CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208159Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	November 20, 2015
Reviewer(s):	Mona Patel, Pharm.D. Division of Risk Management
Acting Team Leader:	Naomi Redd, Pharm.D. Division of Risk Management
Acting Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Subject:	Review to determine if a REMS is necessary
Established Drug Name(s):	Uridine triacetate
Proprietary Drug Name:	Vistogard
Therapeutic Class:	Uridine analogue to 5-Fluorouracil (5-FU) or Capecitabine Toxicity
Dosing Regimen:	Adults: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals. Pediatrics: 6.2 grams/m^2 of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals.
Proposed Indication (s):	(b) (4)
Division:	Division of Oncology Products – 1 (DOP-1)
Application Type/Number:	NDA 208159
Applicant/sponsor:	Wellstat Therapeutics Corporation
OSE RCM #:	2015-310 2015-313

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Vistogard (uridine triacetate). The applicant, Wellstat Therapeutics Corporation, submitted a New Drug Application (NDA) 208159 with the proposed indication (b) (4) Wellstat Therapeutics Corporation did not submit a Risk Management Plan or a REMS.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Wellstat Therapeutics Corporation Clinical Modules (sections 2.5, 2.7.3 and 2.7.4)
- Midcycle Slides, October 29, 2015
- Vistogard (uridine triacetate) draft label, November 9, 2015

3 REGULATORY HISTORY

The review timeline for this application is Standard. Listed below are the pertinent regulatory history milestones for this NDA:

- May 4, 1992 – IND 39571 submitted for uridine triacetate
- May 1, 2009 – Orphan Drug Designation
- January 16, 2015 – Part 1 of Rolling NDA Submission
- July 10, 2015 – Part 2 of Rolling NDA Submission
- August 11, 2015 – Applicant Orientation Presentation
- October 29, 2015 – Midcycle meeting
- March 10, 2016 – PDUFA (Action) date

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT[1]

Over 300,000 patients in the United State (US) receive anti-cancer treatment with systemic 5-FU each year. Studies and reviews consistently report a minimum incidence of approximately 0.5% mortality from 5-FU toxicity. This incidence of mortality is in accord with estimates of approximately 1300 deaths per year from 5-FU toxicity in the US, with an additional 8250 estimated patients with potentially life threatening 5-FU toxicities.[2]

No available treatments beyond supportive care (e.g. hydration, electrolytes, etc.) have been established for treatment of 5-FU toxicity.

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[1] Clinical Overview (section 2.5), TAS-102

[2] NIH (2008) Public Teleconference Regarding Licensing and Collaborative Research Opportunities for: Methods and Compositions Relating to Detecting Dihydropyrimidine Dehydrogenase (DPD). *Federal Register* **73**:1.

Uridine triacetate[3] is an acetylated, orally administered prodrug of the pyrimidine nucleoside uridine. According to the applicant's submission, uridine triacetate is converted to intracellular nucleotides and acts as a precursor for ribonucleic acid (RNA) synthesis and pyrimidine deoxyribonucleotides for deoxyribonucleic acid (DNA) synthesis. Uridine is also a cofactor for sugar transfer reactions such as the synthesis of glycogen and glycoproteins and is a source of cytidine nucleotides required for RNA and phospholipid synthesis. The indication statement was revised by FDA to the following:

- (b) (4) or who exhibit early-onset severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or certain early onset, unusually severe adverse reactions (such as those involving gastrointestinal toxicity and/or neutropenia) within 96 hours of 5-fluorouracil or capecitabine administration.

The recommended dose of uridine triacetate is:

- Adults: 10 grams (1 packet) orally every 6 hours for 20 doses without regard to meals.
- Pediatric: 6.2 grams/m^2 of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals. The uridine triacetate dose to be administered at 6.2 grams/m^2 is outlined under the Dosage and Administration section of the label.

Uridine triacetate was approved on September 4, 2015 under the trade name Xuriden, for the treatment of patients with hereditary orotic acideria. Xuriden was granted orphan drug designation for the above condition, which has been reported in approximately 20 patients worldwide.[4]

4.2 CLINICAL DEVELOPMENT PROGRAM

Efficacy data for uridine triacetate for the treatment of patients at risk of serious toxicity following an overdose of 5-FU and patients exhibiting serious toxicity within 96 hours of 5-fluorouracil administration was derived from the 135 patients in Study 401.10.001 and Study WELL401 which were both expanded access and uncontrolled studies. Most of the patients (approximately 80%) received an overdosage of 5-FU, defined as administration of 5-FU at a dose or infusion rate greater than the intended dose or maximum therapeutic dose for patient's intended regimen, with the remainder classified as having a rapid onset of toxicity, defined as early onset (within 7-10 days of receiving 5-FU) or unusual susceptibility to 5-FU toxicity, such as Grade 3-4 diarrhea, mucositis, neutropenia, neurological toxicities, or severe/sudden onset cardiotoxicity, following a standard dose of 5-FU. Animal data supporting use of uridine triacetate for reducing 5-FU toxicity are provided from 5 studies: Study R.401.14.01, Study R.401.14.02, Study R.401.14.03, Saif and von Borstel, 2006, and study 401.15.01.

