

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208169Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	July 21, 2015
<b>From</b>	Joette M. Meyer, PharmD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 208169
<b>Supplement#</b>	
<b>Applicant</b>	Wellstat Therapeutics Corp.
<b>Date of Submission</b>	January 8, 2015
<b>PDUFA Goal Date</b>	September 8, 2015
<b>Expedited Date</b>	August 6, 2015
<b>Proprietary Name / Established (USAN) names</b>	Xuriden (uridine triacetate)
<b>Dosage forms / Strength</b>	2 gram and (b) (4) oral granules, single-use packets
<b>Applicant Proposed Indication(s)/Populations(s)</b>	Xuriden is a uridine replacement (b) (4) indicated (b) (4) (b) (4) for the treatment of hereditary orotic aciduria.
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Populations(s)</b>	Xuriden is a pyrimidine analog for indicated for the treatment of hereditary orotic aciduria.

EDR Location: <\\CDSESUB1\evsprod\NDA208169\0000>

### 1. Benefit-Risk Assessment

### **Benefit-Risk Summary and Assessment**

Uridine triacetate (Xuriden®) is a pyrimidine analog for uridine replacement indicated for the treatment of patients with hereditary orotic aciduria (HOA), a rare congenital disorder of pyrimidine metabolism caused by a defect in the enzyme uridine monophosphate synthase. I recommend approval of uridine triacetate for this indication.

HOA affects about 20 patients worldwide and can be serious and potentially fatal in those most severely affected (homozygous for the disorder). Currently, there is no approved therapy for HOA and no treatment(s) in development (other than uridine triacetate, the subject of the current NDA). Nucleotide replacement therapy has been the mainstay of treatment for HOA patients for decades. Administration of exogenous uridine replacement therapy orally in doses ranging from 50 mg/kg/day to 300 mg/kg/day has provided apparent clinical benefit for HOA patients. However, uridine is limited by low oral bioavailability, is not being developed as a drug by any sponsor in the US, and is only available in the US as a dietary supplement; therefore, not subject to Good Manufacturing Practices.

Uridine triacetate at a starting dose of 60 mg/kg per day (estimated to correspond approximately to a 200 mg/kg uridine dose) was shown in a single, adequate and well-controlled clinical trial to stabilize individual patient pre-specified hematologic parameters in 2 of 3 patients switched from oral uridine by 6 weeks and maintain these parameters (percent neutrophils and mean corpuscular volume) out to 6 months. The dose of uridine triacetate was increased to 120 mg/kg per day in 3 of the 4 patients between 6 weeks and 6 months of treatment. In the neutropenic patient receiving 60 mg/kg per day, the percent neutrophils increased to the normal range by 6 months. The third patient did not have baseline documentation of an abnormal value in the pre-specified hematologic parameter (WBC count) and was unevaluable. The fourth patient (treatment naïve, dose escalated to 120 mg/kg per day at 4 months, who had not received prior uridine) did not demonstrate an improvement in the pre-specified parameter of mean corpuscular volume (MCV) at either 6 weeks or 6 months. The data on the secondary endpoint of urinary orotic acid concentrations at Week 6 and Month 6 showed concentrations within (or close to) the normal range for all 4 patients and was used as supportive efficacy data (i.e., evidence of a pharmacodynamics response). Data on growth at 6 months was also used to support efficacy in the 3 pediatric patients: both of the pediatric patients switched to uridine triacetate improved weight growth and the treatment naïve patient remained stable; height growth remained stable in all three patients.

Oral administration of exogenous sources of uridine was reported in the literature cases to significantly improve hematologic abnormalities (megaloblastic anemia, leukopenia and neutropenia) within 2 to 3 weeks in almost instances when administered in sufficient amounts. Concentrations of urinary orotic acid were significantly reduced within 1 to 2 weeks of initiating uridine replacement therapy. If treatment was interrupted for longer periods, body weight and other gains receded. Improvements in body weight and other developmental parameters were also documented over time with continued uridine replacement therapy adjusted to body weight gains.

The literature information on uridine response time, and loss of response, supports that the duration of Study 001 was sufficient to capture the treatment effect of uridine triacetate (a pro-drug of uridine). Therefore, the entire efficacy database, 4 patients treated with uridine triacetate in Study 001 and the literature case reports of patients treated with uridine, represents all confirmed cases of patients with HOA worldwide, so the

drug effect (hematologic response and pharmacodynamics response in urinary orotic acid concentrations) is thought to have been adequately characterized during the duration of the trial, such that the results may be generalizable to future patients diagnosed with HOA and treated with uridine triacetate. However, Study 001 may have been of insufficient duration to fully capture the effect on hematologic improvement in the patient who was treatment naïve and on the endpoint of growth for the pediatric patients.

Uridine triacetate has demonstrated a good safety profile in nonclinical and clinical studies conducted to date with no adverse reactions to report in labeling. Uridine triacetate has been administered orally to over 500 people including healthy volunteers, pediatric patients with mitochondrial and neurometabolic disorders (up to 300 mg/kg per day, some for more than 18 years), pediatrics and adults overexposed to 5-fluorouracil chemotherapy, and adults with diabetic peripheral neuropathy. Excluding patients with cancer and those treated under compassionate use, there have been no deaths, no dose-limiting toxicity, no serious adverse reactions and relatively few adverse reactions attributable to uridine triacetate.

There are no identified safety concerns with uridine triacetate and no issues related to risk management have been identified. There are no Contraindications, Warnings and Precautions, Adverse Reactions, or Drug Interactions to include in labeling.

There are no PMRs; two PMCs will be requested: (1) continued collection of safety/efficacy data in patients enrolled in Study 001 and (2) development of a discriminating dissolution method with acceptance criteria from at least 5 commercial batches.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Hereditary orotic aciduria (HOA) is a rare congenital disorder of pyrimidine metabolism caused by a defect in the enzyme uridine monophosphate synthase.</li> <li>Only about 20 cases have been identified worldwide</li> <li>A clinically heterogeneous disorder; individuals who are heterozygous may be asymptomatic or mildly affected.</li> <li>Disease onset occurs during the neonatal or infant period.</li> <li>Clinical manifestations include orotic aciduria, hematologic abnormalities (typically megaloblastic anemia unresponsive to vitamin B12 or folic acid), obstructive uropathy, failure to thrive and developmental delays.</li> <li>The hematologic and other consequences of HOA (i.e., infections) can be fatal if untreated.</li> <li>Source of data: Literature case reports of all known patients with the disease</li> </ul>	<p>HOA is a genetic disorder affecting about 20 patients worldwide and can be serious and potentially fatal in those most severely affected.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Current Treatment Options</a></p>	<ul style="list-style-type: none"> <li>• Currently, there is no approved therapy for HOA and no treatment(s) in development (other than uridine triacetate, the subject of the current NDA).</li> <li>• Nucleotide replacement therapy has been the mainstay of treatment for HOA patients for decades following publication of the first case report in 1959 of HOA in which the authors describe disease remission in a patient treated empirically with a mixture of nucleotides.</li> <li>• Case reports have documented rapid hematologic response (within days to weeks) with administration of exogenous uridine replacement therapy. Patients experience relapse of disease within a similar time frame when administration of uridine is discontinued or suspended.</li> <li>• Uridine administered orally in adequate doses has provided apparent clinical benefit for HOA patients, permitting an essentially normal life if initiated early enough and at sufficient doses to avoid irreversible developmental problems (50 mg/kg to 300 mg/kg per day).</li> <li>• Some patients treated chronically with uridine have reached adulthood.</li> <li>• Uridine is available as a dietary supplement in the US, but is not approved or in development for any indication.</li> <li>• Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.</li> <li>• The evidence for the efficacy of uridine comes from case reports in the literature.</li> </ul>	<p>There is no approved drug for this indication.</p> <p>If initiated early and at sufficient doses, exogenous uridine replacement therapy appears to have an effect on HOA hematologic manifestations, but is limited by low oral bioavailability. Uridine is not being developed as a drug by any sponsor and is only available in the US as a dietary supplement; therefore, not subject to Good Manufacturing Practices.</p>
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>• Study 401.13.001 is considered to be an adequate and well-controlled clinical trial in 4 patients with HOA: 3 switched for uridine therapy and one treatment naïve patient treated with a starting dose of uridine triacetate of 60 mg/kg per day and escalated to 120 mg/kg per day for insufficient clinical response.</li> <li>• A starting dose of 60 mg/kg per day uridine triacetate was estimated to correspond (due to higher bioavailability) with approximately a 200 mg/kg dose of uridine; a dose that was shown to have an effect in HOA patients described in the literature.</li> <li>• Study 001 was non-randomized and designed without a concurrent control; patients served as their own control.</li> </ul>	<p>The evidence for the efficacy of uridine triacetate derives from 4 patients with HOA and previous experience with oral uridine replacement therapy.</p> <p>The single adequate and well-controlled trial (Study 001) included in the application may not have been of sufficient duration to fully capture the effect in patients who are treatment naïve and on growth parameters for the pediatric patients.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• The primary (hematologic parameters) and secondary endpoints (urinary orotic acid concentrations, growth) were objective and reliable.</li> <li>• The patient-specific primary efficacy endpoints (hematologic parameters) were agreed upon with the division during drug development. The parameters for clinical stability or clinical improvement for each hematologic parameter were prespecified in the protocol and statistical analysis plan.</li> <li>• Endpoints were assessed at Week 6 (Day 42) for the primary analysis; data was also collected to Month 6 as part of an extension phase of the trial.</li> <li>• The results of the primary endpoint at Week 6 (Day 42) supported clinical stability in 2 of the 3 patients switched from uridine (percent neutrophils and mean corpuscular volume, respectively). The third patient did not have baseline documentation of an abnormal value in the pre-specified hematologic parameter (WBC count) and was unevaluable.</li> <li>• The 6 week information was not considered sufficient and additional data on the parameters used as both the primary and secondary endpoints of the trial at Month 6 was required to establish the efficacy of uridine triacetate in all 4 patients. In the neutropenic patient, the percent neutrophils increased to the normal range by Month 6.</li> <li>• In a single treatment naïve patient, there was no improvement on the parameter of mean corpuscular volume (MCV) at either 6 weeks or 6 months.</li> <li>• The data on secondary endpoint of urinary orotic acid concentrations at Week 6 being within (or close to) the normal range for all 4 patients was used as supportive efficacy data (evidence of a pharmacodynamics response).</li> <li>• Data on growth at 6 months was also used as supportive evidence of efficacy in the 3 pediatric patients: both of the pediatric switch patients improved weight growth and the naïve patient remained stable; height growth remained stable in all three patients.</li> <li>• Individual case reports of HOA patients treated with uridine, as described in the literature, was also used to as a type of historical control to establish the time course of response to treatment and relapse after discontinuation</li> </ul>	<p>The sponsor will be asked to conduct a postmarketing commitment (PMC) to continue to evaluate the long-term efficacy and safety of uridine triacetate in patients currently enrolled in Study 001 every 6 months for a total duration of 2 years.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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 results are expected to be generalizable to uridine triacetate, a pro-drug of uridine.</p> <ul style="list-style-type: none"> <li>• The entire efficacy 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 (hematologic response and pharmacodynamics response in urinary orotic acid concentrations) is thought to have been adequately characterized during the duration of the trial, such that the results may be generalizable to future patients diagnosed with HOA and treated with uridine triacetate.</li> <li>• However, the trial may have been of insufficient duration to fully capture the effect in patients who are treatment naïve and not switched from uridine and on growth parameters in the pediatric patients.</li> <li>• The sponsor will be asked to conduct a postmarketing commitment (PMC) to continue to evaluate the long-term efficacy and safety of uridine triacetate in patients currently enrolled in Study 001 every 6 months for a total duration of 2 years. The report should include data on growth, hematologic indices, and urine biomarkers (orotic acid and orotidine). Growth data should include height, weight, height velocity and weight velocity. Information should also be collected on any dose adjustments, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments.</li> <li>• There were insufficient patients in the trial to perform any subpopulation efficacy analyses based on age/sex/race.</li> </ul>	
<p><a href="#">Risk</a></p>	<ul style="list-style-type: none"> <li>• In nonclinical studies uridine triacetate had a general favorable safety profile with no overt toxicity in rats and dogs at up to the maximum feasible doses of 2000 mg/kg per day (b) (4)</li> <li>• Uridine triacetate is not genotoxic and is not a reproductive toxin.</li> <li>• Uridine triacetate has been administered orally to over 500 people including healthy volunteers, pediatric patients with mitochondrial and</li> </ul>	<p>Uridine triacetate has demonstrated a good safety profile in nonclinical and clinical studies conducted to date with no adverse reactions to report in labeling.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>neurometabolic disorders (up to 300 mg/kg per day, some for more than 18 years), pediatrics and adults overexposed to 5-fluorouracil chemotherapy, and adults with diabetic peripheral neuropathy. Excluding patients with cancer and those treated under compassionate use, there have been no deaths, no dose-limiting toxicity, no serious adverse reactions and relatively few adverse reactions attributable to uridine triacetate.</p> <ul style="list-style-type: none"> <li>• Gastrointestinal adverse events of diarrhea were described in patients with diabetic nephropathy treated with uridine triacetate. Diarrhea and abdominal cramping were described in the literature in patients treated with uridine, with single and multiple doses at high doses (8 gram/m<sup>2</sup>).</li> <li>• 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.</li> <li>• There were insufficient patients in the safety database to perform any subpopulation analyses based on age/sex/race.</li> <li>• <i>In vitro</i> data showed that uridine triacetate is not an inhibitor or inducer of the major CYP450 enzymes; it is a weak substrate for P-gp (the clinical significance is unknown).</li> </ul>	
<p><a href="#">Risk Management</a></p>	<ul style="list-style-type: none"> <li>• No issues related to risk management have been identified; therefore, no REMS is required.</li> <li>• There are no PMRs; two PMCs will be requested: continue to collect safety/efficacy data in patients enrolled in Study 001 and development of a discriminating dissolution method with acceptance criteria from at least 5 commercial batches.</li> <li>• Labeling will focus on the appropriate preparation, administration and dosing of the drug. There are no Contraindications, Warnings and Precautions, Adverse Reactions, or Drug Interactions. No Medication Guide or Patient Information is needed. An Instructions for Use document will be developed.</li> </ul>	<p>There are no identified safety concerns. A PMC for additional data collection for patients enrolled in Study 001 will be recommended. No additional safety monitoring other than routine pharmacovigilance in the postmarket setting is recommended.</p>

