

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208159Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 7 <sup>th</sup> , 2015
<b>From</b>	Julia A. Beaver, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 208159
<b>Supplement#</b>	N/A
<b>Applicant</b>	Wellstat Therapeutics Corporation
<b>Date of Submission</b>	July 10 <sup>th</sup> , 2015
<b>PDUFA Goal Date</b>	March 10 <sup>th</sup> , 2016
<b>Proprietary Name / Established (USAN) names</b>	Vistogard <sup>®</sup> (uridine triacetate)
<b>Dosage forms / Strength</b>	10 gram oral granules, single <sup>(b) (4)</sup> packets
<b>Applicant Proposed Indication(s)/Population(s)</b>	 <sup>(b) (4)</sup>
<b>Recommended:</b>	Approval
<b>Recommended Indication(s)/Population(s)</b>	<p>VISTOGARD is indicated for the emergency treatment of adult and pediatric patients:</p> <ul style="list-style-type: none"> <li>• following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or</li> <li>• who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration.</li> </ul>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers/Team Leaders</b>
Regulatory Project Manager	Jeannette O'Donnell/ Alice Kacuba
Medical Officer Reviewer	Gwynn Ison/ Julia Beaver (Acting Team Leader)
Statistical Review	Joyce Chen/ Shenghui Tang
Pharmacology Toxicology Review	W. David McGuinn/ Todd Palmby
CMC Review	Xavier Ysern / Donna F. Christner – Drug Substance Xiao Chen/ Olen Stephens (Acting Branch Chief) – Drug Product
Micro process Reviewer	Christina Cappaci-Daniel/ Celia N. Cruz
Facilities	Christina Cappaci-Daniel/ Zhihao Peter Qiu
Biopharmaceutics	Ge Bai and Salaheldin S. Hamed/ Sandra Suarez-Sharp
Clinical Pharmacology Review	Runyan Jin/ Qi Liu
Pharmacometrics Review	Anshu Marathe/ Yaning Wang
Genomics Review	Sarah Dorff/ Rosane Charlab Orbach
DMPP/OPDP	Carole Broadnax/ Nicholas Senior
OSI	Lauren Iacono-Connors/ Susan Thompson
OSE/DMEPA	Grace Jones / Chi-Ming (Alice) Tu
OSE/DRM	Mona Patel/ Naomi Redd
OSE RPM	Frances Fahnbulleh
DEPI	Carolyn McCloskey/ Steven Bird
DPMH Maternal Health	Tamara Johnson/ Lynne Yao
DPMH Pediatrics	Ethan Hausman and Carol Kasten / Hari Sachs
Patient Labeling	Sharon Mills and LaShawn Griffiths/ Barbara Fuller
Safety	Susan Jenny/ Katherine Fedenko

DMPP= Division of Medical Policy Programs, OPDP= Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations, OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis, DRM= Division of Risk Management, DEPI=Division of Epidemiology, DPMH= Division of Pediatric and Maternal Health.

## 1. Introduction

On July 7th, 2015, Wellstat Therapeutics completed the rolling submission of a New Drug Application (NDA) for Vistogard<sup>®</sup> (uridine triacetate (b) (4)

The applicant included the following additional statements in the indication: (b) (4)

. During the review, the indication was amended to the following:

VISTOGARD is indicated for the emergency treatment of adult and pediatric patients:

- following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or
- who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration

Limitations of use:

- VISTOGARD is not recommended for the non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs.
- The safety and efficacy of VISTOGARD initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established.

The approval of uridine triacetate is primarily based on data from two single-arm, open-label, expanded access trials of patients who had either received a fluorouracil or capecitabine overdose, or presented with severe or life-threatening toxicities within 96 hours following the end of fluorouracil or capecitabine administration. The trials enrolled 135 patients who were administered 10 grams (g) of uridine triacetate orally every 6 hours for 20 doses (or 6.2 g/m<sup>2</sup> of body surface area orally every 6 hours for 20 doses in four pediatric patients). Of the 135 patients, 117 were treated with uridine triacetate following an overdose of fluorouracil (n=112) or capecitabine (n=5), and 18 were treated after exhibiting severe or life-threatening fluorouracil

toxicities within 96 hours following the end of fluorouracil administration. A total of six pediatric patients were administered uridine triacetate.

The major efficacy outcome was survival at 30 days or until the resumption of chemotherapy, if prior to 30 days. Of the 135 patients in the two trials, 130 (96%) survived and five (4%) died. Of the five patients who died, two were treated after 96 hours following the end of fluorouracil administration. In comparison, 21 of 25 (84%) historical control patients who were overdosed with fluorouracil and treated with supportive care alone died.

The safety profile of uridine triacetate was acceptable and the toxicities were mild and infrequent. Most common adverse reactions (> 2%) were vomiting, nausea, and diarrhea. Serious adverse reactions and grade  $\geq 3$  adverse reactions were seen in only one patient receiving uridine triacetate (grade 3 nausea and vomiting). No deaths were attributable to uridine triacetate.

