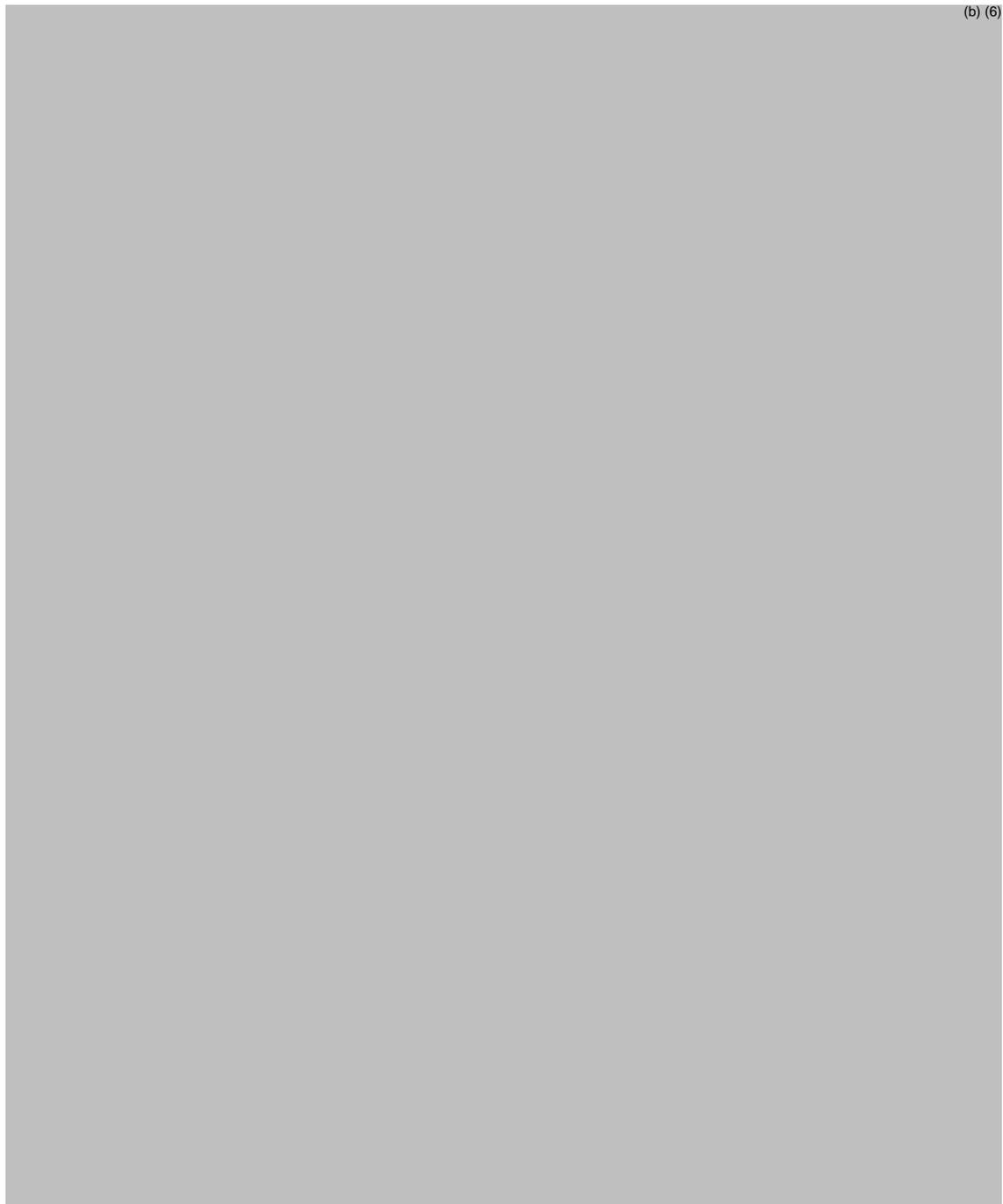
**FDA Response:**

**This will be a review issue.**

***Wellstat  
Preliminary  
Response:***

*Wellstat acknowledges FDA's response.*

(b) (6)



*Question 5. Since approval is based on a single study, Wellstat will not include an ISS and ISE in Module 5 Section 5.3.5. The clinical summaries in Module 2 Section 2.7 will be used to present the summary of efficacy and summary of safety. Clinical studies to be submitted in the original NDA will be summarized individually.*