## 2. Background

### Pathophysiology of Condition

Hereditary orotic aciduria (HOA) is a rare congenital autosomal recessive disorder, and only about 20 cases of this rare disorder have been documented worldwide.

The most severe form of the disease results from a deficiency in the activity of the pyrimidine pathway enzyme uridine 5'-monophosphate (UMP) synthase. These patients cannot convert orotic acid into UMP due to an inactivating enzyme mutation or other enzyme dysfunctions and consequently cannot make uridine normally. The accumulated orotic acid is excreted in the urine, and the reduced de novo pyrimidine synthesis does not provide adequate amounts of uridine nucleotides and their metabolites.

### Clinical Features

Hereditary orotic aciduria (HOA) was first recognized as a defect in pyrimidine nucleotide synthesis by identification of crystals of orotic acid, an intermediate in UMP synthesis, in urine.

HOA is a serious, potentially fatal, condition. Clinical manifestations include, in addition to orotic aciduria, hematologic abnormalities (typically megaloblastic anemia unresponsive to vitamin B12 or folic acid), failure to thrive and physical and intellectual developmental delays. Orotic acid crystals in the urine have caused episodes of obstructive uropathy in the majority of patients. The hematologic and other consequences of HOA can be fatal if untreated.<sup>1</sup>

Disease onset occurs during the neonatal or infant period. HOA is a clinically heterogeneous disorder; individuals who have some UMPS activity (e.g., individuals who are heterozygous for defective UMPS) may be asymptomatic or only mildly affected.

Megaloblastic anemia is the most commonly documented hematologic abnormality, but cases of HOA without anemia are also known. Different cell types have variable capacities for incorporation of exogenous uridine into intracellular nucleotide pools. This may account for variability in the dominant hematological abnormality for individual patients (megaloblastic anemia vs. platelet or neutrophil defects vs. defects in the adaptive immune system). HOA patients may produce sufficient uridine to support hematopoiesis but not sufficient uridine for normal brain development and function.

HOA patients are reported to have a relatively high incidence of malformations at birth, including musculoskeletal anomalies (kyphoscoliosis, scaphoid skull, inguinal and umbilical hernias, and hypertonicity), and heart defects including ventricular septal defects.

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<sup>1</sup> Huguley CM, Bain JA et al., Refractory megaloblastic anemia associated with excretion of orotic acid. *Blood* 1959;14:615-34.

The developing fetus depends on maternal circulating uridine for synthesis of RNA, phospholipids and biosynthetic glycosylation reactions. Mothers of HOA patients are generally heterozygous for defective UMPS, which is usually asymptomatic in the mother, but may limit the amount of circulating uridine available to support fetal development.

The degree and duration of uridine deficiency, as well as other concurrent health issues, may affect the clinical presentation of HOA. A diagnosis of HOA does not preclude additional concurrent genetic or congenital problems.

### **Existing (or Available) Therapies**

There is no approved therapy for HOA. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.

The goal pharmacologic treatment is to provide an alternative precursor of uridine nucleotides that bypasses the block in the *de novo* pathway involving conversion of orotic acid to UMP to compensate for the enzyme defect. Nucleotide replacement therapy has been the mainstay of treatment for HOA patients for decades following publication of the first case report in 1959 of HOA in which the authors describe disease remission in a patient treated empirically with a mixture of nucleotides.<sup>2</sup> Subsequent case reports have documented rapid hematologic response with administration of exogenous oral uridine (within days to weeks). Uridine administered orally in adequate doses has provided apparent clinical benefit for HOA patients, permitting an essentially normal life if initiated early enough and at doses of 50 mg/kg to 300 mg/kg per day to avoid irreversible developmental problems. Some patients treated chronically with uridine have reached adulthood. Several patients who received oral uridine for a number of years fathered or gave birth to normal children.<sup>3</sup>

The amounts of exogenous systemic uridine required to compensate for impaired *de novo* synthesis closely matches daily synthesis of uridine nucleotides. In adults, *de novo* synthesis has been estimated at 450 to 700 mg of orotic acid per day. Orotic acid is quantitatively converted to UMP, with no other metabolic fate. A quantity of 450 to 700 mg of orotic acid corresponds to 700 to 1100 mg of uridine. In a 60 kg adult this means that a minimum of 12 to 18 mg/kg of systemic uridine per day would provide sufficient intracellular UMP to satisfy normal turnover and maintenance of pyrimidine pools.

The oral bioavailability of uridine has been measured at 7% to 10% in humans. Delivery of 12 to 18 mg/kg per day uridine systemically therefore would require oral administration of at least 10 to 15 times that amount to compensate for poor absorption, or a minimum range from 120 mg/kg to 270 mg/kg per day.

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<sup>2</sup> Huguley CM, Bain JA, et al., Refractory megaloblastic anemia associated with excretion of orotic acid. *Blood* 1959;14:615-34.

<sup>3</sup> Webster DR., Becroft DM, et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, *Scriver's Online Metabolic & Molecular Bases of Inherited Disease* 2001, Chapter 113: 1-86.

This calculated estimate of the appropriate oral uridine dosage range corresponds to the oral uridine doses that have been reported to be necessary for treatment of HOA in the literature, generally between 150 to 200 mg/kg per day. At these dosages, improvements in orotic aciduria, hematologic parameters and failure to thrive have been observed. Chronic supplementation with uridine is required to sustain these clinical improvements

### Product Information

Uridine is commercially available in the US as a dietary supplement. However, uridine is not FDA approved and is not being developed for any indication. It was available historically in the US under expanded access protocols (b) (4). See Regulatory History below. No other therapy is in development in the US for the treatment of HOA.

The subject of the current NDA is uridine triacetate, a pro-drug of uridine, which delivers systemic uridine more efficiently than oral uridine itself, by a factor of approximately 4 to 6 in both normal children and adults. (b) (4)

(b) (4) During first passage from the intestinal lumen into the circulation via the liver, the acetate groups are rapidly and quantitatively removed, yielding elevated plasma uridine without detectable amounts of uridine triacetate in blood or plasma.

A starting dose of 60 mg/kg per day uridine triacetate was determined for uridine replacement therapy in HOA, anticipating that this dose would deliver at least as much systemic uridine as an oral dose of 200 mg/kg uridine and would deliver at least as much systemic uridine as is produced by *de novo* synthesis in normal subjects.

Uridine triacetate (b) (4) also being developed in the US by the sponsor (Wellstat) for a separate indication “an antidote indicated 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”. (b) (4) (b) (4)

### Regulatory Background

Prior to Wellstat’s development of uridine triacetate, uridine for HOA patients had been available from Repligen Corporation under IND (b) (4) for the treatment of bipolar depression (RG2417, (b) (4)). Repligen decided to discontinue manufacturing uridine in January, 2013, and alternate sources of the drug for HOA patients were sought.

#### P/IND 118931

*December 2012:* The Agency was informed of an impending drug shortage for patients with HOA being treated with uridine under expanded access protocols due to the sole supplier discontinuing its clinical development programs for uridine. At the time, five patients with HOA were being treated with uridine through expanded access and all five patients received uridine through emergency or individual patient INDs.

*January 2013:* The Agency identified the applicant Wellstat, manufacturer of uridine acetate (a prodrug of uridine) as a potential alternative source of uridine for patients with HOA in expanded access protocols.

*March 22, 2013:* The Agency met with the applicant to discuss development of uridine triacetate as uridine replacement therapy in patients with HOA.

*August 7, 2013:* The Agency held a pre-IND meeting with the applicant to discuss a regulatory pathway for receiving an indication for treatment of patients with HOA. During the meeting, 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.

At the pre-IND meeting on August 7, 2013, the Division recommended that a 6-month repeat-dose toxicity study in rats (with no recovery period), a Segment I Fertility and Early Embryonic Development Study in rats, and a Segment II Embryo-fetal development study in one species would be needed to support the NDA. The Division recommended that the proposed clinical trial could be initiated prior to completion of the Segment I study, provided that the Informed Consent Documents clearly indicate the lack of preclinical data and communicate the risks involved. The Division also recommended that the Segment III study pre- and postnatal development study could be conducted post-approval.

*March 6, 2013:* Request for Breakthrough Therapy Designation; granted

*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.

*November 22, 2013:* New protocol to open IND 118931: Protocol 401.13.001, “Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria.” Protocol revised by sponsor December 16, 2013 to address safety concerns; additional non hold comments sent January 21, 2014, revised protocol sent February 20, 2014 .

*April 30, 2014:* The Agency granted Breakthrough Therapy designation based on clinical data presented from published case studies and clinical summaries from the expanded access INDs.

*October 15, 2014:* Pre-NDA CMC only meeting request; scheduled for December 11, 2014; preliminary responses sent December 5, 2014; meeting cancelled as written comments were sufficient.

*October 20, 2014:* Pre-NDA meeting request; preliminary responses sent December 12, 2014;

*December 16, 2014:* The Agency held a pre-NDA meeting with the applicant. During the meeting, the Agency agreed that the battery of nonclinical studies that the applicant proposed to submit was adequate to support filing of the NDA. The Agency requested that the applicant

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.

January 8, 2015: The sponsor submitted NDA 208-169.

### 3. Product Quality

This 505(b)(1) NME application is *not* deemed ready for **Approval** at this time in its present form, per 314.125(b)(6),(13).

This applicant has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has *not* made a final “Acceptable” recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The labels/labeling issues have *not* been completely resolved as of this review.

Therefore, from the [Office of New Drug Products] ONDP perspective, this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(1)(6) & (13), until the above issues are satisfactorily resolved (see the List of Deficiencies on p. 116).

*CDTL Comment: For additional information, see the complete review in Panorama dated June 13, 2015 from Hamid Shafiei, PhD.*

The following information was abstracted from the Product Quality review.

Xuriden<sup>TM</sup> (uridine triacetate) oral granules (b) (4)  
(b) (4)  
2g packets after the approval of this application. The information and post approval commitments provided in this application adequately support the future marketing of 2g packets.

*CDTL Comment: The sponsor submitted CMC information for both the 2 gram (b) (4) packet sizes. However, they only plan to market the 2 gram packet with the approval of Xuriden for HOA. As noted above, the sponsor is also developing the product (at a higher dose) for use as an antidote to treat patients at risk of excess 5-FU toxicity. (b) (4)*

#### General Product Quality

The drug substance, uridine triacetate is manufactured using (b) (4)  
(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.

During the pharmaceutical development, (b) (4) granules formulations were examined. It was determined that oral granules with maximum API load can provide the flexibility in dosing that is required for pediatric patients for whom the dosage must be adjusted based on the patient's weight. Another consideration for pursuing oral granules as the final drug product was that this type of dosage form enables mixing the drug product with soft foods and further facilitates dosing of pediatric patients.

