

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208169Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 208169
Product Name: Xuriden(uridine triacetate)

PMR/PMC Description: Continue to evaluate the long-term efficacy and safety of XURIDEN (uridine triacetate) in patients currently enrolled in Protocol 401-13-001 every 6 months for a total duration of 2 years in an extension trial. The extension trial 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 trial, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	n/a
	Study/Trial Completion:	June 2016
	Final Report Submission:	November 2016
	(b) (4)	(b) (4)

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

XURIDEN (uridine triacetate) is being developed for the treatment of patients with hereditary orotic aciduria (HOA), a serious and potentially life-threatening condition with clinical features that include megaloblastic anemia, neutropenia, growth and developmental delays. Currently, there are no approved therapies for this condition. However, published case reports document clinical improvement in patients treated empirically with adequate doses of exogenous sources of uridine.

The safety and short-term efficacy of XURIDEN have been established. However, data are needed on the long-term efficacy of the product.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the trial is to evaluate the long-term efficacy of XURIDEN (linear growth and hematological indices) in treatment-naïve patients and patients who were transitioned from other exogenous sources of uridine.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This will be an open-label extension study. Efficacy data will be collected in patients currently enrolled in the extension phase of Protocol 401-13-001.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208169
Product Name: Xuriden (Uridine Triacetate Immediate Release) granules

PMR/PMC Description: 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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/16
	Study/Trial Completion:	02/16
	Final Report Submission:	03/16
	Other:	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

During the review cycle it was determined that the dissolution method proposed by the Applicant did not reflect the true in vitro release profile of the proposed product. Furthermore, it was determined that the dissolution method acceptance criteria were excessively permissive. A PMC is necessary to allow for the development and validation of an appropriate dissolution method and acceptance criteria, which would require time beyond the remaining review clock time. It is noted that the current product's control strategy (e.g., operating closely to the normal operating ranges for the clinical trial batch) ensures the quality of the drug product.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The currently proposed dissolution method shows a

(b) (4)

. The goals of the in vitro dissolution study under the PMC are: 1) to develop and validate a discriminating dissolution method, which follows a canonical behavior so that it can serve its purpose of being a quality control test, and 2) to set an adequate acceptance for the drug product using the dissolution profile data generated with the new dissolution method from at least 5 commercial batches.

(b) (4)

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
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- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., development of a discriminating dissolution method)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

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- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(Signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA M BENJAMIN
08/25/2015

JOETTE M MEYER
08/25/2015

505(b)(2) ASSESSMENT

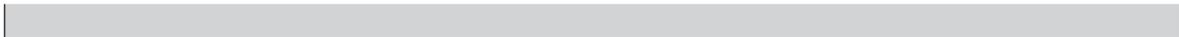
Application Information		
NDA # 208169	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Xuriden Established/Proper Name: uridine triacetate Dosage Form: granules Strengths: 2g, (b) (4)		
Applicant: Wellstat Therapeutics Corporation		
Date of Receipt: January 8, 2015		
PDUFA Goal Date: September 8, 2015		Action Goal Date (if different): August 6, 2015
RPM: Jessica Benjamin		
Proposed Indication(s): uridine replacement therapy (b) (4) with hereditary orotic aciduria		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
published literature (case reports)	Section 8- Data from published case reported were used to evaluate the long-term safety and efficacy of uridine replacement therapy in pediatric patients
published literature (case reports)	Section 14- Data from published case reports regarding hematologic and growth response to uridine replacement therapy were used to support efficacy

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant evaluated the PK profile of uridine and uridine triacetate in the 4 patients enrolled in the pivotal trial (Study 401.13.001). PK results demonstrated that a dose of uridine triacetate that is one-third of a dose of uridine (on a mg/kg/basis) provided an equivalent exposure. The applicant also conducted a comparative bioavailability study (Study 401.09.001-PK) in pediatric patients with another condition (mitochondrial disease) that revealed relative bioavailability information that was comparable to the information from the HOA patients.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA M BENJAMIN
08/25/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Amy M. Taylor, MD, MHS Medical Officer
Division Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD Team Leader
Division of Pediatric and Maternal Health

Lynne P. Yao, MD Acting Director
Division of Pediatric and Maternal Health

NDA Number: 208169

Sponsor: Wellstat Therapeutics

Drug: Xuriden (uridine triacetate)

Dosage form and route of administration: granules, oral

Proposed Indication: For the treatment of hereditary orotic aciduria

Consult request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests DPMH's input on labeling.