*Does FDA concur?*

**FDA Response:**

**Yes.**

**Wellstat Preliminary Response:** *Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.*

*Question 6. As previously agreed with FDA, the long-term clinical safety data with uridine triacetate from compassionate use programs in children and adults with mitochondrial or neurometabolic disorders and from two studies in patients with diabetic neuropathy (Protocol Nos. 401.97.201 and 401.97.202) can be used to support the long-term clinical safety of uridine triacetate in support of the NDA (RE: pre-IND meeting 7 Aug 2013 and 9 Dec 2013 teleconference). In addition, safety, food effects and bioequivalence data from studies in healthy subjects will be submitted. Accordingly, no additional clinical safety studies with uridine triacetate are required.*

*Does FDA concur?*

**FDA Response:**

**We agree that no new clinical safety trials are required. However, you should continue to collect safety data as part of the ongoing extension phase of trial 401.13.001.**

**Wellstat Preliminary Response:** *Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.*  
*Data from the extension phase will be provided in the 120-day safety update.*

*Question 7. The clinical and nonclinical safety profiles for uridine triacetate in all patients and indications treated to date do not indicate the need for a Risk Evaluation and Mitigation Strategy (REMS) or any post-marketing safety studies.*

*Does FDA concur?*

**FDA Response:**

**Based on the data submitted to date, we do not anticipate the need for a REMS. The Division will make a final determination on requirements for post-marketing safety activities upon review of the application.**

**Wellstat Preliminary Response:** *Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.*

*Question 8. Wellstat proposes that there is no need for an Advisory Committee meeting.*

*Does FDA concur?*

**FDA Response:**

**We do not anticipate the need for an Advisory Committee meeting at this time.**

*Wellstat Preliminary Response:* *Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.*

*Question 9. Wellstat plans to file the NDA for uridine triacetate as replacement uridine therapy in pediatric patients with hereditary orotic aciduria in December 2014. Wellstat requests a NDA number for this application.*

**FDA Response:**

**For a pre-assigned application number, please follow the directions on the Requesting Pre-assigned Application Number website, located at:**

**<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm>**

*Wellstat Preliminary Response:* *Thank you. On 05 December 2014 Wellstat received NDA number of 208169 for this application.*

*Question 10. Does the Division have any other comments to the proposed eCTD format and content to be included in the NDA?*

**FDA Response:**

**From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below:**

- **Paper archival copies are not necessary when submitting in electronic format.**
- **For archival purposes, also submit a pdf file of any labeling document submitted in word. Also, when word documents are submitted, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.**
- **For ease of review, a single pdf file can be provided (instead of separate pdf files for each document) in m1.6.3 (Correspondence regarding meetings) and m1.12.1 (Pre-IND Correspondence), with proper bookmarks of all meeting correspondence, table of contents and hyperlinks.**
- **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.**

- **Until new m1 is implemented, you may place your proposed proprietary name and rationale information as a separate document from the cover letter in the module 1 cover letter section, or in m1.12.4 (Request for comments and advice). Be consistent.**
- **Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, case report form need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as “case report form” and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml.**

**Your options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.**

- 1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.**
- 2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g., nda, mf, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word “cross reference to” and the application number (e.g., Cross Ref to ind XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.**

**Prior to using cross application linking in an application, it is recommended that you submit an "eCTD cross application links" sample, to ensure successful use of cross application links.**

**To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov). For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>**

*Wellstat Preliminary Response:* *Wellstat acknowledges FDA's response. No further discussion is necessary at the meeting.*

**FDA ADDITIONAL COMMENTS:**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can describe the location or provide a link to the requested information.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).
  1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
    - a. Site number
    - b. Principal investigator
    - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
  2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
    - a. Number of subjects screened at each site
    - b. Number of subjects randomized at each site
    - c. Number of subjects treated who prematurely discontinued for each site by site

- 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:**
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection**
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.**
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.**
- 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).**
- 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).**

## **II. Request for Subject Level Data Listings by Site**

- 1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:**
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated**
  - b. Subject listing for treatment assignment (randomization)**
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued**
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol**
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)**
  - f. By subject listing, of AEs, SAEs, deaths and dates**
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation**
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.**



In addition, we note that a chemistry pre-submission meeting was scheduled and preliminary comments were sent on December 05, 2014. The meeting was not held following your review of the preliminary comments. We refer you to the preliminary comments, which serve as the minutes of that meeting for any additional agreements that may have been reached.