The drug product contains (b) (4)% uridine triacetate as the active ingredient and (b) (4)% Opardy (b) (4) Clear (b) (4) and (b) (4) natural orange juice flavor S.D. #80618 (flavoring) as the excipients. The total amount of excipients used in this drug product (b) (4) (b) (4) All excipients are appropriately tested and released for use in the manufacture of Xuriden .

To make the dissolution testing (b) (4)

(b) (4)

In a Telcon with the applicant on May 22, 2015, the applicant agreed to post approval commitment that (b) (4) dissolution method will be developed and validated within 6 months after the approval of the application with updated dissolution acceptance criteria.

Based upon an amendment submitted to the NDA on June 1, 2015, the drug product specification (b) (4) is deemed adequate to assure identity, strength, purity, and quality of the drug product.

*CDTL Comment: The sponsor will be asked to 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 as a postmarketing commitment (PMC). See Section 13 Postmarketing Recommendations.*

*CDTL Comment: The HPLC method QCM751/02 for "Identification, Assay and Related Substances" was evaluated and found acceptable for quality control and regulatory purposes. See Methods Validation Report Summary David Keire, PhD dated April 17, 2015 in DARRTS.*

The applicant provided 6-month accelerated and 12-month long term stability results from three registration batches and 31-month long-term stability results from a developmental batch of drug

product in support of the proposed 24-month expiration dating period. Based on the review of the stability data, the proposed expiration period of 24 months is granted.

Uridine triacetate oral granules is manufactured (b) (4)

The manufacturing process for the uridine triacetate oral granules are 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.

The applicant claimed for the exclusion from the Environmental Assessment which is granted.

#### **Facilities Review/Inspection:**

The facilities involved in the manufacturing and testing of the drug substance, uridine triacetate, (b) (4) have been recommended as acceptable based on the inspectional history.

The facility involved in the manufacture, packaging, and release testing of the drug product, (b) (4) was scheduled for inspection (b) (4). The “acceptable” recommendation for this facility as well overall assessment of the facilities is still pending.

#### **Other Notable Issues**

Although granules (b) (4) the applicant has suggested that mixing of the granules with soft foods such as applesauce, vanilla pudding, and yogurt (b) (4). The applicant has also suggested that the granules can be mixed with milk, infant formula, or water as dosing vehicles if needed. The information provided in the application supports the use of all proposed dosing vehicles.

Performance and appropriateness of uridine triacetate granules for dosing of young pediatric patients have been reviewed by Dr. Arzu Selen (Associate Director OPQ/OTR/IO). Dr. Selen has raised concerns about the drug product and whether this drug product can be successfully administered to pediatric patients less than 12 years of age. Her concerns have been discussed with the clinical team and will be further discussed with the applicant during late-cycle communication and may be delineated as a post-approval commitment.

*CDTL Comment: In response to the Late Cycle Meeting (LCM) package sent to the sponsor on June 26, 2015, the sponsor provided additional information in an email dated June 7, 2015 about the preparation of uridine triacetate in milk or infant formula. See additional discussion under Section 12 Labeling.*

## 4. Nonclinical Pharmacology/Toxicology

From a nonclinical standpoint, this product is approvable for indication proposed.

The following information was abstracted from the Pharmacology/Toxicology review.

*CDTL Comment: For additional information, see the complete review in DARRTS dated June 18, 2015 from Sruthi King, PhD.*

The nonclinical safety package for uridine triacetate 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).

In animals, uridine triacetate had a generally favorable safety profile. In repeat-dose toxicology studies in rats (3 months and 6 months) and dogs (3 months), there were no significant, treatment-related toxicities or deaths at up to the 2000 mg/kg/day, which was the maximum feasible dose. The no observed adverse effect level (NOAEL) dose from the 6-month repeat-dose toxicity study in rats was 2000 mg/kg/day, (b) (4)

In *in vitro* studies, uridine triacetate inhibited hERG channel current (IC<sub>50</sub> = 3137 μM) and affected action potential duration (APD<sub>90</sub>) at the doses > 66.3 μM. There was no effect on APD<sub>60</sub> at 9600 μM, which was the highest feasible concentration tested. Furthermore, because uridine triacetate undergoes complete and rapid deacetylation to uridine in the plasma after oral administration, the observed *in vitro* cardiac effects do not warrant concern. This was confirmed in the repeat-dose toxicology studies with uridine triacetate where no adverse cardiac effects were noted (in rats and dogs). Uridine triacetate was not genotoxic in *in vitro* and *in vivo* assays.

*CDTL Comment: As noted below in the Section 5 Clinical Pharmacology, the sponsor was granted a waiver for conducting a Through QT study in humans.*

Carcinogenicity studies were not conducted with uridine triacetate. The sponsor submitted a Carcinogenicity Risk Assessment Document with the NDA to support their request for a waiver on the requirement to conduct a 2-year rodent carcinogenicity study. Therefore, based on review of the submission and consultation with the CDER Executive Carcinogenicity Assessment Committee (ECAC), it is recommended that the sponsor be granted the waiver.

There were no findings suggestive of tumorigenic potential in the 6-month repeat-dose toxicity study in rats. Uridine triacetate did not affect fertility and reproductive ability in rats of either sex and did not produce maternal toxicity (during gestation) or teratogenic effects in developing fetuses at up to 2000 mg/kg/day, which was the highest dose administered. The applicant will conduct a Segment 3 pre- and postnatal development study as a postmarketing study requirement (PMR), per previous agreements with the review division.

*CDTL Comment: In discussions held after this review was finalized, with Abby Jacobs (Associate Director for Pharmacology/Toxicology) it was determined that the sponsor would not be required to do a Segment 3 toxicology study as a PMR, due to the nature of the patient population (rare disease) and the fact that uridine is an endogenous substance.*

## 5. Clinical Pharmacology

The NDA is acceptable from a Clinical Pharmacology perspective.

The following information was abstracted from the Clinical Pharmacology review.

*CDTL Comment: For additional information, see the complete review in DARRTS dated June 5, 2015 from Sandhya Apparaju, PhD.*

### Dose and Dosing Regimen

The proposed dose and dosing regimen are acceptable. The starting dose of the uridine triacetate is approximately one-third 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 pharmacokinetic (PK) data, maintain hematological and pharmacodynamic (PD) endpoints at the patient's baseline (on oral uridine) levels in the patients of the pivotal HOA trial (Protocol 401.13.001). The dosing regimen used in this trial for uridine triacetate was once-daily and the drug will be labeled as such.

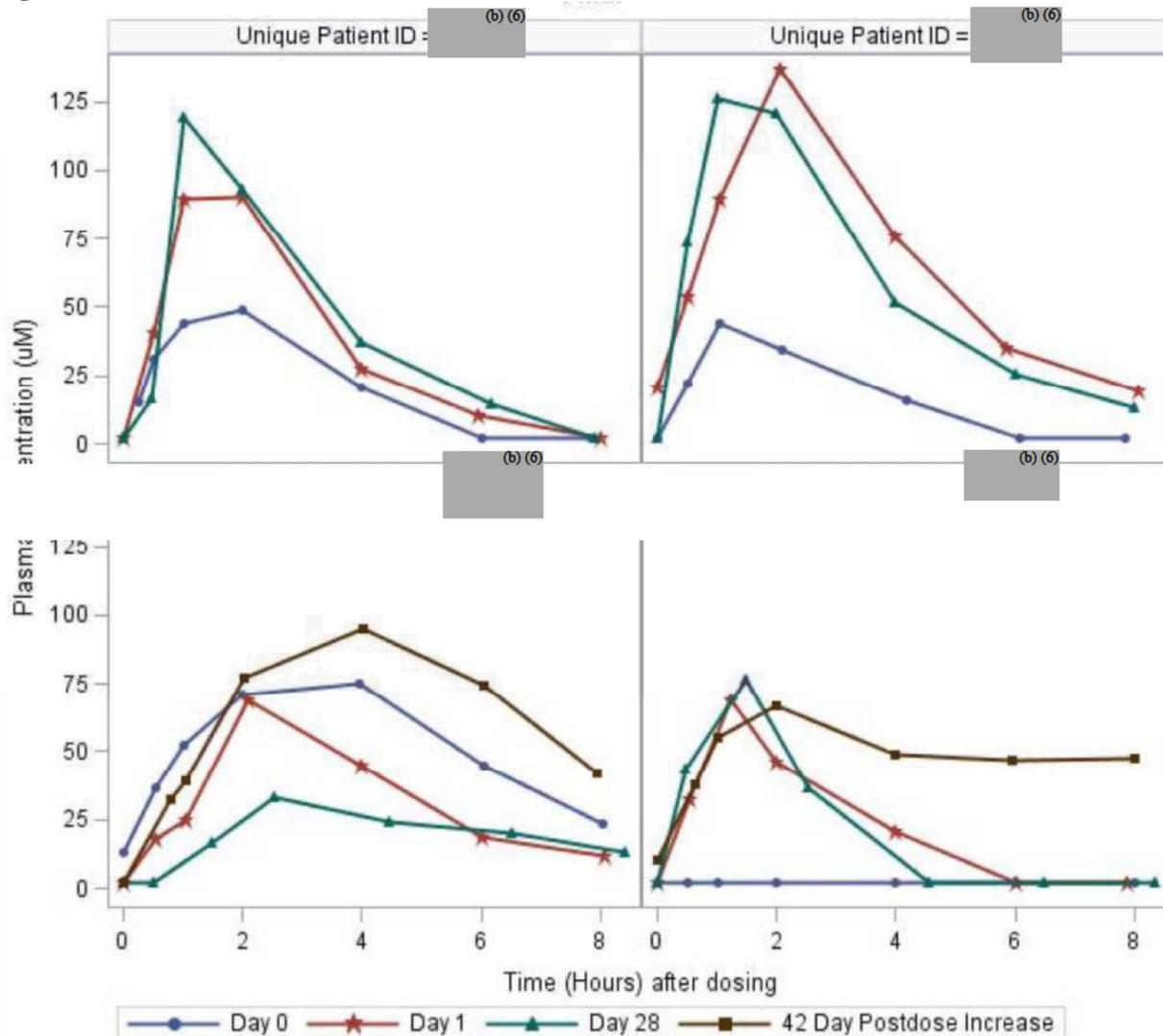
A once-daily dose appears to be adequate. Although the plasma levels decline to baseline by 8 hours after once-daily dosing due to short half-life of approximately 1.5 to 2 hours, uridine that is taken up and trapped intracellularly is primarily responsible for restoring pyrimidine nucleotides and their derivatives, and alleviating disease symptoms.

### Pharmacokinetic Characteristics

Uridine concentrations were measured in the four patients enrolled into the pivotal HOA trial, all of whom received approximately 60 mg/kg once daily during the main study (6 weeks). The starting dose of uridine triacetate was selected to account for higher bioavailability of uridine triacetate compared to uridine, as noted in previous PK studies (PK information from pediatric patients with mitochondrial disease patients). The emphasis was primarily to avoid under-dosing. A dose of 60 mg/kg/day, approximately one-third the daily dose of uridine, was expected to provide systemic uridine concentrations at least comparable to those noted on oral uridine, if not greater.

Plasma uridine was assessed at baseline (day 0) in 3 patients who were receiving oral uridine (150 to approximately 200 mg/kg/day) at study entry. Plasma uridine following oral uridine triacetate was assessed in all four patients on day 1, and on day 28. Additional PK data was obtained from two subjects who received dose escalation to 120 mg/kg/day during the extension phase.

Plasma uridine concentration ( $\mu\text{M}$ )-time profiles are shown for each of the 4 patients in the figures below:



For subject 01-001, Day 0 pre-dose plasma sample drawn 15 mins after subject was dosed with uridine

Source: Clinical Pharmacology Review, June 5, 2015.

Following oral administration of uridine triacetate at 60 mg/kg/day, two patients demonstrated higher plasma uridine exposure (b) (6) compared to their baseline PK on oral uridine at approximately 200 mg/kg/day, while one patient (b) (6) had lower exposure to uridine after uridine triacetate compared to their baseline levels on oral uridine. Inexplicably, the baseline  $\text{AUC}_{0-8}$  hours on uridine therapy was highest in patient (b) (6) (at uridine dose of 150 mg/kg/day), compared to subjects at study site (b) (6) who were receiving a comparable mg/kg/day (200 mg/kg/day) total dose of uridine.