[3] Vistogard (uridine triacetate) draft label, November 9, 2015

[4] FDA approves new orphan drug to treat rare autosomal recessive disorder www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm457867.htm accessed 11/12/15

4.2.1 Efficacy

At the time of this writing, the clinical reviewer, Dr. Gwynn Ison, was still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies submitted to support this application.

Key Efficacy Findings:[3,5] Please refer to the clinical review by Dr. Gwynn Ison for the full review on efficacy and safety. The following is a summary of the key findings from labeling discussions for uridine triacetate as of **November 9, 2015**.

Study 401.10.001 is an ongoing single-arm, open-label expanded access study for patients who were at excess risk of 5-FU toxicity due to overdosage or exhibiting rapid onset (within 96 hours of the end of 5-FU administration) of serious toxicities following 5-FU administration or had known DPD deficiency and who could begin treatment with uridine triacetate no later than 96 hours after the end of 5-FU dosing. The primary endpoint of this study was the survival rate of patients over the 30-day period following 5-FU overdose. Secondary endpoints included assessments of the occurrence, severity and duration of neutropenia, thrombocytopenia, leukopenia, mucositis, diarrhea, skin and neurological toxicities, and system concentrations of uridine and uracil at least 3 times a week during the first 2 weeks following the overdose, and then weekly thereafter, for up to 30 days.

The predominant cancer diagnosis reported by the applicant was colorectal (66.7%), and the most frequently reported reason by the applicant for overdose was pump programmed incorrectly (42.9%) followed by pump malfunction (28.6%).[6]

A total of 60 patients were enrolled in this study and treated with a 5-day course of uridine triacetate treatment with 10 grams administered orally every 6 hours for a total of 20 doses.

Study WELL401 is the same design as the above study but included data from all patients treated from October 1995 to August 2011, prior to the initiation of Study 401.10.001, and patients who did not meet the entry criteria of Study 401.10.001, including patients who received capecitabine (5) or were pediatric patients (5). Study WELL401 was a single-arm, open label, multi-center study (conducted under single-patient INDs) of uridine triacetate as an antidote to treat patients at excess risk of 5-FU toxicity due to overdosage or rapid onset of serious toxicities. The primary and secondary endpoints were the same as the above study.

The predominant cancer diagnosis reported by the applicant was colorectal (48%), and the most frequently reported reason by the applicant for overdose was pump programmed incorrectly (39.4%).[5]

A total of 75 patients were treated with the same dosing regimen as above.

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[5] October 29, 2015 Midcycle Meeting Slides

[6] Vistogard (uridine triacetate) Summary of Clinical Efficacy 2.7.3

For both studies, the median age of the patients was 59 years (range: 1 to 83), 56% were female, 72% were Caucasians, 9% were Black/African American, 6% were Hispanic, 4% were Asian, and 95% had a cancer diagnosis. The data showed clinical meaningfulness, as assessed by the clinical reviewer, as there were 110 patients from the overdose group and 12 from the rapid onset who survived through the 30-day treatment and observation period. For those patients on uridine triacetate, the combined survival rate was 97%.

4.2.2 Safety[3]

The safety of uridine triacetate was based on a combined analysis of data from clinical studies and data from several nonclinical studies. The safety evaluation consisted of 135 patients from expanded access studies 401.10.001 and Well401. As noted above, studies 401.10.001 and WELL401 were currently ongoing. The data presented in this submission was derived from patients who signed informed consent forms prior to or on May 29, 2014 and whose source data was complete prior to database lock. For the nonclinical safety assessment of uridine triacetate, completed Good Laboratory Practice (GLP) and non-GLP studies were included as well as a single-dose oral limit test in rats, a 5-day oral safety study in dogs, a 6-week oral repeated dose toxicity study in rats, 3-month (12-week) oral repeated dose toxicity studies in rats and dogs, and a 6-month oral repeated dose toxicity study in rats when administered up to the maximum feasible doses of 2000 mg/kg/day in rats and 1500 mg/kg/day in dogs.

As observed in the clinical studies, the most common types of cancer in the combined safety population were colorectal (56.3% of patients) and head and neck (16.3%).[7] Overall, the mean duration of treatment for patients treated with uridine triacetate in Study 401.10.001 was 4.56 weeks and 4.35 weeks for patients in Study WELL401. In Study 401.10.001, the mean number of doses per patient in the combined Safety Population was 18.5 for the overdose group and 17.8 for the rapid onset group (18.3 overall).

Adverse events were categorized by system organ class and preferred term, and the safety events were classified by National Cancer Institute Common Terminology Criteria for Adverse Events criteria.

Adverse reactions occurring in > 2% of patients receiving uridine triacetate in both studies was vomiting (10%), nausea (5%), and diarrhea (3%).