#### **4.0 PREA REQUIREMENTS**

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 this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

#### **5.0 PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

#### **6.0 MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/  
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KEVIN B BUGIN  
01/05/2015

CDER Medical Policy Council  
Decisions/Action Items – Breakthrough Therapy Designation Requests  
April 25, 2014

Council Members:

Gerald Dal Pan, OND/OSE  
Pamela Horn, OND/ODEII/DAAAP  
John Jenkins, OND  
Leonard Sacks, OMP  
Robert Temple, CDER  
Janet Woodcock, CDER  
Sandra Benton, Executive Secretary

Attendees:

Julie Beitz, ODE3	Meredith Libeg, OND/OHOP/DOP2
Jennie Chang, OND/OHOP/DOP2	Maitreyee Hazarika, OND/OHOP/DOP2
Lara Dimick, OND/ODE3/DGIEP	Richard Moscicki, CDER
Norma Griffin, OND/OHOP/DOP2	Melanie Pierce, OND/OHOP/DOP2
Robert Guidos, CDER	Donna Przepiorka, OND/OHOP/DHP
Karen Jones, OND/OHOP/DOP2	Marc Theoret, OND/OHOP/DOP2
Patricia Keegan, OND/OHOP/DOP2	James Xu, OND/OHOP/DOP2
Jun Li, OMP/OMPI/DMPD	

Topic 1: To discuss the breakthrough therapy (BT) designation request for Wellstat Therapeutics' IND 118931, Uridine triacetate for the treatment of hereditary orotic aciduria (HOA).  
Background is attached.

Discussion: DGIEP agreed that this drug is intended to treat a serious and life-threatening disease.

DGIEP stated that this drug is intended to treat a disease that has very few patients, possibly less than 10, in the United States. The drug and indication has received orphan drug status as a potential new drug for a rare pediatric disease.

The Council began its review of this request by email. In the background document, it was unclear whether there is an approved available therapy for this condition and the Council asked to meet to discuss. At the meeting, DGIEP clarified that patients were treated with a prior uridine product, oral uridine, that was not marketed, manufactured by another company, and was used under IND. That company was developing the drug for a different indication and decided to discontinue development. HOA patients currently taking this investigational version will soon run out of drug.

The version under development, uridine triacetate, is four times more potent than the other version, allowing patients to fewer pills per day.

Based on the background submitted and the clarification shared at the meeting, the Council agreed with DGIEP's recommendation to grant breakthrough therapy.

Recommendation: The Council recommended granting the breakthrough therapy designation request from Wellstat Therapeutics for its IND 118931, Uridine triacetate for the treatment of hereditary orotic aciduria (HOA).

(b) (4)



**CDER Medical Policy Council Brief  
Breakthrough Therapy Designation  
Division of Gastroenterology & Inborn Errors Products  
April 25, 2014**

**Instructions:** The information below is to help focus the reviewer's attention on aspects of the available information and the Division's analysis that would need to be considered by the MPC in evaluating a breakthrough therapy designation request. Not all the questions will be applicable to every request. The MPC brief should be no more than about 5 pages in length.

Summary Box

1. IND Number: 118,931
2. Company name: Wellstat Therapeutics, Inc.
3. Drug name: Uridine triacetate
4. Indication: Hereditary orotic aciduria
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition?

The drug is intended as monotherapy to treat a serious and life-threatening disease.

6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints?

There are no approved therapies for hereditary orotic aciduria (HOA). Uridine triacetate is a pro-drug of uridine that forms uridine and free acetate upon metabolism. Published case reports document disease remission in patients with HOA treated empirically with uridine, including improvement in megaloblastic anemia and neutropenia, improved growth, and reduction in infections.

Division: Gastroenterology & Inborn Errors Products

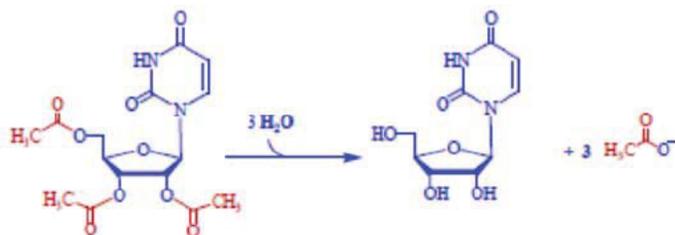
Medical officer: Carla Epps, MD, MPH

Clinical Team Leader: Lara Dimick, MD

**1. Brief description of the drug**

Uridine triacetate is a pro-drug of uridine that forms uridine and free acetate upon metabolism (see Figure 1). The sponsor cited published data and its own pharmacokinetics study data that demonstrated orally administered uridine triacetate delivers about 4 times more bioavailable uridine than equiweight oral doses of uridine.

