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APPLICATION NUMBER:

208169Orig1s000

OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	September 4, 2015
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	NDA 208169
Applicant Name	Wellstat Therapeutics Corporation
Date of Submission	January 8, 2015
PDUFA Goal Date	September 8, 2015
Proprietary Name / Established (USAN) Name	Xuriden/ uridine triacetate
Dosage Forms / Strength	Oral granules/2 gram single-use packets
Applicant Proposed Indication(s)	For uridine replacement therapy in (b) (4) patients with hereditary orotic aciduria.
Action:	Approval
Approved Indication(s)/Populations	A pyrimidine analog for uridine replacement indicated for the treatment of hereditary orotic aciduria.

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	Carla Epps, MD
Statistical Review	Min Min, PhD
Pharmacology Toxicology Review	Sruthi King, PhD
CMC Review/OBP Review	Hamid Shafiei, PhD
Microbiology Review	Jean Tang, PhD
Clinical Pharmacology Review	Sandhya Apparaju, PhD
DPMH	Carol Kasten, MD
DMPP	Shawna Hutchins, MPH, BSN, RN
OPDP	Kathleen Klemm, PharmD
OSI	Susan Leibenhaut, MD
CDTL Review	Joette Meyer, PharmD
OSE/DMEPA	Sherly Abraham, RPh

CMC=Chemistry Manufacturing and Controls
 OBP=Office of Biotechnology Products
 DPMH=Division of Pediatric and Maternal Health
 DMPP=Division of Medical Policy Programs
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

Benefit-Risk Summary and Assessment

Xuriden (uridine triacetate), a pro-drug of uridine, is a pyrimidine analog for uridine replacement. This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Products' approval recommendation for Xuriden for uridine replacement for the treatment of hereditary orotic aciduria (HOA). HOA is an ultra-rare autosomal recessive disorder with no currently approved drug treatment. It is a severe and potentially life-threatening disorder; the most severe forms of the disease manifest in the neonatal or infant period. Clinical manifestations include hematologic abnormalities (megaloblastic anemia, leukopenia, neutropenia), orotic aciduria, obstructive uropathy, failure to thrive and developmental delays. Uridine replacement therapy is intended to mitigate the deficiency of endogenous uridine in patients with HOA and thus facilitate pyrimidine nucleotide synthesis. Replenishment of circulating uridine also helps to correct orotic acid overproduction through feedback inhibition.

The benefits of Xuriden have been demonstrated in the applicant's 6-week phase 3 trial in 4 subjects with HOA; a 6-month extension phase of the trial; and importantly, from data from the published literature on 18 patients with HOA treated with other unapproved formulations of uridine, the active moiety in Xuriden. Other formulations of uridine have been available in the US as dietary supplements, but have limited oral bioavailability and are not subject to GMP. Xuriden delivers systemic uridine 4 to 6 times more efficiently than uridine.

I agree with the review team's determination that central to a finding of the efficacy of Xuriden was the establishment of a scientific bridge between Xuriden (uridine triacetate) and literature data obtained with uridine. I agree with the team's conclusion that such a bridge has been adequately established through the demonstration of comparability in the pharmacodynamic response (urinary orotic acid levels) between Xuriden and equivalent doses of uridine, and the physiological understanding of the metabolic requirements for uridine in humans. Having established that bridge, the totality of evidence demonstrates that HOA patients receiving adequate doses of uridine replacement, whether in the form of uridine or uridine triacetate (Xuriden) experience clinically meaningful improvement in key disease manifestations, including hematologic status, orotic aciduria, and growth. The currently available data support a starting dose of 60 mg/kg/day and a maximum dose of 120 mg/kg/day. Long-term efficacy, including additional dose adjustments of Xuriden, will be further assessed in an ongoing extension trial.

There have been no Xuriden-related safety issues identified in the HOA population out to 9 months of treatment; however, limited data are available at this time. Long-term safety will also be assessed in the ongoing extension trial.