In addition, 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 approximately 60 mg/kg/day, compared to patients in site (b) (6). While this could be due to normal

variability in a small population, other factors such as dosing and sampling errors were considered. Dosing was standardized by the use of digital weighing spoon in all patients. In the treatment-naïve patient (b) (6) the uridine levels fell to baseline sooner, compared to patients who were on uridine therapy, thus resulting in overall lower AUC. The sponsor attributes this to potentially uridine-starved cells taking up uridine more rapidly. Protocol deviations with respect to PK sampling times were noted on day 28 for both subjects at site (b) (6). All PK samples from 1 to 8 hours post-dose were delayed by 30 minutes. PK was calculated using the appropriate time points. The delayed sampling may explain some of the PK differences as the peak may have been underestimated on day 28 in patients (b) (6).

The average relative bioavailability based on AUC<sub>0-8</sub> was 3.6-fold on an equiweight (mg/kg) basis, and 5.5-fold on an equimolar basis. The treatment-naïve patient (b) (6) demonstrated evidence of systemic delivery of uridine from Xuriden. Doubling of the dose during the extension phase in two patients (b) (6) approximately doubled their AUC. Accumulation of uridine was minimal following once-daily administration in individual patients.

Pharmacokinetic parameters are summarized in the table below. Mean exposure to plasma uridine as assessed by C<sub>max</sub> and AUC was greater after oral Xuriden than after oral uridine (approximately 4-fold on an equiweight basis, and 6-fold on an equimolar basis), although individual differences in relative bioavailability were noted. Plasma concentrations of the uridine catabolite uracil were generally below the limit of quantitation in all patients.

(b) (4)

### Assay Methodology

Plasma uridine concentrations were determined using a validated HPLC method. An assay for uridine triacetate (prodrug) was not validated by the sponsor claiming instability of the drug substance in biological fluids. This was based on feasibility studies (60 minute incubations in plasma or whole blood at various temperatures) that suggested rapid degradation of the drug. Although an assay may potentially be developed and validated (for e.g. esterase activity can be inhibited during the development phase e.g. by pre-treatment with sodium fluoride), absence of PK information for the pro-drug and/or documentation of its absence from the systemic circulation as claimed, are not considered deterrents for the review of this drug's potential to provide clinical benefit in this rare, potentially life-threatening disease and its potential to address current drug shortages for oral uridine. For any planned clinical trials, we recommend that the sponsor consider developing an assay to evaluate the systemic concentrations of the prodrug.

### **ADME**

The following is a summary of the ADME characteristics of the drug:

#### Absorption

Following oral administration, uridine triacetate is deacetylated by nonspecific esterases, yielding plasma uridine. The prodrug delivers 4- to 6-fold more uridine into the systemic circulation compared to equimolar doses of uridine itself. This is believed to be due to higher lipophilicity as a result of (b) (4) groups, and lower extent of inactivation of uridine to uracil when administered as a prodrug. Maximum concentrations of uridine in plasma following oral uridine triacetate are generally achieved within 2 to 3 hours, and the half-life ranges from approximately 2 to 2.5 hours.

#### *Food-effect on PK:*

Food did not impact the pharmacokinetics of uridine from a slightly different uridine triacetate granule formulation. While food-effect PK data from the to-be-marketed formulation is not available, at present there is no plan to request a new study in this regard as drug has a wide safety margin and is titrated to effect. In addition both formulations are primarily comprised of active ingredient (> 90 %). Thus Xuriden can be dosed without regard to meals.

#### Distribution

Circulating uridine is taken up into mammalian cells via specific nucleoside transporters, and also crosses the blood brain barrier.

#### Excretion

Uridine can be excreted via the kidneys, but is also metabolized by normal pyrimidine catabolic pathways present in most tissues.

#### Drug-drug Interaction Potential:

*In vitro* data suggests that uridine triacetate or uridine do not inhibit or induce major CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A).

*In vitro* data showed that uridine triacetate was a weak substrate for P-glycoprotein. Due to potential for high local (gut) concentrations of the drug after dosing, interaction of Xuriden with orally administered P-gp substrate drugs cannot be ruled out.

### Specific Populations

No dedicated renal or hepatic impairment PK studies have been conducted.

Due to the limited patient population, it was not possible to evaluate the effects of age/sex/race on the PK of Xuriden.

### **QT Assessment**

During development the sponsor submitted a waiver request for a Through QT study comprised of a multipart rationale why a study with uridine triacetate would not be necessary. The waiver was consulted to the QT Interdisciplinary Review Team (QT-IRT). The QT-IRT agreed with the waiver by stating: *Given the clinical history of uridine, the pharmacology profile of uridine triacetate, and the preclinical cardiac evaluation, we agree with the sponsor that uridine triacetate is unlikely to prolong QT significantly in the targeted population and a TQT seems not needed. (See IND 118931 QT-IRT consult review dated December 17, 2014 in DARRTS).* The sponsor was sent an advice letter that their waiver was granted on December 24, 2014.

### **Pharmacodynamic Characteristics**

Urinary orotic acid (OA) concentrations were assessed in all four patients in Study at baseline, on day 1 (at pre-dose), and at day 28 and day 42 of oral uridine triacetate treatment. The urinary OA concentrations were assayed in (b) (4) genetics laboratory. Orotidine, an OA derivative was also assayed. Urinary OA is an important PD endpoint.

*CDTL Comment: Individual patient' urinary OA levels both pre- and post-treatment in Study 401.13.001 are shown and discussed in Section 7 Efficacy.*

The following figure shows the relationship between urinary OA concentrations and the primary efficacy endpoint (hematologic endpoint of neutrophils) for a representative patient (01-001). For this patient, pre-study data shows a decrease in urinary OA from pretreatment (historic) levels. In addition, this patient demonstrated an increase in UOA during a uridine drug holiday suggesting a correlation between uridine replacement and OA excretion in urine.

At the 120 day safety update (submitted May 11, 2015), patient <sup>(b) (6)</sup> received a dose increase from 60 mg/kg/day to approximately 100 mg/kg/day in an attempt by the investigator to bring the OA levels (3.1 mmol/mol of creatinine) to within normal range (0.3 to 2.8 mmol/mol of creatinine); no additional benefit on OA was noted in this patient with dose increase.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical- Efficacy**

Protocol 401.13.001 entitled “Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria” was developed, discussed, and revised in consultation with the division prior to and following the IND filing. It was an open label study in the 4 known patients in the U.S. diagnosed with HOA, and included collection of safety, pharmacokinetic and efficacy data collected during the 42-day duration of the main study. Three (3) of the 4 patients enrolled had previously demonstrated therapeutic responses to oral uridine administration. Delivery of systemic uridine and pharmacokinetics following oral administration of uridine and uridine triacetate were assessed and demonstration of stable clinical responses following the switch from

oral uridine to oral uridine triacetate was intended to serve as demonstration of efficacy. Following successful completion of the main study, all 4 patients continue to receive uridine triacetate under a protocol treatment extension.

The following specific features of Study 401.13.001 were agreed to by the division during development:

- A single clinical trial is acceptable; protocol will focus on safety and a continuation of response to oral uridine
- The main study was 6 weeks in duration. Patients successfully completing the main study continued to receive the investigational drug under a protocol treatment extension.
- The proposed starting dose for uridine triacetate was 60 mg/kg/day.
- The primary efficacy endpoints in the trial were hematologic and individualized for each patient. Secondary endpoints were based on urinary orotic acid and uridine exposure (PK).
- Demonstration of a “stable response” as assessed by individual hematologic parameters (clinical efficacy endpoints) is acceptable
- For naïve patients, the change in the primary endpoint was compared after treatment with oral uridine triacetate to that at baseline.

The following clinical efficacy information was abstracted from the Clinical and Statistical reviews, where noted.

*CDTL Comment: See complete clinical review by Carla Epps, MD, MPH entered into DARRTS July 2015. See also complete statistical review by Min Min, PhD entered into DARRTS on June 16, 2015.*

#### **Protocol 401.13.001**

This was a 6-week open-label efficacy and safety trial in 4 patients (3 switched from uridine to uridine triacetate and one patient started *de novo* on uridine triacetate) followed by an extension trial (length unspecified). The trial is being conducted at two sites in the United States

(b) (6)

The main trial period was from May 2014 to August 2014; an extension treatment phase is ongoing.

The initial starting dose of uridine triacetate was 60 mg/kg/day for all patients. For patients who were switching from uridine to uridine triacetate, the dose could be escalated up to a maximum dose of 300 mg/kg/day. The dose of uridine triacetate could be given once a day or as equally divided doses twice a day. Patients were instructed to take uridine triacetate granules with or without food. The protocol did not limit what foods could be used for mixing the granules.

#### Primary Endpoint:

For patients switching from oral uridine to oral uridine triacetate, the primary efficacy endpoint was stability of pre-determined hematologic parameters (neutrophil percent, white blood cell count, or mean corpuscular volume) individualized by patient. Stability was defined as:

- Maintenance of a normal baseline value at Days 28 and 42
- Improvement in an abnormal baseline value or worsening no more than 15% to 30% at Days 28 and 42

For patients not previously treated with uridine, stability was defined as improvement in an abnormal baseline value or worsening no more than 15% to 30% at Days 28 and 42.

### Primary Analysis

*CDTL Comment: The statistical reviewer performed the following analyses to assess the primary endpoint:*

#### *Three Patients Switched from Uridine*

The criteria for a stable response in patients previously receiving oral uridine is as follows:

- Assess whether the baseline (Day 0) value is within the laboratory reference range (LRR) expected for that patient.
  - If the value is in the LRR expected for that patient at Day 0 and remains within the LRR expected for that patient at Days 28 and 42, then the response is considered stable.
  - If the value is outside the LRR expected for that patient at Day 0 and improves or the values worsen no more than 15% to 30% when compared to baseline (Day 0) at Day 28 and Day 42, then the responses considered stable.

#### *One Treatment Naïve Patient*

The primary efficacy endpoint is the stability within the LRR or improvement in the patient's principal affected hematologic parameter(s) on Days 28 and 42 compared to baseline (Day 0).

The following table shows the primary efficacy endpoints for each patient along with the rationale for the choice of each variable.

Patient	Primary efficacy variable	Notes
(b) (6)	Neutrophils	Patient (b) (6) had shown increased neutrophil count following institution of uridine treatment and decreased count during a uridine holiday
(b) (6)	White blood cell count	Patient (b) (6) had a 10-year history of stability with uridine treatment. The Principal Investigator noted that early in her history she manifested a low white blood cell count.
(b) (6)	Mean corpuscular volume	Patient (b) (6) has had documented macrocytosis since diagnosis in June 2008. Additionally, the patient had a history of red blood cell counts below current laboratory normal ranges, but with hemoglobin levels within normal range. Treatment with uridine produced stable mean corpuscular volume.
(b) (6)	Mean corpuscular volume	Patient (b) (6) was diagnosed with macrocytosis and began treatment with uridine triacetate during the study with no previous exposure to uridine. This patient also had a history of red blood cell counts below current laboratory normal ranges, but with hemoglobin levels within normal range.

Source: Statistical review dated June 16, 2015 and Sponsor's Table 9-2 of 401-13-001 body.pdf of the NDA

*CDTL Comment: The protocol did not specify whether the primary endpoint for Patient (b) (6) would be based on change in neutrophil percent or neutrophil count. Therefore, the results of both parameters are discussed below.*

Secondary Endpoints:

- Urine orotic acid and orotidine levels
- Plasma uridine levels

Other Endpoints:

During the extension phase of the trial, growth and development assessments will be performed every 6 months.

Clinical Reviewer Comments:

*This reviewer considers the use of patient-specific predetermined hematologic endpoints to be acceptable to evaluate for clinical stability or clinical improvement in patients treated with uridine triacetate who have clinically significant hematologic abnormalities. However, the applicant's definition of clinical stability (any deterioration in value was not more than 15% to 30% worse than the baseline value) for patients with baseline abnormal values is inadequate for identifying clinically significant deterioration in hematologic status. For example, a 15% decline in neutrophil count in a patient with a baseline neutrophil count of 600/mm<sup>3</sup> would not represent a clinically significant decline. However, a 30% decline in neutrophil count in that same patient represents a shift in clinical status from moderate to severe neutropenia. In addition, inpatient day-to-day variability is high for some hematologic indices (neutrophils) and low for other indices (MCV). Published analyses of hematology laboratory values in healthy adults reported about a 20% day-to-day individual variability in neutrophil count, which was attributed to the rapid turnover of*

*neutrophils and sporadic margination of white cells compared to a 2% variability in MCV.<sup>4,5</sup> Therefore, the appropriate margin of change to establish clinical stability should be based on the expected range of inpatient variability for a particular hematologic parameter. As discussed later, based on the aforementioned laboratory references for adults (I did not find similar laboratory reference information for pediatric patients), the trial results for Study 001 indicated that patient hematologic parameters remained clinically stable during the main treatment phase of the trial.*

### Compliance

Treatment compliance was assessed by a dosing log completed by the patient or guardian. The dosing log was reviewed by the physician at each visit. Patient compliance was reported as 100% for all patients through Day 42 of the trial.