Background

The applicant's original NDA 208169 is currently under review by DGIEP for the treatment of hereditary orotic aciduria. DGIEP requests DPMH's assistance with the labeling. The sponsor is relying on case reports from the literature and an open-label study of 4 patients aged (b) (4)

Hereditary orotic aciduria (HOA) is a serious condition that is characterized by developmental delays, anemia and/or other blood cell disorders, and may be fatal if untreated. Less than 20 cases have been identified worldwide. There is currently no approved product to treat this indication. This product has received breakthrough therapy designation, rare pediatric disease designation, and orphan designation.

Prior to Wellstat's development of uridine triacetate, uridine for HOA patients had been available under expanded access protocols from Repligen Corporation under IND (b) (4) for the treatment of bipolar depression. Repligen decided to discontinue manufacturing uridine in January, 2013, and alternate sources of the drug for HOA patients were sought. The five patients who were being treated received uridine through emergency or individual patient INDs.

In March, 2013, the agency met with Wellstat, a manufacturer of uridine acetate (a prodrug of uridine), to discuss development of uridine triacetate as uridine replacement therapy in patients with HOA. In August, 2013, the agency reached agreement with the sponsor that a single adequate and well-controlled trial could serve as the basis for approval and that study endpoints for the trial could be individualized by patient. From November, 2013 to February, 2014, the sponsor discussed a protocol for an open-label study of uridine triacetate in pediatric patients with HOA with the agency. During a pre-NDA meeting with the sponsor in December, 2014, the agency requested that the sponsor submit additional clinical data to support the application, including historical data and data from the extension treatment phase for patients enrolled in the registration trial, and a summary of published case studies on HOA patients treated with uridine.

Current labeling under development by DGIEP (as of 6/4/2015) – selected sections



(b) (4)

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/s/

AMY M TAYLOR
07/21/2015

HARI C SACHS
07/21/2015
I agree with these labeling recommendations.

LYNNE P YAO
07/23/2015

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 7, 2015
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 208169
Product Name and Strength:	Xuriden (uridine triacetate) Oral Granules 2 gram (b) (4) sachets
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Wellstat Therapeutics Corporation
Submission Date:	June 25, 2015
OSE RCM #:	2015-72-1
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Kendra Worthy, Pharm.D.

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised container label (Appendix A) to determine if it is acceptable

from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container label is acceptable from a medication error perspective.

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¹Abraham, A. Label and Labeling Review for Xuriden (NDA 208169). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 06 08. 32 p. OSE RCM No.: 2015-72.

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/s/

SHERLY ABRAHAM
07/07/2015

KENDRA C WORTHY
07/07/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 6, 2015

To: Jessica Benjamin, MPH, Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Pharm.D., RAC, Team Leader, Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208169 XURIDEN (uridine triacetate) oral granules

Reference is made to DGIEP's consult request dated January 20, 2015, requesting review of the proposed Package Insert (PI) and Carton/Container Labeling for XURIDEN (uridine triacetate) oral granules (Xuriden).

OPDP has reviewed the proposed PI entitled, "draft PI sponsor edits.doc" that was sent via email from DGIEP to OPDP on June 22, 2015. OPDP's comments on the proposed PI are provided directly below.

OPDP has also reviewed and has no comments on the following proposed carton/container labels submitted by the sponsor on June 25, 2015 (attached below) and available in the EDR, sequence 0015:

- 2g-draft-carton-container-labels.pdf
-  (b) (4)

Thank you for your consult. If you have any questions please contact Kathleen Klemm at Kathleen.klemm@fda.hhs.gov or 301-796-3946.

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/s/

KATHLEEN KLEMM
07/06/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 30, 2015

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): XURIDEN (uriden triacetate)

Dosage Form and Route: Oral granules, for oral use

Application Type/Number: NDA 208-169

Applicant: Wellstat Therapeutics Corporation

1 INTRODUCTION

On January 08, 2015, Wellstat Therapeutics submitted for the Agency's review an original New Drug Application (NDA208-169) for XURIDEN (uriden triacetate) oral granules, a pyrimidine analog indicated for the treatment of hereditary orotic aciduria.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on January 20, 2015 for DMPP to review the Applicant's proposed Instructions for Use (IFU) for XURIDEN (uriden triacetate) oral granules.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on June 09, 2015.

2 MATERIAL REVIEWED

- Draft XURIDEN (uriden triacetate) IFU received on January 05, 2015, and received by DMPP on January 20, 2015.
- Draft XURIDEN Xuriden (uriden triacetate) Prescribing Information (PI) received on January 05, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on June 24, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 11.

In our review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- The DMPP review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
06/30/2015

MARCIA B WILLIAMS
06/30/2015

LASHAWN M GRIFFITHS
06/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: June 8, 2015

Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)

Application Type and Number: NDA 208169

Product Name and Strength: Xuriden (uridine triacetate) Oral Granules
2 gram (b) (4) sachets

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Wellstat Therapeutics Corporation

Submission Date: January 8, 2015

OSE RCM #: 2015-72

DMEPA Primary Reviewer: Sherly Abraham, R.Ph.