Discussions regarding product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval of this application. The benefit-risk analysis of Xuriden is favorable and supports approval. Xuriden fills an unmet medical need for this ultra-rare potentially life-threatening disorder.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Analysis of Condition</u></p>	<p>Hereditary orotic aciduria (HOA) is an ultra-rare autosomal recessive disorder of pyrimidine synthesis. HOA is due to a gene mutation which causes a deficiency in the bi-functional enzyme uridine monophosphate (UMP) synthase. UMP synthase is involved in the conversion of orotic acid to UMP. UMP synthase deficiency prevents the normal synthesis of uridine, which is needed for the biosynthesis of pyrimidine nucleotides. The deficiency also results in accumulation of orotic acid and orotidine in tissues, due to the loss of feedback inhibition by intracellular nucleotides.</p> <p>Onset of the disease is generally during the neonatal or infant period. Clinical manifestations of HOA, as documented in case reports in the literature, include hematologic abnormalities (megaloblastic anemia, leukopenia, neutropenia), orotic aciduria, obstructive uropathy, failure to thrive and developmental delays; individuals who are heterozygous for defective UMP synthase may be asymptomatic or only mildly affected. The disease can be fatal if untreated, generally from infectious complications.</p> <p>Approximately 20 cases of HOA have been reported worldwide.</p>	<p>HOA is a serious and potentially life-threatening condition. The more severe forms of the disease manifest during the neonatal or infant period. Understanding of the natural history and clinical manifestations of the disease is well-documented in case reports in the published literature.</p>

<p><u>Current Treatment Options</u></p>	<p>There is currently no approved therapy for HOA, and none in development. Supportive therapies include blood transfusion, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.</p> <p>The goal of treatment is to bypass the enzymatic defect and exogenously provide an oral dose of uridine that restores intracellular uridine concentrations, thus reversing or ameliorating the manifestations of the disease. Uridine, commercially available in the U.S. as a dietary supplement, has been used in the treatment of patients with HOA for decades.</p> <p>Physiologically, the substrate requirement for <i>de novo</i> pyrimidine synthesis in non-disease-affected adults is estimated at 12 to 18 mg/kg of uridine per day. Taking into consideration the poor bioavailability of uridine (~10%), an estimate for exogenous uridine doses necessary for replacement therapy in patients with HOA would be 120-270 mg/kg of uridine per day.</p> <p>Evidence for the efficacy of exogenous uridine is derived from case reports in the literature of its use in patients with HOA which document improvement in the hematologic manifestations and on urinary orotic acid levels.</p>	<p>There is no approved drug treatment for HOA. Daily uridine requirement for <i>de novo</i> pyrimidine synthesis in non-affected adults is known, and an estimate of exogenous uridine treatment requirements for patients with HOA can be extrapolated from these data. Case reports from the literature of patients with HOA being treated with exogenous uridine replacement therapy document improvement in the hematologic manifestations of HOA and on urinary orotic acid levels. Exogenous uridine is currently available in the U.S. as a dietary supplement, so it is not subject to GMP. Furthermore, currently available exogenous uridine has poor oral bioavailability.</p>
<p><u>Benefit</u></p>	<p>The subject of this NDA, Xuriden (uridine triacetate) is a pro-drug of uridine. (b) (4)</p> <p>. The acetate groups are rapidly</p>	<p>Data provided by the single phase 3 trial were not sufficiently persuasive to demonstrate the efficacy of Xuriden; however, the</p>

removed during first passage via the liver. Xuriden delivers systemic uridine 4 to 6 times more efficiently than uridine.

Efficacy was assessed in one open-label single arm phase 3 trial in four subjects with HOA administered 60 mg/kg/day of Xuriden (uridine triacetate); in a 6-month extension of the phase 3 trial at doses of 60 mg/kg/day and 120 mg/kg/day; and in 19 case reports of patients with HOA from the published literature, 18 of whom were treated with exogenous sources of uridine at doses of 50-300 mg/kg/day.

Of the 4 patients enrolled in the trial, 3 had been previously treated with exogenous uridine and 1 was treatment naïve. The primary endpoint for patients previously treated with uridine (n=3) was stability in the patient's pre-specified hematologic parameter (neutrophil count or percent, white blood cell [WBC] count, or mean corpuscular volume [MCV]). For the one treatment naïve patient, the primary endpoint was improvement of an abnormal baseline hematologic parameter (MCV). Secondary endpoints were urine orotic acid and orotidine levels. During the extension phase, growth (height and weight) was also assessed. FDA and the applicant had reached agreement on the pre-specified individualized primary efficacy endpoints.