### Dose Adjustments

After approximately 4 months of treatment (116 days), uridine triacetate dosing was increased from 60 mg/kg/day to 120 mg/kg/day for Patients (b) (6) and (b) (6), due to persistent elevated MCV values. The applicant noted that uridine exposure increased in both patients following the dose increase.

### **Results**

The table below summarizes patient demographics and clinical disease status prior to administration of uridine triacetate; abnormal values are noted in bold font. Patient ages were (b) (6) years at study. Age at time of diagnosis ranged from 1.5 years to 10.4 years.

- Patient (b) (6) had a low neutrophil percent (21%) and an elevated urine orotic acid level at baseline and growth delay
- Patient (b) (6) had normal hematologic values at baseline.
- Patients (b) (6) and (b) (6) are siblings and had macrocytosis at baseline; however, their baseline hemoglobin and hematocrit values were normal. Patients (b) (6) also had growth delay.

### Clinical Reviewer's Comment:

Of note, all of the patients had a diagnosis of growth delay in their medical record and/or historical growth measures consistent with a growth delay (i.e., height and/or weight <5<sup>th</sup> percentile for sex and age or clinically significant decrease in height or weight velocity) in infancy; two of the patients also had a history of developmental delays.

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<sup>4</sup>Lacher DA, Barletta J, Hughes JP. Biological Variation of Hematology Tests Based on the 1999-2002 National Health and Nutrition Examination Survey, Natl Health Stat Report 2012;54:1-10.

<sup>5</sup> Winkel P, Statland BE, et al., Within-day physiologic variation of leukocyte types in healthy subjects as assayed by two automated leukocyte differential analyzers, Am J Clin Pathol 1981;75(5):693-700.

**Study 001 Baseline Patient Demographics and Disease Severity\***

	Patient			
	(b) (6)	(b) (6)	(b) (6)	(b) (6)
<b>Prior Uridine Dose</b>	200 mg/kg/day	200mg/kg/day	150 mg/kg/day	--
<b>Duration of Uridine Treatment (yrs)</b>	(b) (6)			--
<b>Age at diagnosis (years)</b>	(b) (6)			
<b>Race</b>	(b) (6)			
<b>Patient- specific Endpoint</b>	Neutrophils	WBC count	MCV	MCV
<b>WBC Count</b>	4.5	7.8	6.0	6.8
<b>Neutrophil Percent/ Neutrophil count (x10<sup>9</sup>/L)</b>	21/0.95	57	Not done	Not done
<b>MCV (fL)</b>	83	88.6	109.9	115.4
<b>Orotic acid</b>	2.9	1.8	0.5	2.3
<b>Height – cm (Height percentile for age)</b>	(b) (6)			
<b>Weight- kg (Weight percentile for age)</b>	(b) (6)			
<b>History of Growth Delay/Abnormal Growth</b>	Yes	Yes	Yes	Yes

MCV= mean corpuscular volume

\*Baseline values were obtained on Day 0 (1 day prior to starting uridine triacetate)

Source: Adapted from Table 5, Clinical Review and Table 11-4 in the Sponsor’s Report for Study 401.13.001

Primary Endpoint

The primary efficacy endpoints for Study (b) (6) were stability (for the three patients who had transitioned from uridine) or improvement (for the newly diagnosed patient) of patient-specific hematologic parameters at Week 6 (Day 42). Results for each patient are shown in the table below. Additional information from Month 6 is also included.

	(b) (6)	(b) (6)	(b) (6)	(b) (6)
<b>Patient- specific Endpoint</b>	Neutrophil %/ Neutrophil Count	WBC count (x10 <sup>9</sup> /L)	MCV (fL)	MCV (fL)
<b>Reference Range*</b>	26 to 48/ 1.5 to 8.0	3.8 to 10.6	75.0 to 91.0	72.0 to 90.0
<b>Historical Range</b>	6.7 to 12.8	7.7	106.6 to 109.9	109.8 to 115.4
<b>Baseline</b>	21/0.95	7.8	109.9	114.6
<b>Day 42 (% Δ from baseline)</b>	23/0.81 (9.6)/(-15)	7.4 (- 5.1)	108.5 (-1.3)	113.4 (-1.0)
<b>Month 6 (% Δ from baseline)</b>	31/1.4 (48)/(47)	6.7 (-14)	108 [month 5] (-2)	114.7 [month 5] (0)

\*age specific

Source: Adapted from Table 7, Clinical Review and Table 3.3 in the Statistical Review and Table 11-6 in the Sponsor's Report for Study 401.13.001

#### Clinical Reviewer Comments:

The applicant provided historical data documenting the presence of hematologic abnormalities in three patients prior to initiation of uridine replacement therapy. There were insufficient data to confirm whether Patient (b) (6) had a low white blood cell count prior to initiation of uridine replacement therapy as reported, therefore this patient was not included in my analysis of the primary endpoint.

After 6 weeks (Day 42) of treatment with uridine triacetate, two patients (Patient (b) (6) and Patient (b) (6)) who transitioned from uridine remained clinically stable. Patient (b) (6) whose neutrophil count had increased while being treated with uridine, experienced a 15% decrease in neutrophil count, meeting the protocol-specified definition of clinical stability. Patient (b) (6) also remained clinically stable unchanged after transitioning from uridine, with a change in his mean corpuscular volume (MCV) of -1%. However, it is unclear whether this finding represents a treatment effect because the patient's MCV values during treatment with uridine and uridine triacetate have remained essentially unchanged from MCV values obtained prior to the patient starting uridine replacement therapy.

No improvement in hematologic status was demonstrated in the treatment-naïve patient (b) (6) whose MCV value did not change from baseline to Week 6.

Thus, based on the primary efficacy data alone, there are insufficient data to support efficacy.

*CDTL Comments on Results of Primary Endpoint (Day 42) with Follow-Up Data to 6 Months: As noted by the Clinical Reviewer, the data at Week 6 (Day 42) was only supportive of efficacy in 2 of the 4 patients treated (b) (6)*

*Patient (b) (6) had insufficient baseline documentation of abnormal WBC count and Patient (b) (6) (naïve) did not respond to treatment. However, if the Month 6 data are also considered, then additional efficacy conclusions can be drawn.*

*Patient (b) (6) 10% increase in neutrophil percent and a 15% decrease in neutrophil count at Day 42 [within the pre-specified margin of a 15% to 30% worsening from baseline]. Neutrophil percent increased by 48% to within the normal range by 6 months. Neutrophil count increased by 47% at 6 months. The sponsor noted that the neutrophil percent and absolute neutrophil count (also increased to almost to the normal range) in this patient were the highest level ever documented in this patient. Also, of note, historically, a one month uridine drug holiday (from a dose of 200 mg/kg per day) in 2013 at age 5½ resulted in neutrophil count reduction to approximately pretreatment levels within about two weeks (0.59 k/μL down to 0.39 k/μL). During that time the neutrophil percent remained the same at 13%. The patient's dosage of uridine triacetate was increased to 95 mg/kg/day within days after the Month 6 visit (based upon the Day 42 orotic acid concentrations being just above the upper limit of normal).*

*Patient (b) (6): 5.1% decrease in WBC count [within the pre-specified margin of a 15% to 30% worsening from baseline] at Day 42, value still within the normal range; however, insufficient documentation that the WBC count was ever below the normal range. WBC count decreased from baseline by 14% at 6 months; no dosage adjustment.*

Patient (b) (6): 1.3% decrease in MCV [within the pre-specified margin of a 15% to 30% worsening from baseline] at Day 42; above the normal range. Dosage of uridine triacetate increased to 120 mg/kg/day after approximately 4 months; MCV value decreased by 2% from baseline at 5 months.

Patient (b) (6): 1.1% decrease in MCV [within the pre-specified margin of a 15% to 30% worsening from baseline] at Day 42; above the normal range. Dosage of uridine triacetate increased to 120 mg/kg/day after approximately 4 months; MCV value essentially the same at 5 months as at baseline.

The trial results indicate that hematologic stability was maintained in two of the three patients that switched from uridine to uridine triacetate (the third patient was unevaluable due to lack of historical documentation). No improvement in hematologic status was demonstrated in the only treatment-naïve patient.

#### Clinical Reviewer Comments:

The clinical experience of Patient (b) (6) provides the most compelling evidence for efficacy on hematologic parameter. Note that this patient had severe neutropenia (neutrophil count <500) prior to starting on uridine replacement therapy. His neutropenia improved with treatment, evidenced by a neutrophil count of 950 at baseline. Most significantly, his neutrophil count increased by to 1400 (47% increase; normal range 1500-8000) at Month 6. The applicant noted that the Month 6 neutrophil count was the highest ever observed for this patient. ..

...It is also difficult to interpret findings for Patients (b) (6), since the MCV values for these patients appear to have been stable prior to initiation of uridine replacement therapy. In addition, the MCV values for Patient (b) (6) had not improved after almost four years of treatment with uridine at 150 mg/kg/day. This reviewer notes that dosing and duration of treatment needed to observe a treatment response on hematologic parameters is variable. Some patients in published case studies experienced clinically significant improvement of hematologic parameters within two or three weeks of treatment with uridine. However, other patients did not improve until their uridine dose was increased and/or until they had been treated for several months. Case studies also illustrate that the dosing needed to achieve a hematologic response may differ from the dose needed for growth. Thus, Patient (b) (6) may not have had a hematologic response to uridine due to underdosing (note that he was being treated a uridine dose of 150 mg/kg/day whereas Patients (b) (6) received doses of 200 mg/kg/day). Similarly, the lower exposures observed in the (b) (6) compared to the patients at the other clinical site during the main treatment phase of the trial suggest that the initial uridine triacetate dosing for the siblings may not have been adequate. In addition, the 8-week period from Month 4 when their uridine triacetate doses were increased to Month 6 may not have been long enough to observe for a treatment effect on MCV parameters.

To further assess uridine triacetate's effect on either stabilizing or improving patients' percent neutrophils, WBC count and MCV, the statistical reviewer produced patient profile graphs (Figures 3.1-3.4) to illustrate the patients' progress over time including pretreatment, during treatment under the main study and extension period. The observations are summarized as follows.

#### Main study

1) Patient (b) (6): the baseline measurement of WBC count was within the LRR and both Day 28 and 42 WBC counts remained in the LRR (3.9 to 10.6);

2) Patients (b) (6): their baseline measurements of Neutrophils% and MCV, respectively were outside the LRRs (26% to 48% and 72 to 91), the changes from baseline in Day 28 and 42 were no more than 30%;

3) Patient (b) (6) is a naïve patient, the baseline measurement of MCV was outside LRR (72 to 91), the changes from baseline in Day 28 and 42 stayed within 1%. But in Figures 5.1 and 5.2, the baseline measurements for Neutrophils% and WBC count were within the LRR, the changes from baseline in Day 28 and 42 stayed in the LRR.

Extension trial

- 1) For Patient (b) (6) the Neutrophils% increased to 31% which is in the LRR.
- 2) For Patient (b) (6) the WBC count stayed in the LRR.
- 3) For Patient (b) (6) and (b) (6), MCV stayed almost the same as those measurements in the main study.

*CDTL Comment: The statistical review contains individual patient profiles created by the reviewer, which are not reproduced here.*

Secondary Endpoints

Plasma uridine concentrations were assessed as a secondary endpoint. The results were previously discussed in this review in Section 5 Clinical Pharmacology/Biopharmaceutics.

Urine orotic acid (OA) and orotidine concentrations were assessed as pharmacodynamic endpoints. The table below shows the results of OA concentrations during the study in relation to each patient’s baseline value. As there were no orotidine historical data on these patients, the data are not presented here (see Clinical Review).