### **Main Issues with this application**

The major review issues are summarized as follows:

- The application was initially under discussion for review using the animal rule according to 21 Code of Federal Regulations (CFR) 314.600. However after an initial assessment early in the review cycle, the animal rule was deemed not appropriate as human efficacy studies were conducted and there was sufficient clinical data to support the efficacy and safety of uridine triacetate.
- The trials supporting the NDA were both single-arm and non-randomized, and the applicant submitted historical case reports for comparison. Due to the life-threatening nature of fluorouracil or capecitabine overdose, and early-onset severe or life-threatening toxicity, it was not ethical to have a randomized design and therefore the trial design and use of historical controls was acceptable. Despite the lack of concurrent control, efficacy was demonstrated with a clear survival benefit (96%) in 135 patients who would have otherwise been expected to have substantial mortality. The historical case reports of patients who were overdosed with fluorouracil and treated with supportive care only were comparable to the doses and rates of overdose seen in the uridine triacetate treated patients and showed a high percentage of deaths (84%). After in-depth and careful review of the patients who exhibited early-onset, severe or life-threatening toxicity after administration of fluorouracil, efficacy was also definitively demonstrated. In addition, there was supportive nonclinical data and a consistent recommendation for approval from all disciplines.
- The indication for early-onset, severe or life-threatening toxicity required detailed review of each case and consideration about the clearest way to phrase this indication so that patients would not be inappropriately treated with uridine triacetate for non-emergent fluorouracil and capecitabine toxicities. After a detailed review of the case narratives, patients presented early with similar symptoms including severe or life-threatening neurologic or cardiac toxicities, and/or various combinations of severe gastrointestinal toxicities (e.g. mucositis, diarrhea, nausea) or neutropenia. The onset of appearance of these symptoms was also consistent between cases and the majority were within 96 hours of fluorouracil administration. Therefore the clinical review team was able to better describe this population in the indication by the timing of early-onset of toxicities within

96 hours of fluorouracil or capecitabine administration, and by a detailed description of the severe or life-threatening organ systems affected.

- The specific time frame for administration of uridine triacetate after overdose or early-onset toxicity required further consideration. Of the 135 patients, 131 were treated within the protocol specified 96 hour window and 98% lived. Four patients were treated outside of the 96 hour window, and 50% died. Additional information from the 120-day safety update was also supportive of specifying treatment as soon as possible within 96 hours and that efficacy after 96 hours was not demonstrated. Non-clinical information was also supportive of the specification of treating as soon as possible within 96 hours as decreasing animal survival was seen with a longer delay in treatment.
- Only five patients were treated with capecitabine in the clinical trials submitted with the NDA. However, all of these patients survived, and based upon the mechanism of action, and understanding of capecitabine as a pro-drug of fluorouracil, as well as additional capecitabine patient cases submitted in the 120-day safety report demonstrating definitive uridine triacetate benefit, the indication was extended to include capecitabine.
- There were only six pediatric patients studied in the clinical trials submitted. However all of these patients survived. In addition, according to section 505B(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, a drug may be considered to be effective in the pediatric population when it has been demonstrated to be effective in adults, if the disease process and the benefits of the drug are expected to be the same as is the case for this application. The safety profile is acceptable with a low risk to pediatric patients with minimal adverse reactions seen in the pediatric population studied. Therefore, due to the cases studied, supportive adult data, and a strong biologic and clinical rationale, the pediatric indication was included.
- There was a concern over the effect of uridine triacetate on the efficacy of fluorouracil and capecitabine. While the applicant concluded there was no effect of uridine triacetate on efficacy of fluorouracil or capecitabine, no substantive clinical data was submitted and mechanistically non-clinical data was conflicting. Therefore, the team decided in order to make this risk clear to patients and prescribers, a limitation of use describing the risk should be added to the label.

In conclusion, uridine triacetate demonstrated efficacy in the emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine overdose, and patients who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration. No approved therapies exist for these conditions and the majority (84%) of historical control patients treated with supportive care die. In contrast, treatment of similar patients with uridine triacetate resulted in the vast majority surviving (96%), with a safety profile that was acceptable and low risk. Despite small numbers in certain subgroups such as early-onset toxicity, capecitabine treated patients, and pediatric patients, the overall benefit: risk profile is favorable to support approval.

This document summarizes the reviews and conclusion of each review discipline. There were no major disagreements among the recommendations of the review disciplines involved with this application.

## 2. Background

### Pathophysiology of Condition

Approximately 300,000 patients in the United States receive treatment with fluorouracil each year. Studies report a minimum incidence of approximately 0.5% mortality (~1300 deaths per year) from fluorouracil toxicity. Another 8,250 estimated patients experience potentially life-threatening toxicities related to fluorouracil annually<sup>1,2</sup>.