The ages of enrolled subjects in Trial 1 were 3 (treatment naïve), (b) (4)

totality of data (the phase 3 trial, its 6-month extension phase, the literature case reports, and the demonstration of pharmacodynamic comparability between uridine and Xuriden) support the efficacy of Xuriden in improving hematologic indices, normalizing urinary orotic acid levels, and stabilizing height and weight growth in patients with HOA.

Treatment duration and dosage may have been insufficient to establish the full benefit potential of Xuriden, in particular on the incidence of obstructive uropathy or crystalluria-induced hematuria and on growth and developmental parameters.

Xuriden will be the first approved treatment for HOA. To provide further assurance of the long-term efficacy of Xuriden, the applicant has agreed to continue evaluating the four subjects enrolled in the ongoing extension trial every 6 months for a total duration of 2 years. Information collected will include data on growth (height, weight,

After 6 weeks of treatment with Xuriden, the hematologic values of two subjects (Subjects (b) (6)) remained stable. No improvement in hematologic status was demonstrated in the treatment-naïve subject (Subject (b) (6)). Historical data provided by the applicant documented the presence of hematologic abnormalities in three subjects prior to the initiation of uridine replacement therapy. Insufficient data were provided for Subject (b) (6) to confirm a low WBC count prior to initiation of uridine replacement therapy.

Supportive data were provided by the 6-month extension phase which demonstrated stability or improvement in hematologic parameters in all 4 subjects, 2 of whom continued on 60 mg/kg/day and 2 of whom underwent dose escalation to 120 mg/kg/day.

Further supportive data were provided by subject profile graphs which illustrated subject progress over time – from pre-treatment through the main trial and through the extension period – on all hematologic parameters in all subjects. All subjects showed relative stability or improvement in neutrophil percent over the treatment duration. Three of four subjects showed relative stability or improvement in WBC count over the treatment duration. All subjects showed relative stability in MCV over the treatment duration.

Secondary endpoint analyses demonstrated stability of urine orotic acid levels in subjects treated with Xuriden. Three

height velocity, and weight velocity, including z-scores), hematologic indices, and urine biomarkers (orotic acid and orotidine). Data on any dose adjustments made during the extension trial, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments will also be collected.

subjects who had achieved normal urine orotic acid levels when they were treated with uridine maintained normal levels 6 weeks after transitioning to Xuriden. This was further supported by analyses of urine orotic acid levels over the lifetime of the three subjects, which demonstrated clear elevations in urine orotic acid levels pre-treatment; dramatic reductions in urine orotic acid levels post initiation of uridine; followed by maintenance of those reductions after transitioning to Xuriden. This analysis allowed for a demonstration of comparability in pharmacodynamic response between replacement therapy with uridine and Xuriden.

Supportive data were also provided in assessments of height and weight growth in the three pediatric subjects. After 6 months of treatment, two subjects experienced improved weight growth. The weight growth remained stable for the third subject. Height growth remained stable in all three pediatric subjects.

Data supportive of uridine replacement therapy were provided by nineteen case reports in the published literature of patients with HOA treated with oral uridine (n=18) at doses of 50 to 300 mg/kg/day. Administration of oral uridine was reported to

- significantly improve megaloblastic anemia within 2 to 3 weeks;
- leukopenia and neutropenia and defective cell-mediated immunity responded more slowly, and appeared to require higher uridine doses;

