CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208169Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Dragos Roman, MD, Acting Associate Division Director /Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
NDA/BLA # Supplement #	208169
Applicant Name	WellstatTherapeutics Corporation
Date of Submission	January 8, 2015
PDUFA Goal Date	September 8, 2015
Proprietary Name / Established (USAN) Name	Xuriden (uridine triacetate)
Dosage Forms / Strength	Oral granules, 2 grams and (b) (4) packets
Proposed Indication(s)	Treatment of hereditary orotic aciduria
Action/Recommended Action for NME:	Approval of the 2 gram presentation

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Carla Epps, MD/ Anil Rajpal, MD
Statistical Review	Min Min, Ph.D./Yeh-Fong Chen, Ph.D/Mike Welch, Ph.D.
Pharmacology Toxicology Review	Sruthi Tallapragada King, PhD/Sushanta Chakder, PhD
CMC Review/OBP Review	Xavier Ysern Ph.D./Hamid R. Shafiei Ph.D./Jean Tang Ph.D./Christina Capacci-Daniel Ph.D./Salaheldin S. Hamed Ph.D./Arzu Selen Ph.D./Michael E. Hadwiger Ph.D./Raanan A. Bloom Ph.D.
Microbiology Review	
Clinical Pharmacology Review	Sandhya Apparaju Ph.D./Sue Chih Lee Ph.D.
OPDP	Kathleen Klemm, Pharm.D.
OSI	Susan Leibenhaut, M.D./Susan D. Thompson, M.D./Kassa Ayalew, M.D., M.P.H
CDTL Review	Joette M. Meyer, PharmD
OSE/DMEPA	Sherly Abraham, R.Ph./Kendra Worthy, Pharm.D.
DPMH	Carol H. Kasten, MD/Tamara Johnson, MD, MS/Lynne P. Yao MD
QT-Interdisciplinary Review Team	Norman L Stockbridge, MD, PhD

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation

DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DPMH=Division of Pediatric and Maternal Health

Division Director Review

1. Introduction

In this application Wellstat proposes to market Xuriden (uridine triacetate) for the treatment of uridine monophosphate synthase (UMPS) deficiency, commonly referred to as hereditary orotic aciduria (HOA), an exceedingly rare, autosomal recessive inborn error of pyrimidine metabolism. Since the original description of this disease approximately half a century ago (1959), there have been only about 20 patients with HOA reported in the medical literature, with only 15 or so having been documented in sufficient detail. There are no approved drugs for the treatment of HOA.

The active ingredient in Xuriden is uridine triacetate, which is a prodrug of uridine; uridine triacetate is rapidly de-acetylated *in vivo* and converted to uridine, which is the biologically active moiety in this drug product (Xuriden is administered orally and is formulated as granules to be mixed in food prior to daily administration).

Uridine itself has been used investigationally for the treatment of HOA, and there is a limited but valuable body of medical literature that describes the role of this compound in the treatment of patients with HOA (uridine has not been approved to date for any indication, but is available in the US as a dietary supplement). Uridine triacetate is a new chemical entity.

This application contains a prospectively designed, baseline-controlled, single-arm, two-center clinical trial of Xuriden conducted in patients with HOA (Study 401.13.001) and a review of the medical literature describing uridine treatment in HOA patients. Due to the rarity of the disease, only 4 patients could be enrolled in Study 401.13.001; these 4 patients, however, represent all patients with HOA that have been identified in the US by the applicant. Because of the severe limitations imposed by the lack of treatment-naïve patients, Study 401.13.001 enrolled primarily HOA patients previously treated with uridine (3 out of 4). The main objective of the trial was to demonstrate that over the duration of 6 weeks of the main phase of the trial (and during subsequent trial extension up to 6 months) Xuriden maintained pre-defined hematological endpoints in the same range as previous uridine treatment. Study 401.13.001 – and the overall Xuriden clinical program - has been discussed by the applicant and the FDA in several meetings held between January 2013 and December 2014.

Because the safety and effectiveness of Xuriden (including dose selection) had to rely in part on published information accumulated with uridine, this application was reviewed under

Section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA); the application was initially submitted under Section 505(b)(1) of the FDCA, and was subsequently amended to reflect this fact.

A detailed description and chronology of Xuriden's regulatory history is provided in the Regulatory Background Section of the CDTL review. Briefly, following the discontinuation of uridine in December 2012 (another company was the sole supplier of uridine to a handful of patients treated under expanded access INDs), the Agency identified Wellstat as a potential manufacturer of uridine in January 2013. Following several meetings in the early part of 2013, an IND was opened by Wellstat for uridine triacetate in November 2013 with the protocol for the above mentioned clinical trial 401.13.001. Uridine triacetate was granted Orphan Drug Designation for in the treatment of hereditary orotic aciduria on August 9, 2013 and received Breakthrough Therapy Designation on April 30, 2014; it also received a rare pediatric disease priority review designation.