**Urinary Orotic Acid Concentration (Reference Range 0.3 to 2.8 mmol/mol of creatinine)**

	(b) (6)	(b) (6)	(b) (6)	(b) (6)
<b>Historical Range</b>	21.7 to 125.0	116. to 17.6	1.4 to 9.5	0.1 to 19.3
<b>Baseline</b>	2.9	1.8	0.5	1.0
<b>Day 42</b>	3.1	2.0	0.3	0.5
<b>Month 6</b>	6.9	2.0	0.4	0.7
<b>Month 11 (unscheduled)</b>	3.2	--	--	--

Source: Adapted from Table 8, Clinical Review

In summary:

Patient 01-001: OA concentration slightly elevated at baseline, continued to have a slightly elevated concentration at Day 42 (3.1 mmol/mol of creatinine). The OA concentration from the Month 6 visit was reported to the clinical site approximately 10 days after the visit. In the meantime, the investigator chose to increase the dose of uridine triacetate from 56 mg/kg/day to 95.5 mg/kg/day based upon the Day 42 result. The urine sample for OA concentration analysis was not sent to the protocol-specified laboratory for biomarker assessments (b) (4). No additional dose adjustments were made. As a result, orotidine concentration was not assessed and the OA concentration was reported as 6.9 mmol/mol. At Month 11, an unscheduled assessment of OA and orotidine concentrations at the protocol-specified laboratory revealed

similar results to the patient's baseline and Week 6 values, still slightly above the reference range (3.2 mmol/mol for OA).

Of note, prior to the study, Patient (b) (6) experienced an increase in orotic acid concentrations while on a drug holiday from uridine (9.6 mol/mol); the OA concentrations returned to the pre-drug holiday range when treatment was restarted (2.9 mol/mol, which was also used as the patient's baseline value for (b) (6).

The other patients (b) (6) had normal values at baseline and remained normal at Day 42 through Month 6.

#### Clinical Reviewer Comments:

There is a clear pharmacodynamic response in patients treated with uridine replacement therapy. Three of the four patients achieved normal urine orotic acid levels when they were treated with uridine and maintained normal levels when they were transitioned to uridine triacetate. Patient (b) (6) who had the highest urine orotic acid level prior to starting uridine replacement therapy, achieved near normal levels on uridine and these levels remained stable after transitioning to uridine triacetate.

To further assess the secondary endpoint of OA levels, the statistical reviewer produced bar graphs to examine patients' stability over time (see Figures 5.4-5.7).

*CDTL Comment: The statistical review contains individual patient bar graphs created by the reviewer, which are not reproduced here.*

#### Urinary Orotic Acid Concentrations

The sponsor provided the following rationale as to why reduction or suppression of the elevated urinary orotic acid may be a primary direct pharmacodynamic indicator for uridine replacement therapy in HOA:

The blockade in orotate conversion to UMP by UMPS results in excretion of unutilized orotic acid, as it has no other significant metabolic fate. Orotic acid biosynthesis is regulated by intracellular nucleotide levels,<sup>6</sup> which cause feedback inhibition of the first step in de novo uridine nucleotide synthesis catalyzed by carbamoyl phosphate synthase 2 (CPS2), so that whole-body daily orotic acid synthesis in normal subjects does not generally exceed daily pyrimidine turnover needs. In HOA, impaired de novo synthesis and consequent low intracellular uridine nucleotides result in overproduction of orotic acid, not merely non-utilization and excretion of normal amounts. In vitro, when steady-state extracellular uridine concentrations exceed about 12  $\mu$ M, the exogenous uridine was sufficient to fulfill cellular needs, and de novo synthesis was suppressed by feedback inhibition up to 95%.<sup>7</sup>

Urinary orotic acid is promptly increased after initiation of an infusion of 6-azauridine, an inhibitor of UMPS that causes uridine-reversible orotic aciduria and anemia,<sup>8,9</sup> and promptly returns to low baseline

<sup>6</sup> Smith LH, Jr. Pyrimidine metabolism in man. *New England Journal of Medicine* 1973;288:764-71.

<sup>7</sup> Karle JM, Anderson LW, Cysyk RL. Effect of plasma concentrations of uridine on pyrimidine biosynthesis in cultured L1210 cells. *Journal of Biological Chemistry* 1984;61:1224-30.

<sup>8</sup> Cornell RC, Milstein HG, Fox RM, et al. Anemia of azaribine in the treatment of psoriasis. *Archives of Dermatology* 1976;112:1717-23.

<sup>9</sup> Fallon HJ, Frei E, 3rd, Block J, et al. The uricosuria and orotic aciduria induced by 6-azauridine. *The Journal of Clinical Investigation* 1961;40:1906-14.

levels within a day after cessation of infusion. This indicates that urinary orotic acid can rapidly reflect changes in intracellular nucleotide concentrations due to blockade of de novo synthesis at the level of UMPS.

Uridine replacement therapy has been reported to result in significant reductions of orotic acid excretion in virtually all treated HOA patients. In the four patients in Study 401.13.001, three of whom were receiving their previous uridine supplementation as a single daily dose, oral uridine generally reduced their elevated urinary orotic acid into or near the normal reference range. Switching to uridine triacetate at 60 mg/kg once per day maintained low urinary orotate/creatinine ratios.

#### *Urinary Orotic Acid Assay Method*

Urinary orotic acid concentrations in the clinical trial were analyzed at [REDACTED] (b) (4), a CLIA- and CAP-certified laboratory, using electrospray tandem mass spectrometry. The division requested assay records, including data on controls, QC samples, standard curves, etc. which were provided by the sponsor.

Normal reference ranges for urinary orotic acid are posted by a number CLIA- and CAP certified testing laboratories and published in the literature.

The sponsor's anticipation is that, in practice, urine samples will be sent to one of a number of CLIA-CAP certified laboratories for assessment of urinary orotic acid. Given the goals of treatment in HOA patients and the similarity of the specified normal reference ranges at the CLIA-CAP certified labs, they do not anticipate that only [REDACTED] (b) (4) could be used for analysis.

*CDTL Comment: The sponsor requested the original validation report from [REDACTED] (b) (4) and agreed to submit it for review when received.*

#### Other Endpoints – Growth

All patients had a history of poor height and/or weight gain prior to starting uridine replacement therapy.

The treatment effect of uridine triacetate on growth was assessed in the three pediatric patients (Patients 01-001, 02-001, and 02-002). At baseline, weight and height measurements were at or below the lower limit of normal for age (<5th percentile for age) for Patients 01-001 and 02-002; height and weight measurements were within the normal range for age for Patient 02-001. After 6 months of treatment, Patients 01-001 and 02-001 experienced improved weight growth, as reflected in increases in their weight-for-age percentiles and weight velocity percentiles. The weight growth remained stable (i.e., weight percentile for age and weight velocity percentile for age was unchanged) for Patient 02-002. Height growth remained stable in all three patients (i.e., height percentiles for age and height velocity percentiles for age were unchanged).

*CDTL Comment: See Table 9 and Figures 4 through 7 in the Clinical Review for a depiction of growth parameters over time, including height and weight Z-scores and a discussion of the methods and sources for reference ranges.*

**Clinical Reviewer's Comments:**

The negative findings in Patient 02-002 for a treatment effect on growth may be due to underdosing. As noted earlier, the patient's uridine triacetate dose was doubled at about Month 4 of treatment. Thus, the patient would not have been treated long enough at the higher dose to evaluate for a change in response.

**Efficacy in Subpopulations of Age/Sex/Race**

There were insufficient patients in the study to perform any subpopulation analyses.

**Literature Review of Oral Uridine for the Treatment of HOA**

Nineteen (19) cases reports of patients with HOA have been documented in published literature. Eighteen (18) were diagnosed as infants or children between the ages of 2 months and 12 years, and one was diagnosed at age 28.

*CDTL Comment: The following summary of the time course of hematologic response to uridine and relapse after discontinuation of uridine in HOA patients was requested by the review team and provided by the sponsor in an addendum to the NDA on April 10, 2015.*

All 19 patients presented with significantly elevated concentrations of urinary OA. Episodes of obstructive uropathy due to crystalluria were reported in most of these patients prior to treatment. Fifteen of 19 had abnormal hematologic parameters at presentation, including 15 with megaloblastic anemia, 8 with leukopenia and at least 2 with neutropenia. Failure to thrive was reported in 12 of the 19 patients and developmental delays were also documented in 12 of the patients (7 had both failure to thrive and developmental delays; 5 other patients had only failure to thrive at the time of diagnosis, and 5 others had developmental delays without concurrent failure to thrive). Many of these 19 patients presented with additional abnormalities including congenital malformations, seizures, cerebral palsy, and reduced immune function.

- Administration of 50 to 300 mg/kg/day (mostly 150 to 200 mg/kg/day) oral uridine was reported to significantly improve hematologic abnormalities (megaloblastic anemia) within 2 to 3 weeks in almost all documented cases when patients received sufficient amounts of exogenous uridine.
- Other hematologic problems in HOA patients, such as leukopenia and neutropenia or defective cell-mediated immune deficiency responded more slowly than anemia after initiation of uridine therapy.<sup>10</sup> Doses of uridine administered to these patients may have been insufficient, as some patients displayed resolution of anemia at a particular uridine dose (for example, 100 mg/kg), but required higher doses (150 mg/kg) to reverse or prevent leukopenia.<sup>11</sup>
- Concentrations of urinary orotic acid were significantly reduced within 1 to 2 weeks of initiating uridine replacement therapy. Some fluctuation in levels of urinary orotic acid were observed, but always at much lower levels than those reported prior to treatment.

<sup>10</sup> Girot R, Hamet M, Perignon JL, et al. Cellular immune deficiency in two siblings with hereditary orotic aciduria. *New England Journal of Medicine* 1983;308:700-4.

<sup>11</sup> Tubergen DG, Krooth RS and Heyn RM. Hereditary orotic aciduria with normal growth and development. *American Journal of Diseases of Children* 1969;118:864-70.

- Instances of obstructive uropathy or hematuria due to crystalluria appear to have been correspondingly reduced.
- Improvements in body weight and other developmental parameters were also documented over time with continued uridine replacement therapy.

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 increases). Within days up to 2 or 3 weeks, most hematologic abnormalities and orotic aciduria reappeared when administration of uridine was stopped or doses reduced. If treatment was interrupted for longer periods, body weight and other gains receded. If absolute dosages were not adjusted adequately to compensate for body weight gains, signs and symptoms of HOA recurred.

*CDTL Comment: See also Table 10 in the Clinical Review for a summary of the published cases including age, presenting features, dosage regimen, and treatment response.*

### **Conclusions on the Substantial Evidence of Effectiveness**

The following is a summary from the Clinical Review of the evidence to support effectiveness of uridine triacetate for the treatment of HOA. The conclusions are based on the published case studies of 18 patients with HOA treated empirically with other unapproved uridine formulations and clinical review findings for four patients enrolled in the single pivotal trial (Study 401.13.001, referred to as Study 001).

- The trial design for Study 001 meets the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126.
- The design provides a reasonable assessment of treatment benefit in patients being switched from uridine to uridine triacetate because interruption or withdrawal of adequate uridine replacement therapy in patients with baseline abnormalities in hematologic parameters is known to result in worsening status within several weeks.<sup>12</sup> Thus, the six-week study duration should be sufficient to evaluate for clinical stability in patients who were previously treated with uridine.
- The use of hematologic endpoints is also adequate to assess treatment benefit in treatment-naïve patients because spontaneous normalization of the pre-specified hematological endpoint (s) is not expected to occur based on the known natural history of the disease.
- The endpoints were patient-specific, based on the individual patient's history of hematologic abnormalities. Thus, the intent of the trial was to establish that patients treated with uridine triacetate would receive the same clinical benefit expected from treatment with uridine (i.e., sustained clinical benefit in patients switched from uridine and improvement in clinical status in treatment-naïve patients). Although all three patients who transitioned from uridine maintained stable hematologic parameters after 6 weeks of treatment, based on the prior evidence (or lack thereof) of a hematologic response with uridine, only the neutropenic patient can be considered to have demonstrated sustained clinical benefit. No improvement in hematologic status was observed in the treatment-naïve patient.
- Therefore, based on the primary efficacy findings for Study 001 alone, there is not sufficient evidence to support efficacy for uridine triacetate.

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<sup>12</sup> Webster DR, Becroft DM et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, Scriver's Online Metabolic & Molecular Bases of Inherited Disease 2001, Chapter 113: 1-86.