DMEPA Team Leader: Kendra Worthy, Pharm.D.

REASON FOR REVIEW

This review is in response to a request by DGIEP to review proposed prescribing information and carton labels for any areas that may cause medication errors.

MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant submitted a 505 b(1) new molecular entity NDA to obtain marketing approval of Xuriden for uridine replacement therapy in pediatric patients with hereditary orotic aciduria (HOA). We reviewed the proposed prescribing information and container and sachet labels. We defer to the Division for the appropriateness of the pediatric dosing information in the label. DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. The recommendations to the division and Wellstat Therapeutics are listed below in 4.1 and 4.2.

4.0 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATION TO THE DIVISION:

Prescribing Information:

1. The dose in the (b) (4) table in Dosing and Administration contains a trailing zero. Consider removing the trailing zero (e.g. 3 g) to avoid a ten-fold misinterpretation.

4.2 RECOMMENDATION TO WELLSTAT THERAPEUTICS CORPORATION

Carton and Container Labels:

1. 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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xuriden that Wellstat Therapeutics Corporation submitted on January 8, 2015.

Table 2. Relevant Product Information for Xuriden	
Initial Approval Date	N/A
Active Ingredient	Uridine Triacetate
Indication	Uridine replacement therapy (b) (4) with hereditary orotic aciduria
Route of Administration	Oral
Dosage Form	Oral granules
Strength	2 grams (b) (4)
Dose and Frequency	60 mg/kg/day to (b) (4) mg/kg/day.
How Supplied	30 x 2 gram sachets in a carton (b) (4)
Storage	Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F).
Container and Closure System:	Sachets supplied within a carton

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/s/

SHERLY ABRAHAM
06/08/2015

KENDRA C WORTHY
06/09/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: May 7, 2015 **Consult Received:** January 23, 2015

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health,
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Acting Team Leader
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Acting Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Gastroenterology and Inborn Errors Products

Drug: Xuriden (Uridine Triacetate) oral granules, NDA 208-169,
IND (b) (4)

Indication: Xuriden is a uridine replacement product indicated for the
treatment of hereditary orotic aciduria

Subject: Labeling for a New Molecular Entity

Applicant: Wellstat Therapeutics Corporation

Consult Request: “Review pregnancy and nursing mothers labeling”

INTRODUCTION

Wellstat Therapeutics submitted this New Molecular Entity (NME) original application for Xuriden® or uridine triacetate, NDA 208169, on January 8, 2015, with the proposed indication for the treatment of hereditary orotic aciduria (HOA). The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for Pregnancy (Section 8.1) and Lactation (Section 8.2) for Xuriden.

BACKGROUND

Brief Regulatory History

Prior to Wellstat's development of uridine triacetate, a form of uridine for HOA patients had been available from Repligen Corporation under their IND. Repligen decided to discontinue manufacturing uridine in January, 2013, and alternate sources of the drug were sought. A pre-IND meeting with Wellstat was held on August 7, 2013. At that time DGIEP informed the sponsor that embryo-fetal studies in only one species would be required at the time the application was submitted; however, a fertility and early embryonic development study, a pre- and postnatal development study and an embryo-fetal study in a second species would still be required prior to approval of the application.¹ On August 9, 2013, uridine triacetate for the treatment of orotic aciduria received an orphan drug product designation as well as designation under the pediatric rare disease priority review voucher program. On April 30, 2014, breakthrough therapy designation was also granted.

Hereditary Orotic Aciduria

HOA is an autosomal recessive disorder caused by mutations in uridine monophosphate synthase (UMPS)² and was first described in 1959 as a refractory megaloblastic anemia associated with excretion of orotic acid.³ Patients with HOA are unable to convert orotic acid to uridine, resulting in a block in pyrimidine synthesis and inducing urinary excretion of very large quantities of orotic acid. The disease is rare with only 15 cases of HOA identified as of 2001 in one report;⁴ however, others have speculated that the disease may be more frequent than this estimate due to inadequate screening.⁵ In addition to a megaloblastic anemia and urinary excretion of orotic acid, other features of HOA include failure to thrive, developmental delay, and T-cell dysfunction; however, not all patients manifest these signs. Congenital malformations, particularly cardiovascular have been reported in four children with HOA. Specifically, one child has been reported

¹ Memorandum of Meeting Minutes – Pre-IND, Primary Author Jessica Benjamin, MPH, RPM. Dated August 14, 2014. Application Number: PIND 118931, Dated DARRTS ID: 3357093.

² Sumi S, Suchi M, *et al.* Pyrimidine metabolism in hereditary orotic aciduria. *J Inher Metab Dis* 1997;20:104-105.