As already indicated, due to the rarity of HOA, this application had to rely both on literature data and on information generated in clinical trial 401.13.001. Therefore, the main question regarding this application is whether the applicant has provided enough evidence to support dose selection, and the effectiveness and safety of Xuriden from these combined data sources. Central to this task is whether the applicant has been successful in building a "scientific bridge" between Xuriden (i.e. uridine triacetate) and the literature data obtained with uridine (the active moiety in Xuriden). I believe that in the final analysis the applicant provided sufficient evidence that a Xuriden regimen of 60-120 mg/kg/day has a therapeutic effect that is comparable to equivalent doses of uridine by establishing a scientific bridge built on 1) the physiological understanding of metabolic requirements of uridine in humans; 2) comparative clinical pharmacology information; and 3) confirmation of efficacy and safety of Xuriden in a prospective, baseline-controlled clinical trial at the dosing proposed for marketing.

2. Background

Uridine monophosphate synthase (UMPS), the enzyme deficient in HOA, is a bifunctional protein and contains two separate enzymatic domains that catalyze two distinct chemical reactions: an orotate phosphoribosyl transferase domain converts orotic acid to orotate monophosphate (OMP), and an orotidine-5'-monophoaphate decarboxylase domain converts OMP to uridine monophosphate (UMP). Patients with HOA cannot produce uridine *de novo* and have a buildup of precursors (e.g. orotic acid and its derivative, orotidine). In addition, and important for the understanding of the pharmacodynamic changes evaluated in this application, there is also an overproduction of orotic acid because of loss of feedback inhibition by intracellular nucleotides. The excess of orotic acid in urine has been recognized early, and has been determinant in giving the name to this condition. Elevations of urinary orotic acid (a compound with poor solubility) can cause crystalluria and obstructive uropathy; other manifestations of HOA include hematologic abnormalities (typically megaloblastic anemia but also neutropenia) failure to thrive, and developmental delay.

The goal of treatment in HOA is to bypass the enzymatic defect and exogenously provide an oral dose of uridine that restores intracellular uridine concentrations, thus reversing or

ameliorating the manifestations of this medical condition. Once absorbed, uridine diffuses readily into the cells and becomes available as an enzymatic substrate. Physiologically, the substrate requirements for *de novo* pyrimidine synthesis in adults are estimated at 450 to 700 mg/day of orotic acid per day which, in unaffected individuals, can be enzymatically converted to 700 to 1100 mg of uridine (or 12 to 18 mg/kg of uridine per day for a 60 kg adult). This understanding of physiological requirements of uridine allows for an estimation of exogenous uridine doses necessary for replacement treatment in patients with HOA. Taking into consideration the poor bioavailability of uridine which is ≤10%, the delivery of 12 to18 mg/kg/day of uridine systemically requires the administration of 120-270 mg/kg/day of uridine. This amount is consistent with the uridine doses that have been used successfully in the past to treat patients with HOA. Indeed, in published clinical reports effective uridine doses have been in the range of 150 to 200 (and as high as 300) mg/kg/day.

Awareness of the daily uridine requirements and knowledge of the doses of uridine that treat various manifestations of HOA have been the basis for the selection of the uridine triacetate dose in the Xuriden HOA clinical program. Because uridine triacetate is more lipophilic (and subsequently more bioavailable) than uridine, Xuriden delivers systemic uridine 4 to 6 times more efficiently. In the Xuriden clinical program the applicant used a conservative starting dose of uridine triacetate of 60 mg/kg/day. This dose was anticipated to deliver as much systemic uridine as an oral dose of 200 mg/kg of uridine, a dose which is in the range of 150-300 mg/kg that has been historically used with uridine in the treatment of HOA patients. The Xuriden dose was subsequently titrated based on pharmacodynamic and hematological response up to 120 mg/kg/day (importantly, Xuriden doses higher than 120 mg/kg/day have not been evaluated in patients with HOA).

Because the demonstration of effectiveness of Xuriden in HOA relies on both published literature (to which the applicant does not have right of reference) and on new clinical data, this memorandum will focus on the relationship between the doses explored in the Xuriden clinical study 401.13.001 and those evaluated with uridine in the past, and will evaluate how the totality of these data support the chosen dose regimen.

Of interest, uridine triacetate is also being currently reviewed in the Division of Hematology and Oncology Products for another indication (as an antidote to treat patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting serious toxicity within 96 hours of 5-fluorouracil administration) under NDA (b) (4)

3. CMC/Device

The review did not identify any deficiencies that preclude approval. Facility inspection has been completed and the application has been found to be “acceptable.”

With respect to drug substance the CMC reviewer concludes that

> … the drug substance, uridine triacetate is manufactured using a well-established well-characterized starting material, (b) (4) and the manufacturing process is controlled through appropriate strategies that allow for production of API with consistent quality batch to batch. This API is tested and released according to an API specification that clearly assures the identity, strength, purity and quality of this new molecular entity. The stability results provided from the batches of API produced to date support the proposed (b) (4) retest date for this drug substance.

Concerning the drug product, the review indicates that the proposed specifications are adequate to assure identity, strength, purity, and quality of the drug product, and all excipients are appropriately tested. Stability data support the proposed expiration period of 24 months.