**Figure 1: Uridine Triacetate Conversion to Uridine**



Source: Protocol 401.13.001, Version 1.0 (dated November 16, 2013), Figure 1.

## 2. Brief description of the disease and intended population

Hereditary orotic aciduria (HOA) is an extremely rare (less than 20 cases identified worldwide) disorder of pyrimidine nucleotide synthesis that is due to a gene mutation that can cause deficiency of the bifunctional enzyme uridine 5'-monophosphate (UMP) synthase that contains two activities (orotic phosphoribosyltransferase and orotidine monophosphate decarboxylase), resulting in accumulation of orotic acid and orotidine in tissues (see Figure 2). Disease onset occurs during the neonatal or infant period. Clinical features of HOA include megaloblastic anemia that is not responsive to treatment with vitamin B<sub>12</sub> or folic acid, neutropenia, increased susceptibility to infections, renal tract obstruction (due to aggregation of orotic acid crystals), physical and intellectual developmental delays. Some patients may present with delayed growth and development prior to developing hematologic abnormalities. There has been at least one confirmed case of HOA without megaloblastic anemia. Biochemical manifestations of the disease are elevated urine levels of orotic acid and orotidine. Mortality in HOA is primarily due to overwhelming infections.

**Figure 2: Pyrimidine Metabolism Pathway**

The following copyright materials have been withheld in full:

Source: Nyhan WL, Disorders of purine and pyrimidine metabolism, Mol Genet Metab 2005; 86: 25-33.

Currently, there is no approved therapy for HOA. However, nucleotide replacement therapy has been the mainstay of treatment for HOA patients for decades following publication of the first case report of

HOA by Huguley et al, in which the authors describe disease remission in a patient treated empirically with a mixture of nucleotides. Subsequent case reports have documented rapid hematologic response with administration of uridine (within days to weeks). Conversely, patients experience relapse of disease when administration of uridine is suspended. Some patients treated chronically with uridine have reached adulthood. There are also case reports of patients treated life-long with uridine that have fathered or given birth to normal children. Uridine dosing has ranged from 50 mg/kg/day to 300 mg/kg/day for patients with HOA. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.

### **3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area**

The sponsor plans to conduct a 6-week, open-label efficacy and safety trial followed by an extension period in 4 to 5 patients with HOA. The proposed study population includes patients previously treated with uridine under individual patient INDs and emergency INDs and one patient naïve to treatment with uridine. Repligen, the supplier of uridine for these patients, has withdrawn its IND for the investigation of uridine to treat bipolar disorders and therefore these patients will no longer have access to treatment with uridine.

One of the primary objectives of the trial is to document the continued clinical benefit of exogenous uridine when patients are switched from oral administration of uridine to oral administration of uridine triacetate. As agreed upon with the Agency, the primary efficacy endpoint will be change from baseline in one of the following hematologic parameters: hemoglobin, platelet count, neutrophil count; each patient will have his or her own individual endpoint. The trial will also evaluate pharmacokinetic (PK) and biochemical pharmacodynamic (PD) endpoints, including uridine (PK endpoint), and orotic acid and orotidine (PD endpoints).

### **4. Brief description of available therapies (if any)**

As noted earlier, there are no approved therapies for HOA.

### **5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation**

There are no drugs being studied for treatment of HOA that have received breakthrough therapy designation.

### **6. Description of preliminary clinical evidence**

Uridine has been shown to be effective for improving neutropenia, megaloblastic anemia, and growth in patients with HOA as noted below in the efficacy data section. The sponsor has conducted PK studies which have established that oral uridine triacetate is converted to uridine and results in exposures 4 times greater than oral uridine.

## **Overview of Clinical Development Program**

The sponsor has completed clinical pharmacology and pharmacokinetic studies of uridine triacetate in healthy volunteers and in pediatric and adult patients for other indications (mitochondrial and neurometabolic disorders, diabetic neuropathy, 5-fluorouracil toxicity and overdose). No new clinical pharmacology or pharmacokinetic studies are planned.