³ Huguley C, Bain J, *et al.* Refractory megaloblastic anemia associated with excretion of orotic acid. *Blood*. 1959 Jun;14(6):615-34.

⁴ OMIM Entry (#258900) Orotic Aciduria. <http://omim.org/entry/258900> . OMIM® and Online Mendelian Inheritance in Man. Copyright© 1966-2015 Johns Hopkins University. Accessed April 13, 2015. Last revision: 09/15/2011.

⁵ Balasubramaniam S, Duley J, Christodoulou J. Inborn errors of pyrimidine metabolism: clinical update and therapy. *J Inher Metab Dis* (2014) 37:687–698. DOI 10.1007/s10545-014-9742-3.

with one of each of the following structural abnormalities: a complex cyanotic cardiac malformation, atrial septal defect, ventricular septal defect and a patent ductus arteriosus.⁶ Some patients have developed a urinary obstruction attributed to orotic acid crystalluria.⁷ Treatment with uridine has appears to improve the megaloblastic anemia in all HOA patients although these studies were without placebo controls or investigator blinding. Other treatment benefits may include a reduction in urinary and serum concentrations of orotic acid.^{8,9}

Clinical Pharmacology

Uridine has poor bioavailability with less than 10% of the administered dose being absorbed from the gut. Uridine triacetate (2', 3', 5'-tri-O-acetyluridine) is an orally bioavailable prodrug of uridine. (b) (4)

The three acetate moieties attached to the uridine are removed in the liver and uridine is absorbed into the systemic circulation, increasing plasma uridine concentrations without detectable levels of uridine triacetate in blood. Xuriden is supplied as granules in (b) (4) sachets to be sprinkled over easily swallowed solids, such as applesauce or yogurt, immediately prior to administration. The applicant provides detailed dosing information based on a sliding dosage scale from 60 to (b) (4) mg/kg/day.¹⁰

DATABASE AND LITERATURE REVIEW OF AVAILABLE PREGNANCY AND LACTATION INFORMATION

Micromedex reports that uridine triacetate has been available via an IND for emergency use to treat 5-fluorouracil toxicity caused by a dosing error or as a rescue agent for patients with dihydropyrimidine dehydrogenase deficiency.¹¹ There was no review of uridine triacetate in either Reprotox¹² or TERIS;¹³ additionally, there was no review of the drug in LACTMED®.¹⁴

Human Data

No English language publications on uridine triacetate and pregnancy or pregnant women were found in PubMed; however, the Online Mendelian and Molecular Basis of Inherited

⁶ See OMMBID DOI Reference Number: <http://dx.doi.org/10.1036/ommbid.141>.

⁷ See OMIM Entry (#258900).

⁸ See Sumi *et al.*

⁹ See OMIM.

¹⁰ Refer to Clinical Pharmacology review by Sandyha Apparaju, Ph.D.

¹¹ Micromedex (<http://www.micromedexsolutions.com>) Last revision December 22, 2014. Accessed April 13, 2015.

¹² Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed XYZ, 2014.

¹³ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.

http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/ Accessed 3/21/2014

¹⁴ LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last Revision Date: 20130907

Disease (OMMBID) provides a summary of the pregnancy outcomes of two women with HOA treated with uridine, however, the form is not clear.¹⁵ The description of the clinical pharmacology of uridine triacetate suggests that treatment with it will likely have the same pharmacologic effect on patients as treatment with uridine. With this caveat, the OMMBID data on two women with HOA who have successfully delivered a total of six infants is described below.

Patient DB

- Four pregnancies and delivery of three female and one male infant all of whom were normal at birth.
- Preconception uridine dose = 1.5 g total daily dose (tdd)
- Pregnancy uridine dose increased to a maximum of 2.5 grams tdd by 7 months gestation.

Patient TH

- Two pregnancies with normal infants at delivery.
- Preconception uridine dose first pregnancy = 1.5 g tdd increased to 24 g at term
- Preconception uridine dose for second pregnancy = 4 g tdd increased to 28 g at term
- Pregnancy uridine dose increases reportedly based on hemoglobin status

While these data provide some information on the use of uridine in HOA affected pregnant women, it is primarily anecdotal and lacks quantification of hemoglobin and urinary or serum orotic acid concentrations. Moreover, there is no information on the pharmacokinetic/pharmacodynamic profile of the drug in pregnant women. Therefore, strict guidelines for dosage modifications during pregnancy cannot be developed. Concerns regarding the possible teratogenic risk of uridine triacetate administration during pregnancy should be balanced with the known risk of serious anemia to a pregnant woman and her fetus.