Regarding the manufacturing process the reviewer comments that

> "The manufacturing process for the uridine triacetate oral granules [is] well controlled through a series of appropriate in-process testing and process controls. Based on the information submitted in the application, it is concluded that the proposed commercial manufacturing process and process controls are satisfactory and will provide the ability to manufacture this drug product with consistent quality for commercialization."

An (b) (4) variability in dissolution testing was observed during facility inspection and testing, but the potential impact, if any, on bioavailability, could not be fully evaluated due to existing limitations of the current dissolution method. Such variability in drug dissolution is not expected to have a clinical impact from an efficacy perspective because Xuriden is titrated to goal (pharmacodynamically and clinically) over a range of doses. In addition, given the prior experience with multiple uridine dose regimens across several patient populations, the safety of Xuriden in HOA patients is not expected to be impacted (refer to the safety section of this memorandum). The CMC reviewer recommends that the applicant develop and validate a new dissolution test using stricter acceptance criteria, and use the updated dissolution method to evaluate the impact of the particle size distribution on dissolution. The results of such an evaluation will be used to update the final drug product particle size specification in the in-process controls. This recommendation was discussed with the applicant who agreed to fulfill this request as a postmarketing commitment (the agreement is further detailed in the Postmarketing Requirements and Commitments Section of this memorandum).

4. Nonclinical Pharmacology/Toxicology

The non-clinical reviewer has not identified any issues that preclude approval of Xuriden for the HOA indication. The reviewer states that "from a nonclinical standpoint, this product is approvable for [the] indication proposed." I agree with this recommendation and the proposed non-clinical labeling recommendations.

The non-clinical safety evaluation was extensive and included safety pharmacology studies, repeat-dose toxicology studies in dogs (3 month) and rats (3 and 6 months), genetic toxicology studies, and reproductive toxicology studies in rats (Segment 1 fertility and early embryonic development study and Segment 2 embryo-fetal development study).

The non-clinical reviewer comments that "in animals, uridine triacetate had a generally favorable safety profile." There were no significant, treatment-related toxicities or deaths for doses up to the maximum feasible dose for testing (2000 mg/kg/day) in repeat-dose toxicology studies in rats and dogs. Doses in excess of 2000 mg could not be tested because they could not be physically administered. Thus, the no observed adverse effect level (NOAEL) dose from the 6-month repeat-dose toxicity study in rats was 2000 mg/kg/day or (b) (4) times the maximum human dose (b) (4) As indicated in the efficacy section, the clinical team recommends human doses (b) (4) no higher than 120 mg/kg/day; this will double the safety margin for the maximum human dose that I will recommend for approval and labeling.

Uridine triacetate did not show any negative effect on fertility and reproductive function in rats of either sex, and was not teratogenic up to the highest administered dose of 2000 mg/kg/day. (b) (4)

Carcinogenicity did not have to be evaluated in a dedicated study. With concurrence from the CDER/Executive Carcinogenicity Assessment Committee, the applicant received a waiver for conducting a 2-year carcinogenicity study. The reasons for granting the waiver are described in detail on page 54 of the non-clinical review and include the following: uridine triacetate is a prodrug that is promptly converted to an endogenous product (uridine); there is no evidence of genotoxicity *in vitro* and *in vivo*; there is extensive long-term animal experience with uridine at exposures in excess of the human equivalent dose, with no evidence that the drug is tumorigenic.

One specific impurity that was identified in the CMC review (b) (4) was qualified by the nonclinical studies conducted with the drug substance containing this specific impurity.

An initial *in vitro* observation that uridine triacetate inhibits the hERG channel did not raise concern because uridine triacetate undergoes complete and rapid deacetylation to uridine following oral administration, and therefore systemic *in vivo* exposure to the prodrug is not anticipated. In addition, during repeat-dose toxicology studies no adverse cardiac effects were noted in rats and dogs. This issue has been also addressed by an IRT consult and will be further discussed in the clinical pharmacology section.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer recommends approval with no additional Phase 4 studies. I concur with the recommendation, since there are no outstanding clinical pharmacology issues that preclude approval. Of the many issues addressed in detail by the clinical pharmacology review, I will highlight those related to dose selection, pharmacodynamic (PD) effect, drug-drug interactions and QT prolongation.

Dose and dose regimen

As previously described in the Background Section of this memorandum, uridine triacetate, the active ingredient in Xuriden, is a prodrug of uridine, and is approximately 4 times more bioavailable than uridine on a weight basis. Consequently, the starting dose of uridine triacetate for the Xuriden clinical trial was calculated at 60 mg/kg/day, which is about 1/3 of a typical uridine dose regimen (150-200 mg/kg /day), supported by literature and derived from decades of uridine use. The clinical pharmacology review confirms the validity of these assumptions and comments that

> The proposed dose and dosing regimen are acceptable. The starting dose of the pro-drug is approximately 1/3rd the typical (historic) dose of oral uridine (on mg/kg basis), owing to the higher bioavailability of uridine from the prodrug as previously established. Switching from oral uridine to uridine triacetate was able to deliver bioavailable uridine as evidenced by PK data, maintain hematological and PD endpoints at the patient's baseline (on oral uridine) levels in the patients of the pivotal HOA trial. …There are no unresolved dosing issues from a Clinical Pharmacology perspective with the proposed starting dose, dose range, and frequency of uridine triacetate.