	<ul style="list-style-type: none"> ○ concentrations of urinary orotic acid were reported to be significantly reduced within 1 to 2 weeks; ○ the incidence of obstructive uropathy or crystalluria-induced hematuria appeared to be decreased; ○ improvements in body weight and other developmental parameters were also reported over time with continued uridine replacement; <p>Other notable findings included the reappearance of most hematologic abnormalities and orotic aciduria within 2 to 3 weeks of cessation of uridine treatment, or upon dose reduction.</p>	
<p><u>Risk</u></p>	<p>The safety of Xuriden has been studied in four subjects with HOA; 53 adult subjects with diabetic neuropathy; 22 children and 8 adults with mitochondrial and metabolic disorders; 46 healthy subjects, 142 adults and 6 children at risk of 5-fluorouracil (5-FU) toxicity, and 288 subjects receiving high-dose 5-FU.</p> <p>Doses studied have included up to 120 mg/kg/day for 9 months (HOA); 4 or 8 grams per day for 6 to 12 months (diabetic neuropathy); 33 to 300 mg/kg/day for up to 18 years (mitochondrial and metabolic disorders); and single doses of 6 g up to 40 g per day for 5 days (5-FU toxicity).</p> <p>Two HOA patients reported adverse events, neither of which was determined to be treatment-related. Non-serious adverse events in the other indications studied included gastrointestinal adverse effects that were felt to be due to</p>	<p>The long-term effects of Xuriden have been evaluated in a limited number of subjects; however, there has been no indication of the emergence of new adverse drug reactions with long-term exposure. The long-term safety of Xuriden in HOA patients will be further assessed in the ongoing extension trial.</p>

	<p>the presence of an excipient in an earlier formulation of uridine triacetate.</p> <p>No deaths occurred among healthy subjects, HOA subjects, or the diabetic neuropathy subjects. There were no serious adverse events (SAEs) reported in the HOA clinical development program that were considered treatment related. SAEs were reported in the diabetic neuropathy subjects, although all were deemed unlikely related to study medication. There were no treatment discontinuations among the four subjects in the HOA clinical trial for adverse events or for any other reason.</p> <p>In repeat dose toxicology studies in rats and dogs, there were no significant treatment-related toxicities or deaths. Uridine triacetate was not genotoxic in the <i>in vitro</i> Ames mutagenicity assay, the mouse lymphoma assay, and the <i>in vivo</i> mouse micronucleus test. Uridine triacetate did not produce adverse effects on fertility or general reproductive performance. In an embryo-fetal development study, there was no evidence of teratogenicity or harm to the fetus and no effect on maternal body weight and overall health. No effects on prenatal and postnatal development were observed in rats.</p> <p>In <i>in vitro</i> testing, <u>uridine triacetate</u> inhibited hERG current as compared to vehicle control, and increased action potential duration and resting membrane potential, and decreased action potential amplitude and rate of depolarization, compared to vehicle. However, <u>uridine</u> did not produce</p>	
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	<p>statistically significant inhibition of hERG current, and did not produce significant changes to action potential parameters. Because uridine triacetate undergoes rapid and complete deacetylation after oral administration and because first pass metabolism of uridine triacetate converts all circulating uridine triacetate to uridine, the observed <i>in vitro</i> cardiac effects seen with uridine triacetate are not predictive of adverse cardiac effects <i>in vivo</i>. In animal toxicology studies, no treatment-related cardiovascular or pulmonary effects were observed in dogs or in rats.</p> <p><i>In vitro</i> data suggest that neither Xuriden nor uridine inhibit or induce major CYP450 enzymes. Uridine triacetate is a weak substrate for and an inhibitor of P-glycoprotein. The potential for Xuriden to inhibit P-gp at the gut level cannot be ruled out.</p>	
<p><u>Risk Management</u></p>	<p>Dosing of the Xuriden is body weight based and patients or caretakers can measure Xuriden doses on a (b) (4) or in a graduated teaspoon.</p> <p>To administer Xuriden, it should be mixed with soft foods or in a syringe with milk or infant formula.</p> <p>There are no serious safety concerns that warrant the need for a REMS.</p> <p>The long-term effects of Xuriden have been evaluated in a limited number of subjects; however, there has been no indication of the emergence of new adverse drug reactions with long-term exposure.</p>	<p>Product labeling and the Instructions for Use will provide detailed instructions on appropriate dosing and administration.</p> <p>There are no serious safety concerns that warrant the need for a REMS.</p> <p>The long-term safety of Xuriden in HOA patients will be assessed in the ongoing extension trial.</p> <p>The dissolution profile of the drug and the potential impact on T_{max} and C_{max}</p>

Dissolution method testing was considered inadequate to provide the true dissolution profile for the to-be-marketed drug product. The method was accepted only on an interim basis for the approval of this application provided that the applicant develops a more suitable dissolution method post approval.