Nonclinical Data

As previously agreed by the Division, nonclinical embryo-fetal studies were completed in only one species (i.e. rats). In that study, no teratogenicity or other toxicity was found in pregnant rats orally administered uridine triacetate at doses which were $\frac{(b)}{(4)}$ times the maximum recommended human dose (MRHD) of $\frac{(b)}{(4)}$ mg/kg/day based on body surface area. Fertility studies in both female and male rats administered uridine triacetate, also at $\frac{(b)}{(4)}$ times the MRHD demonstrated no effect on fertility or general reproductive performance in either sex.

DISCUSSION

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling”¹⁶ also known

¹⁵ See OMMBID

¹⁶ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule¹⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

Labeling for Pregnancy and Lactation

There are only anecdotal human data on the use of *uridine* (not uridine triacetate) in pregnant women with HOA on which to base an estimation of uridine triacetate's teratogenic risk. No teratogenic effect has been reported among the six infants born to HOA affected women treated with uridine during pregnancy. No teratogenesis was observed in rats exposed to uridine triacetate at doses approximately one-third higher than the MRHD. With the caveat that prenatal treatment with uridine is not identical to treatment with uridine triacetate, the use of uridine triacetate in pregnant women with HOA is likely to reduce the risk of serious anemia in pregnancy. This positive effect should be considered against the unknown risk of teratogenesis from uridine triacetate.

There are no data on the presence or absence of uridine triacetate in breast milk. The clinical pharmacology indicates that virtually all uridine triacetate is metabolized in the liver to uridine and it is only uridine which appears in the systemic circulation. If uridine is transferred to a treated mother's breast milk, only about 10% of the drug would be absorbed by the infant due to its low bioavailability. There are no data to demonstrate uridine triacetate poses a risk to the breastfeeding infant whereas there is evidence that the drug provides significant benefit to the mother.

CONCLUSIONS

- Nonclinical data and limited available clinical data do not demonstrate that uridine triacetate poses a teratogenic risk to a developing embryo or fetus.
- HOA-affected women who wish to breastfeed should consider the importance of the drug uridine triacetate to their health weighed against the unknown risk of the drug to their breastfed infant.

The DPMH-MHT attended meetings with DGIEP in March and April, 2015 and provided our labeling recommendations at the April 30, 2015 meeting with the Division.

LABELING RECOMMENDATIONS

The following are the DPMH-MHT recommendations for the proposed labeling for Xuriden. Language was provided in the following sections of the Xuriden labeling:

¹⁷*Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

XURIDEN™ (uridine triacetate) oral granules**FULL PRESCRIBING INFORMATION: CONTENTS*****8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy***Risk Summary*

There are no available data on XURIDEN use in pregnant women to inform a drug-associated risk. When administered orally to pregnant rats during the period of organogenesis, uridine triacetate at doses similar to the maximum recommended human dose (MRHD) of (b) (4) mg/kg/day was not teratogenic and did not produce adverse effects on embryo-fetal development [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

*Data*Animal Data

In an embryo-fetal development study, uridine triacetate was administered orally to pregnant rats during the period of organogenesis at doses up to 2000 mg/kg/day (about (b) (4) times the MRHD of (b) (4) mg/kg/day on a body surface area basis). There was no evidence of teratogenicity or harm to the fetus and no effect on maternal body weight and overall health.

8.2 Lactation*Risk Summary*

There are no data on the presence of uridine triacetate in human milk, the effect on the breastfed infant or the effect on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for XURIDEN and any potential adverse effects on the breastfed infant from XURIDEN or from the underlying maternal condition.

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/s/

CAROL H KASTEN
05/07/2015

LYNNE P YAO
05/08/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 8, 2014

TO: Jessica Benjamin, Regulatory Project Manager
Carla Epps, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 208169

APPLICANT: Wellstat Therapeutics Corporation
DRUG: Uridine triacetate
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Uridine replacement for treating (b) (4) with hereditary orotic aciduria.

CONSULTATION REQUEST DATE: January 16, 2015
 INSPECTION SUMMARY GOAL DATE: June 7, 2015
 DIVISION ACTION GOAL DATE: September 2, 2015
 PDUFA DATE: September 4, 2015

I. BACKGROUND:

Wellstat submitted this NDA for uridine triacetate with the indication of uridine replacement for treating (b) (4) with hereditary orotic aciduria. FDA granted uridine triacetate an orphan drug designation (ODE) to treat hereditary orotic aciduria on August 9, 2013. Hereditary orotic aciduria (HOA) is a rare condition characterized by the accumulation of orotic acid in the urine. Less than 20 cases of this rare congenital autosomal recessive disorder have been identified worldwide. There is currently no approved treatment for this disorder. Although patients are typically treated with oral uridine, this drug has low bioavailability, and it is not currently approved for marketing for any indication. Uridine triacetate, the subject of this application, is an acetylated pro-drug of uridine.