Although the uridine dose has been historically given in multiple daily administrations (primarily to handle the large doses required by some of the investigational regimens, but also to reduce incidence of osmotic diarrhea associated with some formulations), once-daily dosing appears adequate. Maximum concentrations of uridine in plasma following oral Xuriden are generally achieved within 2-3 hours, and the half-life ranges from approximately 2 to 2.5 hours. Given uridine's short half-life, the plasma uridine levels decline to baseline by 8 h after once-daily dosing; however, the main pharmacological marker of uridine availability *in vivo* (orotic acid) measured constantly in the normal range in the clinical trial, suggesting that the pharmacodynamic effect lasts longer, and supports once a day dosing.

Urinary orotic acid and orotidine, an orotic acid derivative, are the PD markers that were assayed in the Xuriden clinical trial. The PD response is very important in demonstrating similarity of response between comparable uridine and uridine triacetate doses, and it is in many respects a measure of efficacy of uridine/uridine triacetate treatment; therefore changes in orotic acid during Xuriden treatment will be further discussed in the efficacy section (in essence the urinary concentrations of orotic acid during the trial remained closely similar to the pretreatment values on uridine, and largely within the normal range). The clinical

pharmacology reviewer reviewed the uridine and orotic acid assays and found them to be acceptable. (b) (4) I am in agreement with the clinical pharmacology reviewer that a validated uridine assay is informative by itself because *in vivo* uridine triacetate is rapidly metabolized to the active drug (uridine) by intestinal and plasma esterases.

Drug-Drug Interaction
The potential for drug-drug interactions was studied only *in vitro*. The clinical pharmacology review concludes that the *in vitro* data suggest that uridine triacetate and uridine do not inhibit or induce major CYP450 enzymes; that uridine triacetate is a weak substrate and an inhibitor of P-glycoprotein; and that, on the basis of the latter observation, and due to the theoretical possibility that the drug may reach high local (gut) concentrations after dosing, interaction of Xuriden with orally administered P-gp substrate drugs cannot be ruled out and it should be labeled as such. I agree with this labeling recommendation.

QT assessment
After consultation with the QT Interdisciplinary Review Team, the applicant was given a waiver for conducting a Thorough QT study. The waiver decision was based on the safety data accumulated with uridine across different patient populations, the pharmacology profile of uridine acetate and the preclinical cardiac evaluation.

6. Clinical Microbiology

Not applicable. The product is not an antimicrobial product.

7. Clinical/Statistical-Efficacy

The evidence of Xuriden's effectiveness in the treatment of HOA comes from two clinical sources: 1) published literature with uridine covering decades of clinical experience, and 2) the results of the clinical trial 401.13.001. These two sources of information will be discussed next.

7.1 Literature summary for uridine in the treatment of HOA

Both the CDTL review and the clinical review summarize the information provided by 19 individual case reports published over several decades describing the clinical response of patients treated with uridine; 18/19 patients were diagnosed in childhood (age of diagnosis: 2 months to 12 years), and one patient was diagnosed as an adult (28 years). These case reports provide important information about the clinical and biochemical features present at the time the diagnosis of HOA was made, the pharmacodynamic and clinical response to a range of

uridine doses , the time course of pharmacodynamic and clinical (primarily hematological) response, and the durability of treatment effect. In summary:

- uridine doses needed to improve anemia (the most common disease manifestation in HOA) ranged between 50 and 300 mg/kg/day (the most consistent effective dose was 150 mg/kg/day)
- doses that corrected anemia varied among patients (some patients responded at doses as low as 50 mg/kg, while others failed to improve at doses of 100 mg/kg /day and required further dose escalation)
- improvement or resolution of anemia on appropriate uridine doses occurred within 2 to 3 weeks following treatment initiation
- an increase in reticulocyte count can be seen within days of therapy
- pharmacodynamic response measured as reductions in urinary orotic acid can be seen within 1 to 2 weeks of initiating uridine replacement therapy, but full normalization on therapy does not always occur (some of the clinical observations are 45 years old and normal standards for children are not always provided in references)
- if treatment was interrupted, anemia re-developed and orotic aciduria returned to pre-treatment levels within 3-4 weeks (this information is relevant to the clinical trial and will be discussed in that context)
- other hematologic manifestations such as leukopenia and neutropenia may require different doses, although some patients responded to the same doses that improved anemia
- information on treating non-hematological manifestations (e.g. failure to thrive) is more limited
- the effects of exogenous uridine were maintained over months and years, as long as treatment continued at sufficient doses (with appropriate dose increases based on body weight changes).

In summary, the totality of the data submitted from the literature support a uridine dose of 150-300 mg as an effective dose in the treatment of HOA. Most of the data come from observations made in the treatment of anemia, but other manifestations of the disease (hematological or not) have been reversed by this dose regimen in individual patients.