### Efficacy Data

As stated earlier, data on the efficacy of treatment with uridine in HOA patients consists of published case reports of patients with a confirmed diagnosis of HOA (n=14). In addition, data are available for two patients currently being treated with uridine under an individual patient IND and an emergency IND (see Table 1). Both patients have experienced improvements in hematologic values (although values have not normalized) and growth. Urine orotic acid levels have normalized in both patients.

**Table 1: Clinical Summaries for Patients with HOA Currently Being Treated with Uridine.**

Pt ID	Age/Sex*	Baseline Clinical Features	Uridine Dose (mg/kg/day)	Change in Hematologic Values	Change in Urine Orotic Acid Levels-	Clinical Update
(b) (4)	22 mos/M	Megaloblastic anemia, orotic aciduria, failure to thrive (FTT), ? developmental delay	150	Baseline MCV- not available; 5/13- MCV was 105 (normal range 75-88 fl)	Baseline level-not available; 5/13: level was 1.4 (reported as within normal range)	5/13: Child now (b) (4) years old, still has abnormal MCV. FTT resolved, normal development.
(b) (4)	18 mos/M	FTT, recurrent otitis media, severe neutropenia, developmental delay	150	Baseline neutrophil count not available, 7/13-neutrophil count was 390-590	Level prior to treatment was 21.7; level on treatment ranges from 1-4 nmol/mol/Cr (normal range <2.8)	7/13: Child now (b) (4) years old, still has neutropenia. No recurrent infections. Developmental delay appears to be unrelated to HOA.

\*Age at start of treatment with uridine

### Safety Data

The sponsor noted there have been no reports to date of dose-limiting toxicity, serious adverse events (SAEs) or significant adverse events (AEs) attributed to uridine triacetate. AEs reported as possibly related to uridine triacetate in clinical trials included gastrointestinal discomfort, diarrhea, flatulence, nausea, vomiting, and headache; most events were reported as mild to moderate in severity.

### 7. Division's recommendation and rationale

- Recommendation: Approval of breakthrough therapy designation request
- Rationale: There are published data of the effectiveness of exogenous uridine in treating significant clinical features of HOA, including megaloblastic anemia, neutropenia, and growth retardation.

### 8. Division's next steps and sponsor's plan for future development

The Division held a pre-IND meeting with the sponsor on August 7, 2013 to discuss the clinical development plan for uridine triacetate. On November 22, 2013, the sponsor submitted a protocol for

the proposed pivotal trial, which included clinical safety data. The Division determined that there were adequate clinical data to support chronic dosing and deemed the trial to be safe to proceed pending revisions agreed upon by the sponsor. The Division agrees with the sponsor's plan to request an End-of-Phase 2 meeting following the completion of the first 6 weeks of the pivotal trial. Uridine triacetate was granted orphan drug product designation for HOA on August 9, 2013 and granted a rare pediatric disease designation under the Pediatric Disease Priority Review Voucher Program on August 9, 2013.

#### **9. References (if any)**

Webster DR et al., *Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism*, in *The Metabolic and Molecular Bases of Inherited Disease* (Vol II), C.R. Scriver, et al., Editors. 2001, McGraw-Hill.

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/s/  
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SANDRA J BENTON  
05/23/2014

LARA DIMICK-SANTOS  
05/23/2014

PATRICIA KEEGAN  
05/29/2014



IND 118931

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Wellstat Therapeutics Corporation  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate.

We also refer to your March 6, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that uridine triacetate for uridine replacement therapy [REDACTED] <sup>(b) (4)</sup> with hereditary orotic aciduria (HOA) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of uridine triacetate for HOA to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*<sup>2</sup> for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

If you have any questions, contact Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Andrew E. Mulberg, M.D., FAAP, CPI  
Deputy Director  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**Attachments:**

Attachment 1: Breakthrough Designated Product, Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor, Potential Topics for Discussion

**Attachment 1: Breakthrough Designated Product**  
**Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor**  
**Potential Topics for Discussion**