The review division requested inspection of both clinical sites that participated in the clinical trial submitted for licensure, Protocol 4 01.13.001 was entitled "Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria". The sponsor was also inspected because this product is a new molecular entity.

II. RESULTS (by Site):

Type of Inspected Entity, Name and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*
(b) (6)			VAI
(b) (6)			VAI
Sponsor: Wellstat Therapeutics Corporation 930 Clopper Rd Gaithersburg, MD 20878	Protocol 4 01.13.001	May 5 to 7, 2015	Preliminary NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1.

(b) (6)

- a. **What was inspected:** At this site, for Protocol 4 01.13.001, two subjects were screened, enrolled, and completed the study. The inspection included review of informed consent documents (ICDs), institutional review board (IRB) correspondence and approvals, source documents, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, and electronic case report forms (eCRFs).
- b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. All demographic data, height, weight, adverse events, protocol deviations, and other listings could be verified except that the listings for the plasma uridine had not been returned to (b) (6) so they could not be verified. The dosing times for Day 28 could not be confirmed because of discrepancies as described below and cited on the Form FDA 483. A Form FDA 483 was issued for inadequate and/or inaccurate records for the 2 instances noted below:
- i. For Subject (b) (6), there were two different documents that had two different times for dosing: 7:55am and 7:45am. The CI response notes that the test article was actually administered at 7:55am and recorded in the dosing log, but the parent incorrectly entered 7:45am in their own log after the fact. The line listing has 7:55am as the dosing time.
 - ii. For Subject (b) (6), there were no source documents to support a case report form change from 8:30am to 8:43am made to the dosing time for the Day 28 dose. The study nurse did not record the dosing time because there was no place to record this. The first entry for the time was based on the parent entry, but on further review, the decision was made to change the time to 8:43am based on the times when the PK samples were due per the Wellstat requisition form. The line listing has 8:43am as the dosing time.
- c. **Assessment of data integrity:** The violations cited above appear to be minor and isolated and do not impact data integrity. These were discussed with the review division. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. [REDACTED] (b) (6)
- a. **What was inspected:** At this site, for Protocol 4 01.13.001, two subjects [REDACTED] (b) (6) were screened, enrolled, and completed the study. Source documents and informed consent documents were reviewed. In addition, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, and eCRFs were reviewed.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. All demographic data, height, weight, adverse events, protocol deviations, and other listings could be verified except for that the listings for the plasma uridine; these had not been returned to [REDACTED] (b) (6) so they could not be verified.

No discrepancies were noted between the line listings and the source documents. A Form FDA 483 was issued for inadequate drug distribution records. Specifically records showed that 160 sachets of investigational product were dispensed to each subject between the August 6 and December 1, 2014 visits. Each subject should have used 117 sachets during this time. The accountability records show that 126 partially utilized packets were returned to the site for each subject. There was no documentation to account for the additional packets in accountability or subject records.

The clinical investigator (CI) acknowledged the observations and responded to the inspection findings in a written communication on March 10, 2015. The drug reconciliation was recounted by the pharmacy to cross-verify the drug administration diaries. The count was revised to 106. In addition, the numbers from the original drug accountability for the referenced period were incorrect because the remaining medication was not returned until the February 1, 2015 visit. All the sachets were combined, so the drug reconciliation was imprecise.

The violations noted are issues with drug accountability. According to the diaries kept by the parents, the subjects were compliant with dosing, and the findings are considered minor.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication

3. Wellstat Therapeutics Corporation 930 Clopper Rd, Gaithersburg, MD 20878

Note: Observations below for this sponsor inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** This inspection evaluated compliance with sponsor responsibilities for the protocol noted above including selection and oversight of clinical investigators, monitor, contract research organizations, financial disclosure, FDA Form 1572s, and quality assurance (QA). The inspection included review of general correspondence and study master files, site monitoring, and handling of adverse events and other sponsor/monitor related activities.
- b. **General Observations/Commentary:** The monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. Data receipt and handling and test article accountability were considered adequate.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Both investigator sites and the sponsor were inspected for this application. Data from all clinical sites appears reliable and the sponsor appears to have adequately fulfilled the sponsor responsibilities. Although violations were cited during inspection of the two clinical sites, these violations are considered minor. The inspection of the sponsor has a preliminary classification of NAI. An addendum will be written if the conclusions change upon review of the final EIR.

The study appears to have been conducted adequately, and the data generated by the study appear acceptable in support of the respective indication.