7.2 Clinical trial 401.13.001

The HOA clinical program for uridine acetate consisted of a single-arm, open-label, baseline-controlled, prospective clinical trial conducted in 4 patients. The trial was 6 weeks in duration and was followed by an extension which is ongoing; efficacy data up to 6 months were submitted, and provided evidence of durability of effect for this duration.

The trial enrolled three U.S. patients with a known diagnosis of HOA (ages (b) (6) and a treatment-naïve patient (b) (6) All 3 previously diagnosed patients had received standard uridine doses in the range of 150 to 200 mg/kg/day orally, and were switched to a starting uridine triacetate dose of 60 mg/kg, administered orally once daily. As previously indicated, the 60 mg/kg Xuriden dose was selected on the basis of prior experience with uridine in treating patients with HOA, and took into consideration the differences in bioavailability between uridine and uridine triacetate. Although the protocol allowed Xuriden

dose escalation up to a maximum of 300 mg/kg/day, patients received the 60 mg/kg dose for the duration of the trial (6 weeks) and two of them had their doses escalated up to 120 mg/kg in the extension trial. Doses greater than 120 mg/kg were not evaluated in this trial.

The primary efficacy analyses were patient-specific, in that they evaluated the stability of the hematologic parameters that constituted the main manifestation of HOA in each individual patient prior to enrollment. As such, because each patient had a different hematological manifestation, the primary endpoints were different among patients and included neutrophil count, total white cell count (one patient each), and red blood cell mean corpuscular volume (two patients). The secondary efficacy endpoints were shared by all 4 patients and measured pharmacological markers of drug activity: urine orotic acid and orotidine concentrations.

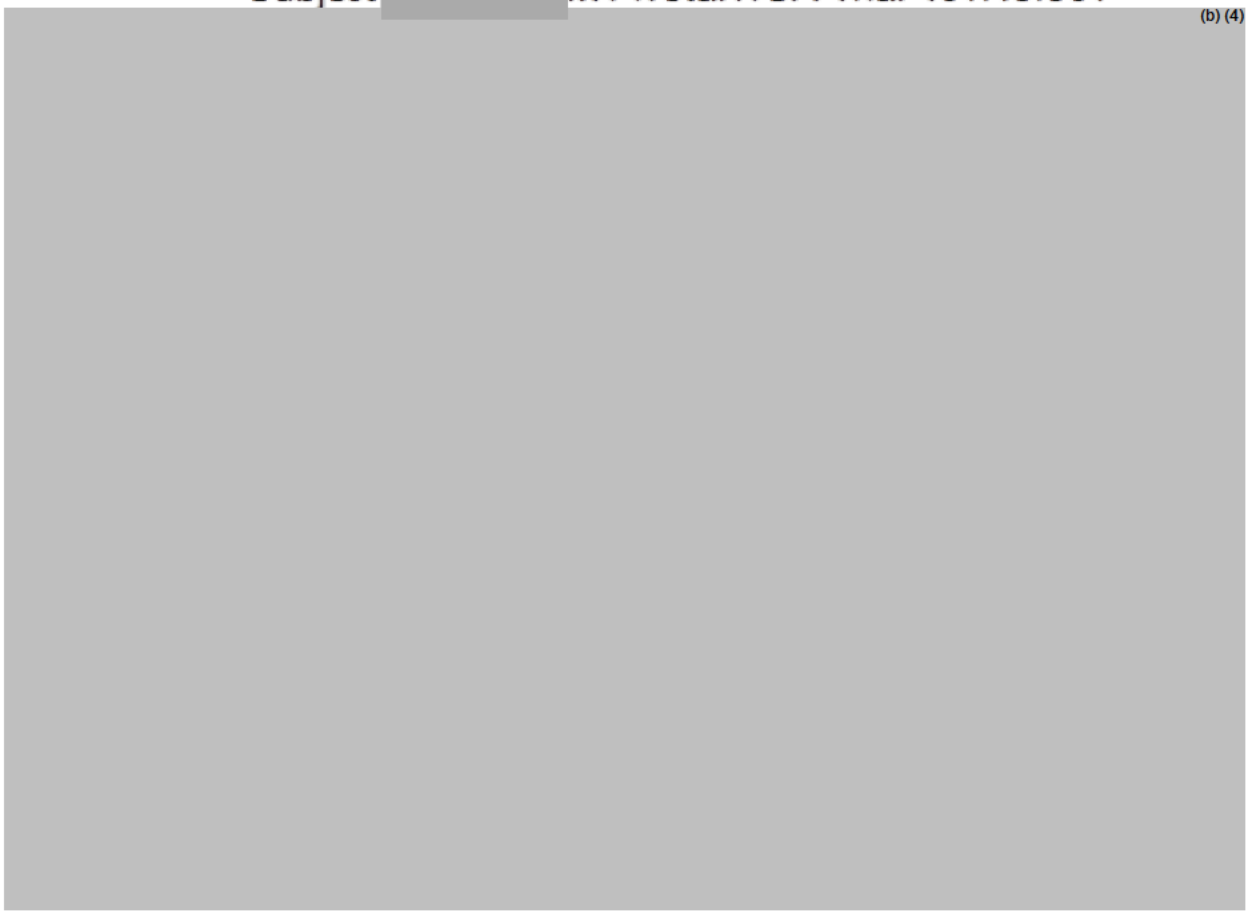
The information for the three patients who have been previously treated with uridine and subsequently switched to Xuriden is displayed below in a series of figures reproduced from page 10 of the clinical pharmacology review. These figures depict individual patient data for the main pharmacodynamic endpoint, orotic acid, which was used, along with clinical response, to guide Xuriden titration. These figures are particularly informative because they include lifetime data and display the time course of the orotic acid concentrations prior to any treatment, for the duration of uridine treatment before enrollment in Study 401.13.001, and during Xuriden treatment in Study 401.13.001 (the red horizontal lines represent the upper limit of normal; vertical lines represent initiation of uridine treatment and switchover to Xuriden).