**General/Regulatory:**

- Planned target date for NDA/BLA submission, including plans for rolling review
- Other indications in development
- Expanded access plans, including intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive studies or trials, including those to be conducted as postmarketing commitments/postmarketing requirements (PMC/PMRs)
- Rationale for proposed flexibility in study and trial design
- Plans for submission of a proprietary name request
- If a drug/device combination product, device development information and plan
- In-vitro diagnostic development plan with the Center for Device and Radiologic Health (CDRH)
- Target product profile for proposed indication
- Gantt chart of development timeline, including information on all areas noted below
- Proposed communication plan for periodic development program updates to the FDA, including timelines and content

**Clinical Activity and Data Analysis:**

- Existing and planned clinical sites and accrual data
- Efficacy
  - Status of all clinical studies and topline summary results
  - Preliminary evidence of proof of concept
  - Planned or completed clinical trials intended to support efficacy, including:
    - Overall study design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials, Type I error control, and expected initiation/completion dates
    - Validity of the outcomes and endpoints. If using drug development tools, such as a patient reported outcomes or biomarkers, plans for the development and validation of the instrument, if appropriate.
- Safety
  - Potential safety issues from nonclinical studies/early clinical trials
  - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, and immunogenicity safety profile
  - Clinical trials safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for post-market drug safety and surveillance (pharmacovigilance)
    - Proposed size of safety population
    - Plan or need for long-term safety studies

- Pre-approval
  - Post-approval
- Plans to mitigate/minimize risk, proposed Risk Evaluation and Mitigation Strategy (REMS)
- Specific Populations
  - Dose, study design, efficacy endpoints, size and composition of population, additional safety trials, for populations such as:
    - Geriatrics
    - Pediatrics
    - Hepatically/Renally Impaired
  - Proposed pediatric development plan with outlines/synopses of additional studies.

### **Clinical Pharmacology and Pharmacokinetics:**

- Justification for all dose selections, including number of doses, dose intervals, etc
- Clinical pharmacology, pharmacodynamics, and pharmacokinetics studies: completed, ongoing, planned, and requests for deferral, such as:
- Immunogenicity
- Dosing
  - Single ascending dose
  - Multiple ascending dose
  - Dose response study
- Food-effect
- Drug-drug interactions (DDI)
- Thorough QT/QTc
- Organ impairment
- Pharmacogenomics
- Plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
- Plans for conducting population pharmacokinetics, exposure-response modeling/simulation analyses
- Plans to describe dose modifications in labeling based on DDI, age, organ impairment, etc.
- 

### **Nonclinical Pharmacology, Pharmacokinetics, and Toxicology**

- Nonclinical studies completed, ongoing, and planned, including, the number and sex of animals per dose, doses, route of administration, toxicities, duration of study and study results. For studies planned timelines for initiation and submission of study reports. Examples of such studies include:
  - Subacute and chronic toxicology
  - Gene toxicology
  - Reproductive toxicology
  - Carcinogenicity studies
  - Animal models of disease and PK parameters associated with efficacy

- Evidence of mechanism of action
- Safety pharmacology, where appropriate
- Disease specific animal models

**Chemistry, Manufacturing, and Controls:**

- Drug product:
  - Dosage form
  - Formulation description
  - Administration instructions, delivery systems (e.g. vials, pre-filled syringes, etc.) proposed draft packaging, and disposal instructions
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life and required stability studies
- Drug substance:
  - Characterization
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
  - Manufacturing process, in process controls, scale-up plans
  - Comparison of proposed commercial manufacturing processes to clinical manufacturing processes
  - Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
  - Current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
  - Current release and stability testing site(s) and proposed commercial testing site(s), if different
  - Anticipated market demand at launch
- Proposed validation approaches:
  - Drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - Analytical methods

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ANDREW E MULBERG  
04/30/2014



IND 118931

**ACKNOWLEDGE -  
BREAKTHROUGH THERAPY REQUEST**

Wellstat Therapeutics Corporation  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate.

We acknowledge receipt on March 6, 2014, of your March 6, 2014, request for Breakthrough Therapy designation submitted under section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) for uridine replacement therapy in pediatric patients with hereditary orotic aciduria (HOA). We are reviewing your request and will respond to you within 60 days of the receipt date. We will contact you if we have any questions or require additional information.