{See appended electronic signature page}

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CONCURRENCE:

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
05/08/2015

SUSAN D THOMPSON
05/08/2015

KASSA AYALEW
05/08/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: NDA208169

Application Type: New NDA

Name of Drug/Dosage Form: Xuriden (uridine triacetate) oral granules

Applicant: Wellstat Therapeutics

Receipt Date: January 8, 2015

Goal Date: September 8, 2015

1. Regulatory History and Applicant's Main Proposals

Breakthrough therapy designation was granted on April 30, 2014, and this product/indication received a rare pediatric disease designation on August 9, 2013. This product was also granted orphan designation on August 9, 2013, as well as designation of uridine triacetate as a Potential New Drug for a Rare Pediatric Disease for the treatment of hereditary orotic aciduria on August 9, 2013.

A Pre-NDA CMC only meeting was scheduled for December 11, 2014, to quality aspects for the NDA however, the sponsor found the FDA preliminary comments issued on December 5, 2014, sufficient and the meeting was cancelled. A Pre-NDA meeting with the Division of Gastroenterology and Inborn Errors Products was held on December 16, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Division is discussing internally whether this drug should have a Patient Package Insert (PPI) that includes information on how to prepare or administer the dose.
2. In Section 2.2 Administration: The sponsor should include step-by-step instructions on how to mix and administer the dose.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and

RPM PLR Format Review of the Prescribing Information

resubmit the PI in Word format by April 6, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

The Highlights are not currently in a two-column format. Please see appendix for correct format.

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

The Dosage and Administration and Drug Interactions Sections have statements that do not reference the corresponding section or subsection of the FPI

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

Selected Requirements of Prescribing Information

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Established Pharmacologic Class will be decided during the review.

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- NO** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs and possible benefit. Only known hazards and not theoretic possibilities should be included. A contraindication in patients with hypersensitivity reactions should be included only when there are demonstrated cases of hypersensitivity with the product or such reactions may be anticipated based on data from similar pharmacological class with similar chemical structures, or when cross-sensitivity with a class is a recognized phenomenon. The statement “none” should be listed here.

Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

If known, the sponsor should insert the name of manufacturer instead of “XXX.”

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Selected Requirements of Prescribing Information

Comment:

Revision date must be bolded and right justified.

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- NO** 25. The TOC should be in a two-column format.

Comment:

Please correct so that the TOC is in two column format.

- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

- NO** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

Section headings are not bolded.

- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

Numerical bullets should be indented.

- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

Subsection headings not consistent with FPI. The sponsor should revise the Table of Contents to be consistent with changes made to the Full Prescribing Information. For example, Section 12.4 is reserved for Microbiology, instead of the current section heading “Uridine and Uracil Levels in Plasma”.

- NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Selected Requirements of Prescribing Information

Comment:

When a subsection is optional in the full prescribing information and there is no supportive information than a Subsection, for example Section 8.7 Hepatic Impairment, can be omitted from the TOC.

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

Selected Requirements of Prescribing Information

Sponsor should not use numbering beyond the section and subsection level (e.g., 12.4.1 Hereditary Orotic Aciduria). Also, Section 12.4 is reserved for "Microbiology".

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]" or "[see *Warnings and Precautions (5.2)*]".

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION**". This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

- NO** 38. If no Contraindications are known, this section must state "None."

Comment:

A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs and possible benefit. Only known hazards and not theoretic possibilities should be included. A contraindication in patients with hypersensitivity reactions should be included only when there are demonstrated cases of hypersensitivity with the product or such reactions may be anticipated based on data from similar pharmacological class with similar chemical structures, or when cross-sensitivity with a class is a recognized phenomenon. If no Contraindications are known, this section must state "None."

ADVERSE REACTIONS Section in the FPI

Selected Requirements of Prescribing Information

- NO** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

The verbatim statement should start with the word “Because” not “Since.”

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/02/2015

RICHARD W ISHIHARA
04/13/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208169 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Xuriden Established/Proper Name: uridine triacetate Dosage Form: granule Strengths: 2 gram, (b) (4)		
Applicant: Wellstat Therapeutics Corporation Agent for Applicant (if applicable):		
Date of Application: 01/08/2015 Date of Receipt: 01/08/2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: 09/08/2015		Action Goal Date (if different): 09/08/2015
Filing Date: 03/09/2015		Date of Filing Meeting: 02/06/2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Uridine replacement therapy in pediatric patients with hereditary orotic aciduria.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none">• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)• The product is a Qualified Infectious Disease Product (QIDP)• A Tropical Disease Priority Review Voucher was submitted• A Pediatric Rare Disease Priority Review Voucher was submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 118931; IND (b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Not required Orphan Designation Exempt from User Fee <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested: 7 years (Orphan); 5 years (NCE)					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	01/21/2015
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels (Sachet) <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 12/16/2015 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 6, 2015

BACKGROUND:

IND 118931 for uridine triacetate became active on December 22, 2013 for the treatment of pediatric patients with hereditary orotic aciduria (HOA).