The Office of Process and Facilities' performed batch testing of three pre-sachet samples of drug product and observed a high degree of variability in dissolution. (b) (4)

This variability is thought to be due to variability in the particle size of the granules. It is anticipated that the impact of the dissolution variability would be to delay T_{max} , and possibly lower C_{max} . But, given that patients are titrated to an effect (urinary orotic acid levels and laboratory values of hematologic parameters), and given that there is a range of efficacious doses, and given prior experience with multiple uridine dose regimens across several patient populations and the lack of a safety signal observed with the product to date, the clinical review team determined that the potential effects on T_{max} and C_{max} are likely to pose minimal risk to patient safety or efficacy.

were determined to have minimal potential impact on patient safety or efficacy. The clinical review team concluded that the observed variability in dissolution should not preclude product approval, and that this issue can be resolved post-approval in a study that evaluates the effect of particle size on dissolution and provides updated final drug product particle size specification. This should facilitate any needed improvements to the manufacturing process, in-process controls, and final specifications to assure a more consistent product. I concur with this conclusion and recommendation. The applicant has agreed to conduct the PMC as requested by the agency.

Other Background

Regulatory History

In 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 program for uridine.

In January 2013, the Agency identified Wellstat Therapeutics Corporation as a potential alternative source of uridine for patients with HOA in expanded access protocols.

In March 2013, the Agency met with Wellstat Therapeutics Corporation to discuss development of uridine triacetate as uridine replacement therapy in patients with HOA.

In August 2013, a pre-IND meeting was held to discuss a regulatory pathway for receiving an indication for treatment of patients with HOA. Additionally, in August 2013, uridine triacetate for the treatment of HOA received orphan drug designation, as well as designation as a potential new drug for a rare pediatric disease.

On April 30, 2014, the applicant's request for Breakthrough Therapy designation was granted, based on clinical data presented from published case studies and clinical summaries from the expanded access INDs.

A pre-NDA meeting was held in December 2014.

The NDA was submitted on January 8, 2015 and granted priority review.

Wellstat Therapeutics Corporation, the sponsor of the NDA under review, is also developing uridine triacetate "as an antidote to treat patients at risk of excess toxicity due to 5-fluorouracil overdose or patients exhibiting rapid onset of serious toxicity following 5-fluorouracil administration," under NDA (b) (4).

Dosing

Xuriden is available as single-use packets of orange-flavored oral granules containing 2 grams uridine triacetate. The recommended starting dose of Xuriden is 60 mg/kg/day administered once a day. The dose may be increased up to a maximum of 120 mg/kg/day as clinically indicated. (b) (4)

Because a dose of 120 mg/kg/day would be close to the maximum dose of 300 mg/kg/day for which we have supportive data from the literature, and because the 120 mg/kg/day of Xuriden was tested in the extension phase of the phase 3 trial, the review team has recommended a maximum dose of 120 mg/kg/day of Xuriden. I concur with this recommendation. It is acknowledged, however, that the maximum dose could be modified in the future if supported by additional data from the ongoing extension trial.

The Xuriden dose should be mixed with soft foods such as applesauce, pudding or yogurt and ingested (b) (4) in infants, the dose may be mixed in a syringe with milk or infant formula, and administered (b) (4)

Product Quality

An expiration dating period of 24 months for uridine triacetate drug product when stored at 25°C (77°F) with excursions permitted to 15° to 30°C (59° to 86°F) was recommended.

While the coated uridine triacetate granules exhibit lower C_{max} and delayed T_{max} relative to the unformulated API, ONDP concluded that there is not sufficient evidence to suggest that the product is an extended-release product. Therefore, the product is designated as an immediate-release product.

The 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 raised concerns about whether the drug product can be successfully administered to pediatric patients less than 12 years of age. Her concerns have been adequately addressed by the clinical team and the applicant and appropriate revisions to product labeling and instructions for use have been made.

The applicant submitted a claim for categorical exclusion from the Environmental Assessment for Xuriden (uridine triacetate) citing 21 CFR 25.31(b), “no extraordinary circumstances”, which was accepted. The drug substances were reviewed for any signals of estrogenic, androgenic, or thyroid activity, and no signals were found.