Observing the time course of orotic acid for patient (b) (6), one can see a clear pharmacodynamic response to uridine and a decline in orotic acid urinary concentrations. Of interest, this patient experienced an increase in (b) (6) urine orotic acid level during a drug holiday, and the level returned to baseline with resumption of therapy. Following the switch to Xuriden, orotic acid levels were maintained at similar levels as during uridine treatment. Hematologically, this patient's % neutrophil count improved and normalized on uridine, and improved further on Xuriden (the % neutrophil count was the primary efficacy endpoint). This patient also met the pre-specified criteria for hematological stability.

Patient ID (b) (6); Pivotal HOA trial 401.13.001

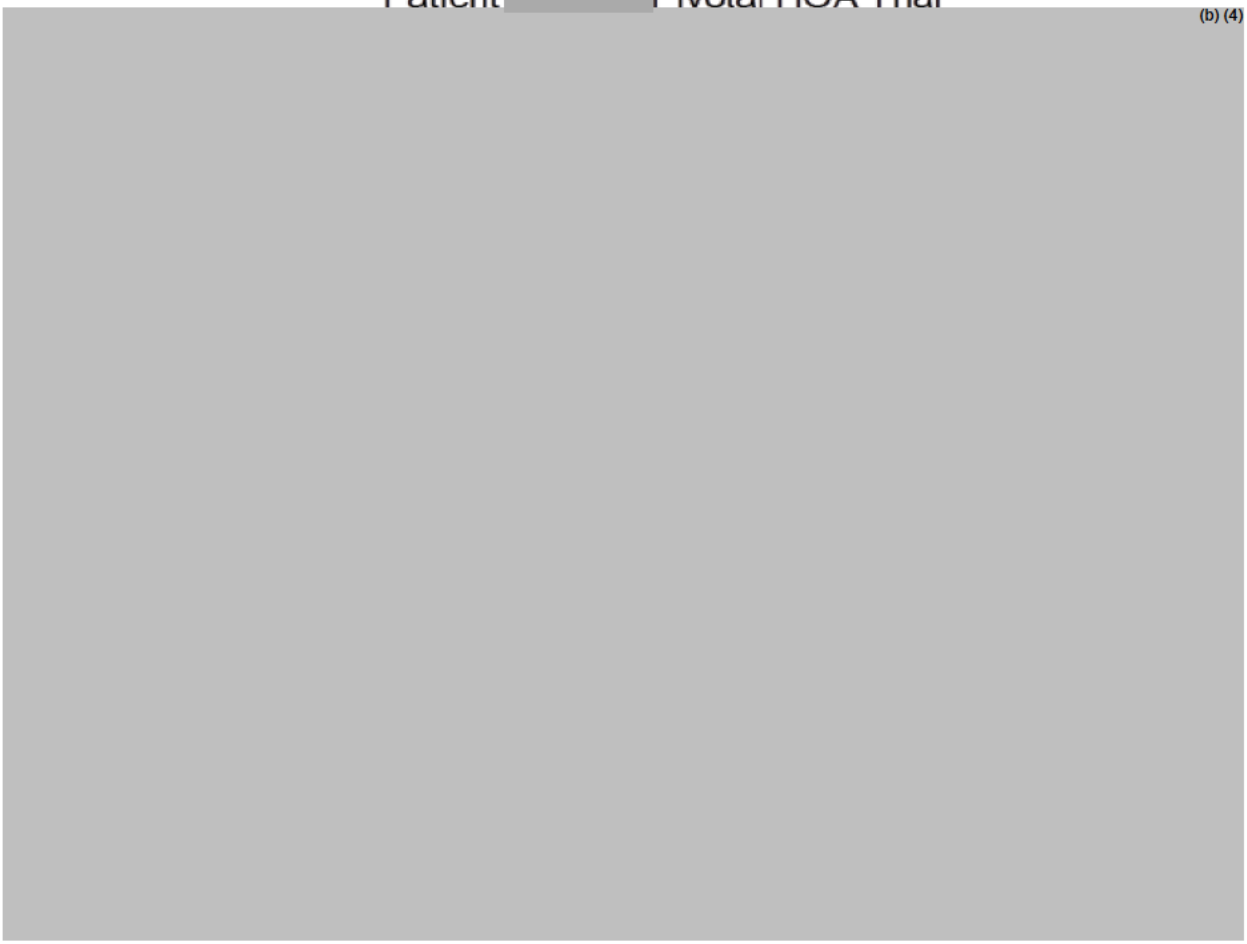
Patient (b) (6) showed a similar pattern of reduction of urine orotic acid during uridine treatment, which remained suppressed after switch to Xuriden. The hematological endpoint for this patient was in the normal range and remained largely so. However, due to lack of documentation of a low white blood cell count prior to study initiation, this patient could not be evaluated according to the pre-specified efficacy criteria.