On August 9, 2013, uridine triacetate was granted orphan-drug designation for the treatment of HOA (#13-4010) and also received designation as a potential new drug for a rare pediatric disease for the same indication (#13-4010V). On April 30, 2014, breakthrough therapy designation was granted for uridine replacement in pediatric patients with HOA.

A Pre-NDA meeting held December 16, 2014 at which the discussion concluded that major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The sponsor agreed to submit a complete application and therefore, there were no agreements made for late submission of application components.

On December 24, 2014, FDA granted a waiver request for a thorough QT study because uridine triacetate is unlikely to prolong QT significantly in the targeted population.

NDA was submitted on January 8, 2015.

The sponsor requested Priority Review and also requested a priority review voucher to be awarded upon approval of uridine triacetate as uridine replacement therapy in pediatric patients with HOA.

Because the drug product for this indication has an orphan drug designation, NDA 208169 is exempt from the PREA requirements.

Under IND (b) (4), the sponsor is also developing uridine triacetate as “an antidote to treat patients at risk of excess 5-fluorouracil (5-FU) toxicity due to overdose or impaired elimination.” The drug product received orphan drug designation for this indication (#08-2738).

(b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Maureen Dewey	y
	CPMS/TL:	Richard Ishihara	y
Cross-Discipline Team Leader (CDTL)	Joette Meyer		y
Division Director/Deputy	Donna Griebel/Dragos Roman		y
Office Director/Deputy	Julie Beitz		n
Clinical	Reviewer:	Carla Epps	y
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sandhya Apparaju	y
	TL:	Sue Chih Lee	y
Biostatistics	Reviewer:	Min Min	y
	TL:	Yeh Fong Chen	y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sruthi King	y
	TL:	Sushanta Chakder	y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hamid Shafiei	n
	TL:	Marie Kowblansky	y
Biopharmaceutics	Reviewer	Tien Mien Chen Hamed Salaheldin Sandra Suarez	n
	TL:	Tapash Ghosh	n
Quality Microbiology	Reviewer:	Jean Tang	n
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Christina Cappaci-Daniels	n
	TL:		
OSE/DMEPA (proprietary name, carton/container labels) OPDP/DDMAC	Reviewer:	Sherly Abraham Adewale Adeleye	y
	TL:	Kendra Worthy	
OSE/DRISK (REMS) OSE – Palatability/Patient Compliance	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	y
	TL:	Susan Thompson	y
Department of Pediatric and Maternal Health	Reviewer:	Amy Taylor/Carol Kasten	y
	TL:	Hari Sachs/Tamara Johnson	y
Other reviewers/disciplines DMPP	Reviewer:	Shawna Hutchins	n
	TL:	Marcia Britt Williams	n
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p> <ol style="list-style-type: none"> 1. Please provide the latest available data for hematologic parameters and growth parameters from the extension phase of Study 401.13.001 as part of the 120 Day Safety Update. 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>2. Please provide a rationale for the twice daily dosing regimen.</p>	
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <p>The application did not raise significant safety or efficacy issues</p>
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments: Information Requests: 1. The food-effect PK study PN401.07.002 was conducted using a granule formulation that differs in composition from the proposed commercial formulation for pediatric HOA patients. Please comment on the applicability of the 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) (6) had lower systemic exposure of uridine after the starting dose of ~60 mg/kg/day, compared to patients in site (b) (6). Please comment on the likely causes for this lower exposure. Also address whether instructions for accurate weighing of the dose (granules) across the two study sites were standardized.</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: The sponsor has not submitted carcinogenicity studies with the NDA and is requesting a waiver from the requirement for a 2-year rodent carcinogenicity study as a condition of approval of uridine triacetate for the indication of treatment of HOA. Reviewer will consult with ECAC prior to making a decision regarding the sponsor's waiver request.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (protein/peptide products only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
New Molecular Entity (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If no, was a complete EA submitted?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If EA submitted, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Quality Microbiology</u>	<input checked="" type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments: Not a sterile product	
<u>Facility Inspection</u>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Establishment(s) ready for inspection? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Facility/Microbiology Review (BLAs only)</u>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)		<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<ul style="list-style-type: none"> If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 		
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
REGULATORY PROJECT MANAGEMENT		
Signatory Authority: Julie Beitz, M.D., Director, ODE III Date of Mid-Cycle Meeting: April 8, 2015 Mid Cycle Communication: April 22, 2015 21st Century Review Milestones (see attached) Late Cycle Meeting: July 8, 2015 Comments:		
REGULATORY CONCLUSIONS/DEFICIENCIES		
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:	
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.	

	<p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
03/06/2015

RICHARD W ISHIHARA
03/06/2015