- The duration of the main treatment portion of the trial may not have been sufficient to evaluate for *improvement* in hematologic parameters. Although the majority of case studies report improvement in hematologic parameters within the first few weeks of treatment, some patients required dose increases and/or treatment for several months before clinically significant changes in hematologic parameters were observed.
- Clinical data from the extension phase of the trial lend further support of efficacy. Two patients who were transitioned from uridine demonstrated clear improvement in clinical status after 6 months of treatment with uridine triacetate. The neutropenic patient achieved a neutrophil count that was just below the lower limits of normal- his highest recorded neutrophil count. He also experienced clinically significant increases in weight (as measured by weight and weight velocity z-scores) and height (as measured by height and height velocity z-scores). The second transition patient also experienced improved weight growth (weight and weight velocity z-scores improved); the third transition patient was an adult and therefore was not included in growth analyses. No clinical improvement was observed in the treatment-naïve patient's growth parameters.
- The clinical experience of the three patients who were treated with uridine prior to enrolling in Study 001 is consistent with findings in the published literature.
- Published literature for 18 patients with HOA documented improvement or normalization of hematologic, growth and orotic acid levels with uridine replacement therapy. Reductions in orotic acid levels were typically observed within the first week of treatment. The time to treatment response in patients with anemia varied from less than 2 weeks to several months. A similar variability in time to response was observed for white cell abnormalities. Growth delays, most commonly poor weight gain, improved over a span of several months. The majority of patients received the same dose throughout treatment; some patients required a dose increase to achieve their optimal response.
- The totality of evidence indicates that patients receiving adequate doses of a replacement source of uridine (the active metabolite of uridine triacetate) experience clinically meaningful improvement in key disease manifestations, including hematologic status and growth.
- 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.
- I recommend approval action for uridine triacetate for treatment of hereditary orotic aciduria" (HOA).

The Statistical Review does not comment on whether the evidence supports efficacy of uridine triacetate, but does state that the statistical reviewer confirmed the sponsor's efficacy findings.

*CDTL Comment: I agree with the Clinical Reviewer's conclusions as outlined above. Study 401.13.001 had a clear statement of the objectives and the proposed methods of analysis as reported in the study report were agreed upon with the sponsor during pre-submission meetings.*

*The study was non-randomized and designed without a concurrent control. The patients served as their own control. The primary and secondary endpoints reported (hematologic parameters, urinary OA concentrations) are objective and reliable. The urinary OA concentrations were analyzed in a certified laboratory using an assay validated in that laboratory. These endpoints are laboratory parameters and not considered to be clinical endpoints of how a patient feels, functions, or survives, but during pre-submission discussions with the sponsor, it was determined that demonstration of a "stable response" in patient-specific hematologic parameters would be considered as clinical efficacy endpoints to support approval.*

*While the results of Study 001 at Day 42 (Week 6) supported the efficacy in 2 of the 4 patients (clinical stability in the primary endpoint parameter for the 2 of the 3 patients switched from uridine; one patient was unevaluable, and there was no improvement in the treatment naïve patient), this information was not considered sufficient and additional information on parameters used as both the primary and secondary endpoints of the trial collected during the extension phase (Month 6 and beyond) was required to establish the efficacy of uridine triacetate in all 4 patients. The data on secondary endpoint of urinary orotic acid concentrations at Week 6 being within (or close to) the normal range for all 4 patients was used as supportive efficacy data (evidence of a pharmacodynamics response). Data on growth at 6 months was also used as supportive evidence of efficacy in the 3 pediatric patients: both of the pediatric switch patients improved weight growth and the naïve patient remained stable; height growth remained stable in all three patients/*

*Also, 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 to treatment 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 efficacy 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 (hematologic response and pharmacodynamics response in urinary orotic acid concentrations) is thought to have been adequately characterized during the duration of the trial, such that the results may be generalizable to future patients diagnosed with HOA and treated with uridine triacetate. However, the trial may have been of insufficient duration to fully capture and effect on growth parameters and in patients who are treatment naïve and not switched from uridine. Therefore, the sponsor will be asked to conduct a postmarketing commitment (PMC) to continue to evaluate the long-term efficacy and safety of uridine triacetate in patients currently enrolled in Study 001 every 6 months for a total duration of 2 years. The report should include data on growth, hematologic indices, and urine biomarkers (orotic acid and orotidine). Growth data should include height, weight, height velocity and weight velocity. Information should also be collected on any dose adjustments, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments. See Section 13 Postmarketing Recommendations.*

## 8. Safety

In addition to the 4 patients treated for HOA (with doses up to 120 mg/kg/day for 6 months) in Study 401.13.001, uridine triacetate has been administered orally to 565 healthy subjects and patients and for various indications:

### Safety Database

(b) (4)

### IND 39571

- Single doses of 6 grams [46 healthy subjects]
- Patients at risk of excess 5-fluorouracil (5-FU) toxicity due to overdosage or impaired elimination (adults: 10 grams every 6 hours for 20 doses; children 6.2 grams/m<sup>2</sup> every 6 hours for 20 doses) [N=142 adults and 6 children]
- Use of high-dose 5-FU enabled by uridine triacetate (9.9 grams every 6 hours for 10 doses) [N=288]

The following is a summary of the safety data in healthy subjects, HOA, diabetic neuropathy patients, and mitochondrial and metabolic disorders populations. Safety data from cancer patients is not included in this summary.<sup>13</sup>

#### **Study 401.13.001 – HOA Patients**

There were no treatment-related adverse events reported in the 4 patients with HOA enrolled in this study; two patients experienced mild adverse events that were unrelated to treatment (sunburn and elevated baseline alkaline phosphatase level).

#### **Deaths**

No deaths occurred within the healthy subjects, HOA, or diabetic neuropathy populations. Several patients in the compassionate use program died due to disease progression.

#### **Serious Adverse Events**

There have been no serious adverse events (SAEs) considered related to uridine triacetate in any clinical study.

The following SAEs were reported in studies of diabetic neuropathy. All were deemed by the investigator to be unlikely related to study medication: cerebrovascular accident, osteomyelitis R great toe, second degree burn R calf, GI bleed, viral infection, viral symptoms/dehydration, fainting, and myocardial infarct.

#### **Common, Non-Serious Adverse Events**

Gastrointestinal adverse events (AEs) of mild to occasionally moderate nausea and vomiting and episodes of headache were reported in studies with healthy volunteers (single doses of 6 g of uridine triacetate). Mild to moderate gastrointestinal AEs (diarrhea, flatulence, nausea) were reported in studies with patients who had diabetic neuropathies (4 or 8 g/day of uridine triacetate for 6 to 12 months). Early tablet formulations used in the diabetic neuropathy studies contained (b) (4), a known gastrointestinal irritant. The gastrointestinal effects were

<sup>13</sup> The sponsor (Wellstat) intends to file NDA (b) (4) in support of a separate indication of uridine triacetate “as an antidote to treat patients at risk of excess 5-FU toxicity”. (b) (4)

considered to be due primarily to the presence of the excipient (b) (4) in the tablet formulation. Other adverse events reported were those typically observed in an advanced diabetic population.

(b) (4)

### Long-Term Safety

Patients taking uridine or uridine triacetate for many years have tolerated the drug and reported no chronic or recurring adverse events. While long-term treatment effects of uridine triacetate have been evaluated in a limited number of patients, there has been no indication of the emergence of new adverse drug responses with long-term exposure.

### Literature Review of Safety of Uridine

Two HOA patients died after withdrawal from uridine replacement therapy. Both died of infection within about one month after discontinuing treatment.<sup>14,15</sup>

Diarrhea and abdominal cramping were described as adverse event in 6 healthy volunteers and 2 patients with metastatic colorectal cancer (in good general health) treated with a single dose of up to 8 grams/m<sup>2</sup> per dose of oral uridine (prepared as a 20% solution in water by the hospital pharmacy).<sup>16</sup> Another 6 patients with metastatic colorectal cancer (in good general health) received multiple dosing with uridine every 6 hours for 12 doses. 2 patients received doses of 5 grams/m<sup>2</sup>; 1 received 8 grams/m<sup>2</sup> for all 12 doses, however, 2 patients started at 8 grams/m<sup>2</sup> and 2 patients started at 10 grams/m<sup>2</sup> required a dosage reduction to 5 grams/m<sup>2</sup> due to development of diarrhea that subsided upon administration of a lower dose.

### Safety in Subpopulations Based on Age/Sex/Race

There were insufficient patients in the safety database to perform any subpopulation analyses.

### Conclusions on Safety

The following is a safety summary from the Clinical Review:

The safety profile of uridine triacetate has been evaluated in HOA patients and other patient populations. No treatment-related adverse events were reported for the pivotal trial. Diarrhea has been reported in patients administered high doses of uridine triacetate (>4 grams/day).

*CDTL Comment: 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*

<sup>14</sup> Huguley CM, Jr., Bain JA, Rivers SL, et al. Refractory megaloblastic anemia associated with excretion of orotic acid. *Blood* 1959;14:615-34.

<sup>15</sup> Fox RM, Wood MH, Royse-Smith D, et al. Hereditary orotic aciduria: types I and II. *The American Journal of Medicine* 1973;55:791-8.

<sup>16</sup> van Groeningen CJ, Peters GJ, Nadal JC, et al. Clinical and pharmacologic study of orally administered uridine. *Journal of the National Cancer Institute* 1991;83:437-41.

((b) (4)) compared to the to-be-marketed granule formulation (>95% active ingredient).

## 9. Advisory Committee Meeting

No advisory committee meeting was held.

## 10. Pediatrics

Uridine triacetate for hereditary orotic aciduria has been granted orphan drug designation and is exempt from the requirements of the Pediatric Research Equity Act (PREA).

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.

A Rare Pediatric Disease Priority Review Voucher eligibility checklist was completed by the Office of New Drugs, Rare Diseases Program indicating the product met the requirements for the voucher.

*CDTL Comment: See document in DARRTS dated May 6, 2015 from Larry Bauer.*

## 11. Other Relevant Regulatory Issues

### Application Type

The application for uridine triacetate was submitted by the sponsor as a 505(b)(1) application. During the review process it was determined that the efficacy of uridine in the treatment of HOA, as described in the published literature, was necessary to support the efficacy of uridine triacetate (see Section 7 Clinical/Statistical-Efficacy). The sponsor was informed and a revised Form 356h was received on May 22, 2015 indicating a 505(b)(2) application.

### Clinical Inspection Summary

Uridine triacetate is a new molecular entity (NME); therefore a clinical inspection was requested by the division of the Office of Scientific Investigations (OSI). The sponsor and both clinical sites that participated in the clinical trial (Protocol 4 01.13.001 “Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria”) and the sponsor were inspected with the following results:

Type of Inspected Entity, Name and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*

Type of Inspected Entity, Name and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*
(b) (6)	Protocol 4 01.13.001 (b) (6)	(b) (6)	VAI
	Protocol 4 01.13.001 (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.

OSI concluded study appears to have been conducted adequately, and the data generated by the study appear acceptable in support of the respective indication. Data from both clinical sites appeared reliable and the sponsor appeared to have adequately fulfilled their responsibilities. Although violations were cited during inspection of the two clinical sites, these violations were considered minor.

*CDTL Comment: See complete document in DARRTS dated May 8, 2015 from Susan Leibenhaut, MD. Of note at the time the document was written, the inspection of the sponsor had a preliminary classification of NAI. An addendum will be written by Dr. Leibenhaut if the conclusions change upon review of the final Establishment Inspection Report (EIR).*

**Division of Pediatric and Maternal Health Consult**

The Maternal Health (MH) team was asked to review and provide labeling recommendations for Pregnancy (Section 8.1) and Lactation (Section 8.2) for Xuriden.<sup>17</sup> Upon review of the available nonclinical and clinical data, the MH review concluded:

- 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 following is a discussion of the data used to support the above conclusions abstracted from the MH consult review.

<sup>17</sup> Under the Pregnancy and Lactation Labeling Rule (PLLR) format.

*CDTL Comment: See complete document in DARRTS dated May 8, 2015 from Carol Kasten, MD.*

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 maximum recommended human dose (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.

*CDTL Comment: Specific recommendations for language to include in Pregnancy (Section 8.1) and Lactation (Section 8.2) for Xuriden were incorporated into labeling. See Section 12 Labeling.*

## 12. Labeling

### Prescribing Information

#### Highlights

Established Pharmacologic Class (EPC): The sponsor proposed "uridine replacement (b) (4) "as the FDA EPC text phrase. The Pharmacology/Toxicology team recommended "nucleoside analog" to which the sponsor objected, as it is the EPC for various antimetabolites and anticancer drug products. The Pharmacology/Toxicology team, along with Paul Brown, proposed "pyrimidine analog" instead, which is a new EPC and would be unique to this product. In a preliminary response to the Late Cycle Meeting (LCM) package (sent by email on July 6, 2015), the sponsor also objected to "pyrimidine analog" because they felt it was just as misleading as nucleoside analog due to the fact that referred to by this nomenclature by the WHO and NIH are all anticancer agents. The sponsor requested that the EPC contain words describing the physiological function of the drug, and not just the structure, such as "pyrimidine analog for uridine replacement." The Pharmacology/Toxicology review team consulted further with Paul Brown, after the LCM and agreed "pyrimidine analog for uridine replacement" is acceptable as the EPC text phrase.