Subject (b) (6) in Pivotal HOA Trial 401.13.001



Patient (b) (6) showed a similar pharmacodynamic response on two doses of uridine (50 mg/kg/day and 150 mg/kg/day) and after being switched to Xuriden. Hematologically there was no change on Xuriden (in this case, the primary efficacy endpoint was RBC mean corpuscular volume). This patient met the pre-specified criterion for hematological stability.

Patient (b) (6) Pivotal HOA Trial



In summary, maintenance of pharmacodynamic response after a switch to Xuriden was seen for all 3 patients who were previously treated with uridine. In addition, in 2 of these 3 patients the prespecified hematological parameter was stable on Xuriden, while in one patient it could not be formally evaluated.

Importantly, the stability of the PD and hematological effect after switch to Xuriden cannot be attributed to a carryover effect related to prior uridine use because, as known from several publications referenced in the clinical review, the uridine effect is lost in less than 3 weeks after the drug is discontinued; of note, the PD and hematological endpoints in Study 401.13.001were assessed at a far later time (6 weeks and beyond).

Finally, the data on the 4th patient enrolled in Study 401.13.001, the only treatment-naïve patient, are hard to interpret. Despite having a diagnosis of HOA, this patient has variable levels of orotic acid before treatment, which were followed by normal values after the initiation of Xuriden, but the hematological manifestation chosen as primary efficacy endpoint did not change on treatment.

In the final analysis I believe that the applicant has been able to identify a starting dose of Xuriden (60 mg/kg/day) and a dose range of effective Xuriden doses (60-120 mg/kg/day) despite the small size of the available HOA patient population available for study. The applicant did accomplish this by referencing the uridine experience in HOA (to which the applicant doses not have the right of reference). Reliance on these data is appropriate because the applicant has established a "scientific bridge" supported by

- knowledge of the daily physiological requirements of uridine;
- an understanding of the mass ratio between uridine and uridine triacetate which allowed calculation and selection of Xuriden doses intended to provide similar molar concentrations as specific uridine doses;
- an understanding of the clinical pharmacology characteristics of both uridine and Xuriden, including differences in bioavailability;
- selection of doses of Xuriden similar to the doses already characterized for uridine in patients with HOA;
- the demonstration that Xuriden maintains similar pharmacodynamic and hematological effects as uridine in a small group of patients with HOA.

The statistical review and the clinical reviews agree that the current application has demonstrated efficacy, although they emphasize somewhat different aspects of the application.

The clinical reviewer concludes that

> "Based on my review of the totality of evidence, there appears to be sufficient evidence of the efficacy of uridine triacetate for the treatment of hereditary orotic aciduria. "

The CDTL concludes

> …, the evidence of effectiveness of uridine triacetate was supported by published data documenting the results of treatment with uridine (of which uridine triacetate is a pro-drug), which established the time course of response and relapse after discontinuation of uridine in HOA patients. This type of historical control is acceptable as normalization of the endpoints studied is not expected to occur based on the known natural history of the disease. The entire database, 4 patients in the clinical trial conducted by the sponsor and the literature, represents all confirmed cases of patients with HOA, so the drug effect is thought to have been adequately characterized such that the results may be generalizable to future patients diagnosed with HOA and treated with uridine triacetate.

Finally, the statistical review concludes that

> Treatment with uridine triacetate resulted in stable assessments for the primary endpoints in the three [treatment] experienced patients. Hematologic parameters for all four patients continued to show stability or improvement during the 6-month treatment extension period. In addition, all four patients' urinary orotidine and OA [orotic acid] levels remained stable over the 6 weeks of treatment after the initiation of treatment

> with uridine triacetate. Three patients' OA levels remained well-controlled in the treatment extension period except for one patient, whose OA level increased by more than twofold. All patients exhibited increase or stability in height and body weight in the 6-week study period and the 6-month extension trial…..The statistical reviewer confirmed the sponsor's efficacy findings….

Although the Xuriden clinical program has provided evidence of efficacy only for the 60 mg/kg/day and 120 mg/kg/day doses, (b) (4) Based on experience accumulated with uridine triacetate in other patient populations (see comments in the safety section) it seems that doses greater than 120 mg/kg are likely to be safe, but they have not been formally evaluated for efficacy in the Xuriden clinical program. (b) (4) Therefore, I recommend that the Xuriden label should not exceed at this time doses greater than 120 mg/kg/day.