There were no dose reductions reported for either study. In Study 401.10.001, no patients discontinued uridine triacetate because of adverse events. Three patients discontinued study treatment because of adverse events in study WELL401. Severe nausea and vomiting, moderate nausea and acute respiratory distress were indicated as the primary reasons for discontinuation that led to death.

To combat nausea and vomiting, antiemetic agents had been administered 20-30 minutes prior to each dose to help ensure retention of the dose, and if patient should require them. If the patient vomited within 2 hours of taking a dose of uridine triacetate, another complete dose was to be initiated within 15 minutes of the vomiting episode. The next

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[7] Vistogard (TAS-102) Summary of Safety (2.7.4)

dose was to be taken at the regularly scheduled time, regardless of whether the patient experienced additional vomiting episodes.[8]

There were no adverse events of concern except that the effect of uridine triacetate on the efficacy of 5-FU based products has not been established. (b) (4) The label will also plan to discuss hematological toxicity and damage to intestinal mucosa seen in mice under the Nonclinical Toxicology section. There are no clinical data on the use of Vistogard in pregnant women, however, nonclinical data in rats do not show evidence of teratogenicity or adverse effects on embryo-fetal development at doses one-half the maximum recommended human dose of 40 grams per day.

Deaths: Two patients died during Study 401.10.001 and 3 patients died in Study WELL401. None of the deaths in either study were related to uridine triacetate.

The applicant proposed to communicate all safety events through labeling and therefore did not submit a REMS.

4.3 ASSESSMENT OF RISK

There are no available treatment options beyond supportive care for patients following an overdose of 5-FU or capecitabine, or who exhibit early-onset severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or certain early-onset, unusually severe adverse reactions (such as those involving gastrointestinal toxicity and/or neutropenia) within 96 hours of 5-fluorouracil or capecitabine administration. The anticipated duration of use for uridine triacetate in adult patients is 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals. In pediatric patients, the dose is 6.2 grams/m^2 of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals. In this setting, uridine triacetate will be used by adult or pediatric patients with a cancer diagnosis who have received an overdose or exhibit serious toxicity within 96 hours of 5-FU or capecitabine administration. Based on data from the National Institute of Health, it is estimated that 1300 deaths per year can occur from 5-FU toxicity in the US, with an additional 8250 estimated patients with potentially life threatening toxicities. The use of this drug is expected to be initiated by emergency room doctors, hematologists, and oncologists in the inpatient emergency setting for at least 6 hours after the first dose. Patient monitoring and medical equipment will be available in this setting. If tolerated, this drug could also be continued by patients in the outpatient setting.

There were no serious or severe adverse events that rose to the level of Warnings & Precautions. Labeling for Vistogard contains Limitations of Use, that state treatment is not recommended for adverse reactions associated with 5-FU or capecitabine that are not severe or life-threatening because it may diminish the efficacy of these products. (b) (4) These events were not graded for severity. In the clinical trial program, nausea, vomiting, and

[8] Study 401.10.001 Protocol (August 1, 2013)

diarrhea were reported in 5%, 10%, and 3% of patients respectively. Nausea and vomiting are events that can be recognized and managed by prescribers should patients have to continue this drug in an outpatient setting. To combat nausea and vomiting, antiemetic agents had been administered 20-30 minutes prior to each dose to help ensure retention of the dose and if patient should require them. The use of antiemetic agents to ameliorate or prevent vomiting are communicated in the label as well as a patient package insert with further instructions on what the patient should do if vomiting occurs within 2 hours of taking a dose. Furthermore, the maximum dose for uridine triacetate for this indication is 20 doses, limiting the amount of time the patient may experience these potential adverse events.

Uridine triacetate is a potential treatment option for overdose or toxicity of 5-fluorouracil or capecitabine which can become life-threatening or fatal if left untreated, and up until now could only be managed with supportive care. Efficacy results have shown that patients treated with uridine triacetate had a 97% survival rate which was clinically meaningful. Based on the data provided in this application, a REMS is not necessary to ensure the benefits of uridine triacetate outweigh the risks of gastrointestinal adverse events. The risks associated with uridine triacetate will be communicated through labeling which also includes a patient package insert.

5 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

There are no PMR's or PMC's for this application.

6 CONCLUSION

DRISK and DOP-1 concur that, at this time, a REMS is not necessary to ensure that the benefits outweigh the risks for uridine triacetate for the agency's proposed indication, for the treatment of patients following an overdose of 5-fluorouracil or capecitabine, or who exhibit early-onset severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or certain early onset, unusually severe adverse reactions (such as those involving gastrointestinal toxicity and/or neutropenia) within 96 hours of 5-fluorouracil or capecitabine administration. The risks associated with uridine triacetate will be communicated through professional labeling. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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

/s/

MONA G PATEL
11/20/2015

CYNTHIA L LACIVITA
11/20/2015
Concur