If you have any questions, call me at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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JESSICA M BENJAMIN  
03/13/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 208169

**LATE-CYCLE MEETING MINUTES**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 8, 2015.

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

If you have any questions, call Jessica Benjamin, Regulatory Project Manager at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Joette M. Meyer, PharmD  
Associate Director for Labeling  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** July 8, 2015 from 10:00 AM to 11:00 AM  
**Meeting Location:** teleconference

**Application Number:** NDA 208169  
**Product Name:** Xuriden (uridine triacetate) oral granules  
**Applicant Name:** Wellstat Therapeutics Corporation

**Meeting Chair:** Joette M. Meyer  
**Meeting Recorder:** Jessica M. Benjamin

**FDA ATTENDEES**

Office of Drug Evaluation III

Julie Beitz, MD, Director  
Amy Egan, MD, Deputy Director  
Maria Walsh, Associate Director for Regulatory Affairs  
Richard Ishihara, Regulatory Scientist

Office of Drug Evaluation III/Division of Gastroenterology and Inborn Errors Products

Dragos Roman, MD, Acting Deputy Director  
Joette Meyer, PharmD, Cross Discipline Team Leader  
Anil Rajpal, MD, Clinical Team Leader  
Carla Epps, MD, Clinical Reviewer  
Sushanta Chakder, PhD, Nonclinical Team Leader  
Brian Strongin, RPh, MBA, Chief Project Management Staff  
Jessica Benjamin, MPH, Senior Regulatory Project Manager, DGIEP

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Sue Chih Lee, PhD, Clinical Pharmacology Team Leader  
Sandhya Apparaju, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Hamid Shafiei, PhD, CMC Application Team Leader  
Salaheldin Hamed, Biopharmaceutics Reviewer  
Sandra Suarez, PhD, Biopharmaceutics Reviewer  
Arzu Selen, PhD, Associate Director, Scientific Development, OTR

Office of Biostatistics/Division of Biostatistics III

Min Min, PhD, Biostatistics Reviewer  
Yeh-Fong Chen, PhD, Biostatistics Team Leader

Office of Surveillance and Epidemiology

Aleksander Winiarski, Regulatory Project Manager

Kimberly Swank, PhD, Pharmacist, Division of Pharmacovigilance I

Sherly Abraham, Safety Evaluator, Division of Medical Error Prevention and Analysis

Office of Medical Policy/Division of Medical Policy Programs

Shawna Hutchins, Patient Labeling Reviewer

Office of Drug Evaluation IV/ Division of Pediatric and Maternal Health

Carol Kasten, MD, Clinical Reviewer

Tamara Johnson, MD, Acting Clinical Team Leader

Rare Disease Program

Jonathan Goldsmith, Associate Director

**EASTERN RESEARCH GROUP ATTENDEES**

Marc Goldstein, Independent Assessor

**APPLICANT ATTENDEES**

Michael Bamat, PhD, VP Research and Development

Joan Helton, Manager Regulatory Affairs and Clinical Quality Assurance

Jeffrey Miller, PhD, Director Analytical R&D and Manufacturing

Rita O'Neil, PhD, Senior Director, Regulatory Project Manager

Julie Vanas, Director, Clinical Projects

Reid von Borstel, PhD, VP Discovery Research

Nadine Wohlstadter, President

**1.0 BACKGROUND**

NDA 208169 was submitted on September 8, 2015 for Xuriden (uridine triacetate) oral granules.

Proposed indication(s): treatment of hereditary orotic aciduria (HOA)

PDUFA goal date: September 8, 2015

FDA issued a Background Package in preparation for this meeting on June 26, 2015.

**2.0 DISCUSSION**

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

**Discussion:**

***No further discussion.***

2. Discussion of Minor Review Issues

- Sponsor's plans for commercialization of the 2 gram, (b) (4) packets.
- FDA recommends "pyrimidine analog" as the Established Pharmacologic Class (EPC) in the Indications statement in the Highlights section of the PI.
- Preparation in Milk or Infant Formula



**Discussion:**

*Wellstat confirmed they plan to commercialize only the 2 gram packets (b) (4) packets for the HOA indication, given the doses required to treat these patients (b) (4)*

*Wellstat proposed that the EPC text phrase be clarified as follows: "Xuriden is a pyrimidine analog for uridine replacement". FDA agrees with this change.*

*Wellstat provided preliminary responses and clarifications regarding the preparation of Xuriden in milk or infant formula (see submission dated July 14, 2015). The FDA is still discussing the final mixing instructions for the Dosage and Administration section of the Prescribing Information and the patient Instructions for Use.*

*FDA requested samples of Xuriden packets and oral syringes to perform their own tests.*

3. Information Requests – 5 minutes

Carton and Container Labels: Information Requests issued on June 15 and 17, 2015.