8. Safety

The clinical reviewer did not identify any safety findings of concern in the published clinical studies describing uridine use in HOA patients, or in the Xuriden Study 401.13.001. Dr. Epps concludes that "chronic treatment with uridine triacetate was well tolerated in patients with hereditary orotic aciduria and other conditions." In her review, Dr. Epps looked at several uridine triacetate safety datasets in addition to that of Study 401.13.001 (the latter provided safety data for 4 patients followed for up to 9 months of Xuriden treatment). Uridine triacetate has been administered orally under several INDs to 565 subjects including patients with diabetic neuropathy (53 adults), mitochondrial and metabolic disorders (22 children, 8 adults), patients at risk of 5-fluorouracil toxicity (a total of 482 patients and healthy volunteers). Of note, some of the doses used in the non-HOA uridine triacetate programs were in excess of those submitted for approval under this NDA.

The CDTL review also concludes that

> "Uridine triacetate appears to be well tolerated and without any specific adverse reactions at doses higher than used for the treatment of HOA and lower than the doses of uridine that produced gastrointestinal adverse reactions in the literature. The adverse event of diarrhea reported with uridine triacetate in patients with diabetic nephropathy is thought to be related to an earlier tablet formulation containing a higher percentage of excipients (b) (4) compared to the to-be-marketed granule formulation (>95% active ingredient)."

In Study 401.13.001, there were no deaths, no SAEs, no discontinuations, and no treatment-related adverse events. The good tolerability and relatively unremarkable safety profile identified to date for Xuriden in HOA patients may simply reflect the fact that uridine

triacetate is rapidly metabolized *in vivo* to uridine, an endogenous molecule, and that the Xuriden doses were calculated to match our current understanding of daily physiological requirements.

Based on the absence of significant safety findings in the Xuriden HOA program, neither the clinical reviewer, nor the CDTL reviewer recommends any specific language for the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections of the Xuriden label. I am in agreement with their recommendations.

9. Advisory Committee Meeting

This application did not require an Advisory Committee meeting. The clinical program was designed with FDA input, there were no efficacy or safety issues identified in the review of this application.

10. Pediatrics

Uridine triacetate was granted orphan drug designation for the treatment of hereditary orotic aciduria. Therefore, this application is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

The Office of Scientific Investigations concludes that "the study [401.13.001] appears to have been conducted adequately, and the data generated by the study appear acceptable in support of the respective indication."

The Clinical Review concludes that the "the overall quality of the data submitted by the applicant was adequate", that the clinical study were conducted in accordance with Good Clinical Practices (GCP) and met international ethical standards for clinical research and patient protection. A review of the financial disclosure documents was also found acceptable.

12. Labeling

The CDTL review includes a comprehensive review of labeling. I am in agreement with the recommendations made by the CDTL, recommendations that consolidate labeling comments from multiple disciplines. At the time of this memorandum, a label has been largely agreed

with the applicant. Of note, the proposed proprietary name, Xuriden was found acceptable by Division of Medication Error Prevention and Analysis (DMEPA.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend approval of this NDA. There is agreement across all disciplines that reviewed this NDA that Xuriden should be approved for the indication of treatment of hereditary orotic aciduria. There are no outstanding issues to preclude approval. This recommendation is for the 2 gram packet presentation (b) (4)

- Risk Benefit Assessment

Hereditary orotic aciduria is a rare and potentially fatal disease for which there is no approved pharmacological treatment. In this application Wellstat has characterized a Xuriden drug product that meets current manufacturing standards, and has identified a dose range of Xuriden (60-120 mg/kg/day) that maintains, improves or reverses several manifestations of the disease such as orotic aciduria (a finding that has been associated with nephrolithiasis and obstructive uropathy) and hematological abnormalities (anemia, neutropenia). Benefit on other manifestations of the disease could not be demonstrated directly because of the extreme rarity of the disease, but are suggested by past observations made with equivalent doses of uridine, the active moiety in Xuriden. The safety profile of the Xuriden dose regimen recommended for approval (60-120 mg/kg/day) has been unremarkable. In absence of any identified safety risks and given the proven efficacy of Xuriden, the risk benefit is favorable, and supports a recommendation of approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None (no issues requiring risk management in the postapproval phase have been identified).

- Recommendation for other Postmarketing Requirements and Commitments

There are no recommendations for PMRs from any of the review disciplines. Two PMCs have been recommended by the Biopharmaceutics and by the Clinical Reviewer/CDTL and were agreed by the applicant. I am also in agreement with these PMCs, listed .

Biopharmaceutics
Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches. Determine the particle size distribution of the final drug product and, using the updated dissolution method, evaluate the impact of the particle size distribution on dissolution. The

studies should also include an evaluation of batches submitted in the application (e.g., W017891, W017893, W017895, W012785, and W021129). Based on findings from these studies, update the final drug product particle size specification and the in-process controls.

Schedule Milestones:

Final Protocol Submission:	09/15
Study/Trial Completion:	02/16
Final Report Submission:	03/16

Clinical

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

(b) (4)

Study/Trial Completion:	June 2016
Final Report Submission:	November 2016

(b) (4)

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/s/

DRAGOS G ROMAN
09/04/2015