#### Full Prescribing Information

*Indications and Usage:* The proposed indication (a uridine replacement [REDACTED] indicated [REDACTED] for the treatment of hereditary orotic aciduria) was abbreviated [REDACTED]. The final indication is:

XURIDEN™ is indicated for the treatment of hereditary orotic aciduria.

*Dosage and Administration*

[REDACTED]

*Maximum Dose by Body Weight*

[REDACTED]

The sponsor also provided the following information on conversion between uridine doses used in the literature, and uridine triacetate:

(b) (4)

*CDTL Comment: The maximum dose studied in the clinical trial of HOA patients (Study 001) was 120 mg/kg per day.* (b) (4)

*If patients in Study 001 are escalated to doses higher than 120 mg/kg during the follow-up period, future consideration can be given to revising the maximum dosage in labeling upon submission of that additional clinical efficacy data.*

#### Maximum Absolute Dose in Grams

The sponsor was also asked to cap the dose for patients above a certain weight category in the tables. They agreed that a maximum daily dose of 8 grams should not be exceeded, regardless of patient weight. The sponsor noted that there is no known safety issue with administration of high doses of uridine triacetate. (b) (4)

Patients receiving uridine triacetate for other indication have received higher doses:

- Patients overexposed to the chemotherapy 5-fluorouracil receive (b) (4) for 5 days as an antidote to 5-FU.
- Patients with mitochondrial diseases and/or “uridine responsive neurological syndrome” treated under compassionate use have received up to 300 mg/kg per day for more than 15 years. Four of these patients (formerly pediatric) take a total daily dose of 12.4, 18.6, 18.6 and 26 grams per day. An additional 7 patients with mitochondrial cytopathy each receive between 5 and 12 grams per day. However, the sponsor notes that the purpose of administering uridine triacetate to these patients is not uridine replacement therapy for a deficiency state as it is in HOA patients.

In an HOA patient weighing 73 kilograms this dose, a maximum absolute daily dose of 8 grams of uridine triacetate would be equivalent to a dosage of approximately 110 mg/kg per day. The rationale for this maximum daily dose is based upon:

- The goal of delivering to HOA patients at least as much systemic uridine as a person without HOA would normally make each day. Normal, healthy adults synthesize approximately 5 millimoles of uridine equivalents (or 1.25 grams uridine) per day.<sup>18</sup> A

<sup>18</sup> Weissman SM, Eisen AZ, Fallon H, et al. The metabolism of ringlabeled orotic acid in man. The Journal of Clinical Investigation 1962;41:1546-52.

dosage of 60 mg/kg to 120 mg/kg per day uridine triacetate in HOA patients provided this necessary amount of systemic uridine.

- The apparent benefit of oral uridine and uridine triacetate observed in HOA patients at comparable dosages and exposures;
- The PK profiles in HOA patients treated with 60 to 120 mg/kg uridine triacetate; and
- The PK profiles observed in adults following a single 6 gram dose of uridine triacetate

#### Measuring the Dose -- Digital Dosing Spoon vs. Graduated Teaspoon

In the clinical trial, a digital spoon scale was used by patients/caregivers. During the site initiation visits and subsequently, the sponsor communicated to the sites that doses should be rounded up to the nearest 0.1 grams. A digital spoon (model no longer commercially available) was provided to the clinical sites by the sponsor for patient use.

The sponsor provided standardized weighing instructions for uridine triacetate to the two clinical study sites and the document (“Digital Weighing Spoon Instructions”) was included in the NDA submission. These instructions were provided to the patients/caretakers for this study to help them weigh accurate doses each time, including step-by-step instructions for use of the digital weighing spoon provided for each patient.

The proper use of the weighing spoon was demonstrated to all site staff (pharmacists, study coordinator and Principal Investigator) during each Initiation Visit, including a review of the “Patient Treatment Instructions for Use of Uridine Triacetate” (included in the NDA submission) and the above weighing instructions so they could train patients/caregivers in the standardized procedures for weighing and administering each dose of uridine triacetate.

The division requested the sponsor provide dosing tables in labeling converting mg/kg doses to teaspoons for those patients who do not have access to a digital scale or (b) (4). It was noted by the division to the sponsor that kitchen spoons, including measuring spoons for cooking or baking are not standardized and will not provide accurate doses. The sponsor proposed use of a graduated teaspoon.

The sponsor also stated that the weight of one level standard measuring teaspoon of drug product is approximately 3 grams.

Labeling will give the option for either weighing the dose on a (b) (4) or using a teaspoon:

Measure the dose using either a (b) (4) accurate to at least 0.1 gram, or a graduated teaspoon, accurate to the fraction of the dose to be administered.

#### Preparation and Administration

- Food – studies with uridine triacetate showed that it is stable in applesauce, yogurt and pudding for at least 3 hours. Those specific soft foods are listed as appropriate for mixing the dose
- Milk or Infant Formula – The division noted that milk or infant formula may be a preferred vehicle for administering drug to some patients, especially infants who are not old enough to ingest soft foods (1 to 6 months of age). (b) (4)

drug (b) (4) could be accomplished by mixing a dose in 5 mL of milk or infant formula (b) (4) and then delivering it between the cheek and gum at the back of the mouth via (b) (4) syringe. A regular bottle of formula or milk could be given following this administration, if desirable. (b) (4)

(b) (4)

(b) (4)

(b) (4)

*Dosage Forms and Strengths and How Supplied Storage and Handling*

Although the sponsor submitted CMC information to support both the 2 gram and (b) (4) packets of Xuriden, and the data was found acceptable by the Product Quality team, the sponsor only plans to market the 2 gram packet size to the HOA patients. (b) (4)

*Contraindications and Warnings and Precautions*

None

*Adverse Reactions*

(b) (4)

*Clinical Studies:*

(b) (4)

The efficacy of XURIDEN was evaluated in an open-label study in 4 patients with hereditary orotic aciduria (3 male, 1 female; age range from 3 to 19 years). Three patients were previously treated with uridine and were switched at study entry to XURIDEN. All patients were administered XURIDEN orally at a daily dosage of 60 mg/kg once daily. The study duration was 6 weeks.

The study assessed changes in the patients' pre-specified hematologic parameters during the 6-week trial period. The pre-specified hematologic parameters were: neutrophil count and percent neutrophils (Patient 1), white blood cell count (Patient 2), and mean corpuscular volume (Patients 3 and 4).

For patients switched from oral uridine to oral XURIDEN (Patients 1, 2, and 3), the primary endpoint was stability of the hematologic parameter; for the treatment-naïve patient (Patient 4), the primary endpoint was improvement of the hematologic parameter. Secondary endpoints were urine orotic acid and orotidine levels, and growth (height and weight) for all patients.

After six weeks of treatment, hematologic (b) (4) remained stable (b) (4). Table 1 summarizes the primary efficacy results.

**Table 1: Primary Efficacy Results for Study 1**

Patient	Pre-specified hematologic parameter (Age-specific reference range)	Primary Endpoint	Baseline (Day 0)	Week 6 (Day 42)	% Change from Baseline
Patient #1	Neutrophil count (1.5 to 8.0 x 10 <sup>3</sup> /mm <sup>3</sup> )	Stable hematologic value	0.95	0.81	-15%
	Neutrophil % (26 to 48%)	Stable hematologic value	21	23	10%
Patient #2	White Blood Cell Count (3.8 to 10.6 x10 <sup>9</sup> /L)	Stable hematologic value	7.8	7.4	-5%
Patient #3	Mean Corpuscular Volume (75 to 91 fL)	Stable hematologic value	109.9	108.5	-1%
Patient #4	Mean Corpuscular Volume (72 to 90 fL)	Improved hematologic value	114.6	113.4	-2%

At baseline, three patients had normal urine orotic acid levels and all four patients had normal urine orotidine levels. After 6 weeks of treatment, (b) (4).

During an extension phase of the trial, patients continued to receive (b) (4). Dosing during the extension phase ranged from 60 mg/kg to 120 mg/kg once daily. After 6 months of treatment, Patient #1's neutrophil count and neutrophil percent value normalized; hematologic parameters for the other three patients remained stable. Orotic acid and orotidine levels also remained stable for all four patients.

The treatment effect of XURIDEN on growth was assessed in the three pediatric patients (Patients 1, 3, and 4). At baseline, weight and height measurements were at or below the lower limit of normal for age (<5th

percentile for age) for Patients 1 and 4; height and weight measurements were within the normal range for age for Patient 3. After 6 months of treatment, Patients 1 and 3 experienced improved weight growth, as reflected in increases in their weight-for-age percentiles and weight velocity percentiles; Patient 4's weight growth remained stable (i.e., weight percentile for age and weight velocity percentile for age was unchanged). Height growth remained stable in all three patients (i.e., height percentiles for age and height velocity percentiles for age were unchanged).

#### Case reports

Nineteen (19) case reports of patients with (b) (4) have been documented in published literature. Eighteen (18) were diagnosed as infants or children between the ages of 2 months and 12 years and were treated with exogenous sources of uridine. One patient, diagnosed at age 28, was not treated with exogenous uridine.

All 19 patients presented with significantly elevated levels of urinary orotic acid. Fifteen of 19 had abnormal hematologic parameters at presentation, including 15 with megaloblastic anemia, 8 with leukopenia and at least 2 with neutropenia. Oral administration of exogenous sources of uridine was reported to significantly improve hematologic abnormalities (megaloblastic anemia, leukopenia and neutropenia) within 2 to 3 weeks in almost all documented cases when administered in sufficient amounts. Concentrations of urinary orotic acid were significantly reduced within 1 to 2 weeks of initiating uridine replacement therapy. Some fluctuation in levels of urinary orotic acid were observed, but always at much lower levels than those reported prior to treatment. Improvements in body weight were also documented over time with continued uridine replacement therapy.

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 increases). Within days up to 2 or 3 weeks, most hematologic abnormalities and orotic aciduria reappeared when administration of uridine was stopped or doses reduced. If treatment was interrupted for longer periods, body weight receded. If absolute dosages were not adjusted adequately to compensate for body weight gains, signs and symptoms of (b) (4) recurred.

#### Proprietary name

The sponsor previously submitted the proposed proprietary name, Xuriden, on October 20, 2011 under IND 039571. The Division of Medication Error Prevention and Analysis (DMEPA) found the name, Xuriden conditionally acceptable (OSE# 2011-4185); letter dated April 16, 2012. The sponsor also requested Xuriden as the proprietary name under IND 118,931 submitted May 6, 2014. DMEPA found the name acceptable from both a promotional and safety perspective on July 29, 2014 (see review in DAARTS; Matt Barlow, RN, BSN); "conditionally acceptable" letter dated August 1, 2014.

The proposed proprietary name, Xuriden, was re-assessed by DMEPA, previously found acceptable under IND 118,931. It was concluded that Xuriden is acceptable from both a promotional and safety perspective under the NDA 208169.

*CDTL Comment: See DMEPA Proprietary Name Memorandum in DARRTS by Rhiannon Leutner, PharmD dated February 18, 2015.*

#### Carton and Immediate Container Labels

Comments on the carton and container labels, regarding the NDC number, were communicated to the sponsor on June 16, 2015. The sponsor only plans to market the 2 gram packet, (b) (4). Comments regarding the 2 gram carton/container label were addressed by the sponsor in a submission dated on June 25, 2015. (b) (4)

*CDTL Comment: See DMEPA Label and Labeling reviews in DARRTS by Sherly Abraham, RPh dated June 8, 2015 and July 7, 2015. DMEPA agreed to the version of the 2 gram carton/container label submitted on June 25, 2015.*

### **Patient Labeling**

(b) (4) The review team decided that it would be helpful to have an Instructions for Use (IFU) as there are preparation and administration instructions to be communicated to the patient/caregiver. The Patient Labeling Team agreed to draft an IFU for the sponsor, (b) (4)

*CDTL Comment: See consult reviews in DARRTS from Shawna Hutchins, MPH, BSN, RN dated June 30, 2015 and July 17, 2015. The review was amended based upon team discussions that took place after the initial review was finalized on the most appropriate step-by-step method of preparing the drug in milk or infant formula.*

## **13. Postmarketing Recommendations**

### **Risk Evaluation and Management Strategies (REMS)**

No issues related to risk management have been identified; therefore, no REMS is required.

### **Postmarketing Requirements (PMRs) and Commitments (PMCs)**

No PMRs have been requested.

The following two PMCs were discussed with the sponsor at the LCM on July 8, 2015 and the sponsor agreed:

#### 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.

#### 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 (b) (4) 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 (b) (4), 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)

*CDTL Comment: On July 14, 2015 the sponsor submitted milestone dates for the PMCs.*

## **14. Recommended Comments to the Applicant**

None.



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/s/  
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JOETTE M MEYER  
07/21/2015