The Division of Pharmaceutical Analysis (DPA) evaluated the identity, assay, and related substances for uridine triacetate and concluded that the methods are acceptable for control and regulatory purposes.

Other Non-clinical Pharmacology/Toxicology

Carcinogenicity studies were waived for uridine triacetate. There were no findings suggestive of tumorigenic potential in the 6-month repeat-dose toxicity study in rats.

Other Clinical Pharmacology

The pharmacokinetic (PK) characteristics of Xuriden were assessed in all four subjects enrolled in the pivotal HOA trial. Maximum concentrations of uridine in plasma following oral Xuriden are generally achieved within 2 to 3 hours; the half-life ranges from approximately 2 to 2.5 hours. PK parameters for plasma uridine from the four HOA subjects are summarized in the table below.

Accumulation of uridine is minimal following once-daily administration of Xuriden in individual patients.

Plasma uridine triacetate was not assayed in the trial. According to the applicant, the parent drug is not expected in systemic circulation due to its rapid conversion to uridine by ubiquitous esterases. The absence of PK information for the pro-drug is not considered a deterrent to the review and approval of this application. The Office of Clinical Pharmacology has recommended that the applicant consider developing an assay to evaluate the systemic concentrations of the pro-drug in future clinical trials if planned. The assay method for analyses of uridine and uracil, as well as the assay for urinary orotic acid and orotidine were found to be acceptable.

Food effect information from the to-be-marketed formulation of uridine triacetate is not available. No food effect was seen with a slightly different uridine triacetate formulation. Both formulations are primarily comprised of active ingredient (>90%). Therefore, no food effect with the to-be-marketed formulation is anticipated and the drug can be dosed with or without food.

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

The applicant submitted a QT study waiver request which was granted by the Agency's QT Interdisciplinary Review Team.

Other Clinical/Statistical Efficacy

The table below provides a summary of the primary efficacy results of the 6-week, single-arm, phase 3 trial in 4 subjects with HOA, 3 of whom were previously treated with exogenous uridine and 1 of whom was treatment naïve.

Table 1: Primary efficacy results*

Subject	Pre-specified hematologic parameter (age-specific reference range)	Primary Endpoint	Baseline	Week 6	% Change from baseline
(b) (6)	Neutrophil % /Neutrophil count (26-48/1.5-8)	Stable hematologic value	21 /0.95	23 /0.81	10% /-15%
(b) (6)	White blood cell count (3.8-10.6 x 10 ⁹ /L)	Stable hematologic value	7.8	7.4	-5%
(b) (6)	Mean corpuscular volume (75-91 fL)	Stable hematologic value	109.9	108.5	-1%
(b) (6)	Mean corpuscular volume (72-90 fL)	Improved hematologic value	114.6	113.4	-2%

*Adapted from page 26 of CDTL memo.

During the extension phase, subjects received doses of Xuriden ranging from 60 mg/kg/day (Subjects (b) (6) to 120 mg/kg/day (Subjects (b) (6) and (b) (6) once daily. After 6 months of treatment:

- Subject (b) (6) neutrophil percent value increased by 48% to within the normal range, and the neutrophil count increased by 47%.
- Subject (b) (6) WBC count decreased from baseline by 14%
- Subject (b) (6) MCV decreased from baseline by 2%
- Subject (b) (6) MCV remained unchanged

The Office of Scientific Investigations (OSI) conducted inspections of both clinical sites that participated in the clinical trial, as well as the applicant site. OSI classified both clinical sites as VAI, and the applicant site as NAI. The clinical site deviations did not impact data integrity and

OSI determined that the data generated by both sites could be used in support of the respective indication.

Advisory Committee Meeting

No Advisory Committee input was sought on this application. Although Xuriden is a New Molecular Entity, the application did not raise significant public health questions, and there were no novel or complex regulatory issues that required the input of an advisory committee.

Pediatrics

Pediatric Use: The safety and effectiveness of Xuriden have been established in pediatric patients. Use of Xuriden is supported by a single open-label clinical trial of Xuriden in four subjects and a retrospective review of the clinical course of 18 patients with HOA who were treated with uridine beginning at ages 2 months to 12 years. There are no apparent differences in clinical response between adults and pediatric patients with HOA treated with uridine; however, data are limited.