**Discussion:**

*The revised carton and container labels for the 2 gram packets were submitted on June 24, 2015 and are acceptable.*

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

**Discussion:**

*FDA stated they are no longer requiring a Segment III pre- and postnatal development study with uridine triacetate in rats.*

*Regarding the biopharmaceutics Post-Marketing Commitment, the FDA clarified that the commercial batches of Xuriden can be released using the existing dissolution method as long as the batch is retested using the new method when available. Wellstat plans to submit 6-month stability data for the 2 gram packets along with the final report from the Comparability Study of 2 Gram and (b) (4) Uridine Triacetate Oral Granules Packet no later than July 17, 2015. (b) (4)*

*Regarding the clinical Post-Marketing Commitment, Wellstat agreed to obtain the requested data for the 4 currently treated patients. Wellstat stated that obtaining data on any new patients could be difficult and would depend on many factors. FDA indicated they would like to see the clinical sites collect data (including dose adjustments) from existing and future patients since this is an extremely small patient population.*

5. Review Plans – 5 minutes

Anticipated early action: early August 2015

**Discussion:**

*No further discussion.*

6. Wrap-up and Action Items – 5 minutes

**Discussion:**

*Wellstat will send 2 gram packets of Xuriden and syringes to the attention of Jessica Benjamin.*

*Wellstat will submit milestone dates for both the biopharmaceutics and clinical Post-Marketing Commitments.*

*The 6-month stability data from the 2 gram packet manufacturing and the final comparability report will be provided to FDA by July 17, 2015.*

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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JOETTE M MEYER  
08/10/2015



NDA 208169

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Wellstat Therapeutics Corporation  
Attention: Michael K. Bamat, Ph.D.  
Vice President, Research and Development  
930 Clopper Road  
Gaithersburg, MD 20878

Dear Mr. Bamat:

Please refer to your New Drug Application (NDA) dated and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xuriden (uridine triacetate) oral granules.

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 8, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, MD  
Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** July 8, 2015 from 10:00 AM to 11:00 AM EDT  
**Meeting Location:** Teleconference

**Application Number:** NDA 208169  
**Product Name:** Xuriden (uridine triacetate) oral granules  
**Indication:** Treatment of hereditary orotic aciduria (HOA)  
**Sponsor/Applicant Name:** Wellstat Therapeutics Corporation

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

There are no substantive review issues at this time.

### ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

## REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

### Potential Post-Marketing Commitments/Requirements (PMRs/PMCs)

#### Post-Marketing Requirements (PMRs)

At this time there are no PMRs.

*Nonclinical:* We are no longer requiring a Segment III pre- and postnatal development study with uridine triacetate in rats.

#### Post-Marketing Commitments (PMCs)

*Biopharmaceutics:* Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches.

Please provide dates for the following milestones: final protocol submission, study completion and final report submission.

*Clinical:* Continue to evaluate the long-term efficacy and safety of XURIDEN in patients currently enrolled in Protocol 401-13-001 every 6 months for a total duration of 2 years in an extension study. The extension study should collect data on growth, hematologic indices, and urine biomarkers (orotic acid and orotidine). Growth data should include height, weight, height velocity and weight velocity. Ensure that the growth data are submitted also as z-scores. Provide information on any dose adjustments made during the extension study, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments. [REDACTED] (b) (4)

[REDACTED] Please provide dates for study completion and final report submission.

Note that the above request for additional data supersedes and replaces the Information Request for additional efficacy information issued on May 22, 2015.

If any new patient with HOA is started on treatment with Xuriden while Study 001 is still ongoing, we would like to discuss with you the possibility of collecting data on this patient(s) as well.

## LCM AGENDA

### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 10 minutes

- Sponsor's plans for commercialization of the 2 gram, (b) (4), packets.
- FDA recommends "pyrimidine analog" as the Established Pharmacologic Class (EPC) in the Indications statement in the Highlights section of the PI.
- Preparation in Milk or Infant Formula



3. Information Requests – 5 minutes

Carton and Container Labels: Information Requests issued on June 15 and 17, 2015.

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

5. Review Plans – 5 minutes

Anticipated early action: early August 2015

6. Wrap-up and Action Items – 5 minutes

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/s/  
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DRAGOS G ROMAN

06/26/2015

Signing on behalf of Dr. Griebel