Pediatric Rare Disease Voucher. Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA) modified the Rare Pediatric Disease Priority Review Voucher Incentive Program to allow the issuance of a “priority review voucher” to the sponsor of a rare pediatric disease product application. The holder of such voucher is entitled to priority review of a single human drug application submitted under section 505(b)(1) after the date of approval of the rare pediatric disease product application. Under the statute, ‘rare pediatric disease’ is defined as:

1. The disease primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.
2. The disease is a rare disease or condition, within the meaning of section 526.

The term ‘rare pediatric disease product application’ means a human drug application that

1. is for a drug or biological product—
 - a. that is for the prevention or treatment of a rare pediatric disease; and
 - b. that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of this Act or section 351(a) or 351(k) of the Public Health Service Act;
2. is submitted under section 505(b)(1) of this Act or section 351(a) of the Public Health Service Act;

3. the Secretary deems eligible for priority review;
4. that relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
5. that does not seek approval for an adult indication in the original rare pediatric disease product application; and
6. is approved after the date of the enactment of the Prescription Drug User Fee Amendments of 2012.

On August 9, 2013, the Office of Orphan Products Development (OOPD) granted the applicant's request for rare pediatric disease designation for the treatment of HOA. In the NDA submission, the applicant requested that a Rare Pediatric Disease Priority Review Voucher be awarded at the time of product approval. In a memo dated May 6, 2015, OOPD provided a checklist that supported that HOA meets the FDASIA definition of a rare pediatric disease, and that the Xuriden NDA submission represents a rare pediatric disease product application as defined above. A Priority Review Voucher will be granted at the time of approval.

Other Relevant Regulatory Issues

Tradename Review

The Division of Medication Error Prevention and Analysis concluded that the applicant's proposed proprietary name "Xuriden" is acceptable from both a promotional and safety perspective.

Consults

Division of Medical Policy Programs (DMPP)

DMPP provided consultative recommendations to the applicant's proposed Instructions for Use (IFU) for Xuriden.

Division of Medication Error, Prevention, and Analysis (DMEPA)

DMEPA provided consultative recommendations to increase the readability and prominence of important information in labeling to promote the safe use of the product.

Division of Pediatric and Maternal Health (DPMH)

DPMH reviewed relevant data pertaining to the effects of uridine triacetate or uridine exposure during pregnancy and lactation, and concluded that "Non-clinical 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.” DPMH further noted, however, that the use of uridine triacetate in pregnant women with HOA is likely to reduce the risk of serious anemia in pregnancy, and that this positive effect should be considered against the unknown risks. Appropriate edits were recommended for the Xuriden label to ensure compliance with the Pregnancy and Lactation Labeling Rule guidelines.

Labeling

There were no complex labeling negotiations. The major areas of labeling involved the dosing and administration of the product. [REDACTED] (b) (4)

[REDACTED] Labeling will note a starting dose of 60 mg/kg/day and a maximum dose of 120 mg/kg/day. Detailed dosing instructions have been provided in the labeling – based both on product weight (in grams) and volume (in teaspoons) – as well as parameters to use for dose escalation. The Instructions for Use details how to mix and administer the drug in milk or infant formula.

Risk Evaluation and Mitigation Strategies (REMS)

There are no serious safety concerns that warrant the need for a REMS.

Postmarketing Requirements and Commitments

To provide further assurance of the long-term efficacy of Xuriden, the applicant has agreed to the following PMCs:

1. Continue to evaluate the long-term efficacy and safety of XURIDEN in patients currently enrolled in Protocol 401-13-001 every 6 months for a total duration of 2 years in an extension study. The extension study should collect data on growth, hematologic indices, and urine biomarkers (orotic acid and orotidine). Growth data should include height, weight, height velocity and weight velocity. Ensure that the growth data are submitted also as z-scores. Provide information on any dose adjustments made during the extension study, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments.
2. Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches.

Determine the particle size distribution of the final drug product and, using the updated dissolution method, evaluate the impact of the particle size distribution

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

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/s/

AMY G EGAN
09/04/2015