Fluorouracil and capecitabine (a pro-drug of fluorouracil) are cytotoxic antimetabolites that interfere with nucleic acid metabolism in normal and cancer cells. There are two primary sources of fluorouracil cytotoxicity, the inhibition of thymidine synthesis by inhibition of thymidylate synthase as required for DNA replication and repair, and the incorporation of fluorouracil's metabolite 5-fluorouridine triphosphate (FUTP) into RNA. The incorporation of FUTP into RNA is proportional to systemic fluorouracil exposure and results in RNA damage and toxicity.

### Clinical Features

Overdose of fluorouracil or capecitabine can result in death. These outcomes are further explored in historical control case reports provided by the applicant and described in Section 7. Overdoses of fluorouracil most commonly result from infusion rate overdoses (from pump failures and incorrect programming) as opposed to dose overdoses. In addition, early-onset, severe or life-threatening toxicities from these drugs can also result in death as demonstrated by an Office of Surveillance and Epidemiology (OSE) Consult performed for the Office of Hematology and Oncology Products (OHOP) in 2014 (see Section 7).

### Existing (or Available) Therapies

There are no existing therapies for fluorouracil or capecitabine overdose or early-onset, severe or life-threatening toxicities of fluorouracil or capecitabine.

### Product Information

The active ingredient of Vistogard<sup>®</sup> is uridine triacetate, a pyrimidine analogue, and acetylated pro-drug of uridine. After oral administration, uridine triacetate is deacetylated by nonspecific esterases present throughout the body, yielding uridine in circulation. Uridine competitively inhibits cell damage and cell death caused by fluorouracil. Excess circulating uridine is converted to uridine triphosphate (UTP) which competes with FUTP for incorporation in RNA.

### Regulatory Background

- **May 1992-** IND 039571 for uridine triacetate was submitted (b) (4) for the treatment of solid tumors treated with fluorouracil.
- **May 1<sup>st</sup>, 2009-** Uridine triacetate received orphan drug designation (b) (4) in the treatment of fluorouracil poisoning.
- **July 5<sup>th</sup>, 2010-** EOP2 meeting occurred. The FDA expressed concern regarding the quality and adequacy of data collected from single patient INDs and recommended that the applicant conduct a prospective trial for the proposed indication.

- **September 2011-** Protocol 401.10.001 (Expanded Access Protocol) opened.
- **April 2014-** The Sponsor submitted an application [REDACTED] (b) (4)
- **May 2014-** FDA recommended [REDACTED] (b) (4). FDA also recommended that the Sponsor request a meeting with FDA to discuss the potential of an NDA submission and that the animal rule might be used to support the marketing application.
- **July 2014-** Fast-track designation was granted for “uridine triacetate [REDACTED] (b) (4) to treat patients at risk of excess fluorouracil toxicity due to overdose”.
- **January 15<sup>th</sup>, 2016-** The first portion of the rolling submission of NDA 208159 was submitted.
- **September 4<sup>th</sup>, 2015-** Uridine triacetate received approval under NDA 208169 for the indication of hereditary orotic aciduria under the trade name Xuriden™. This approval was based primarily on data from four pediatric patients who were treated chronically with uridine triacetate.

### 3. Chemistry, Manufacturing, and Control (CMC)

The clinical CMC reviewers (Xavier Ysem Ph.D. and Xiao Chen Ph.D.) and Branch Chief (Olen Stephens Ph.D.) concluded that the NDA is recommended for approval. Adequate data were provided for the manufacture and controls of the drug substance and drug product. The Office of Compliance issued an overall “acceptable” recommendation dated November 6<sup>th</sup>, 2015, for all facilities used for manufacturing and control of the drug substance. The following summary of chemistry assessments is excerpted from the CMC reviews.

#### General product quality considerations

##### *Drug Substance:*

Uridine triacetate is a pyrimidine analog. The chemical name for uridine triacetate is (2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione. The molecular weight is 370.3 g/mole and it has an empirical formula of C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>9</sub>. The starting material, [REDACTED] (b) (4) is a well-characterized compound and is commercially available. Uridine triacetate is [REDACTED] (b) (4)

[REDACTED] This drug substance is tested and released according to a drug substance specification that clearly assures the identity, strength, purity and quality of the drug substance. The stability results provided from the batches of drug substance produced to date support the proposed [REDACTED] (b) (4) retest date for this drug substance.

*Drug Product:*

Each single-dose 10 gram packet of Vistogard® orange-flavored oral granules (95% w/w) contains 10 g of uridine triacetate and the following inactive ingredients: ethylcellulose (0.309 g), Opadry® Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.077 g), and natural orange juice flavor (0.131 g). The total amount of excipients used in this drug product is less than 5% (b) (4)

(b) (4) All excipients are appropriately tested and released for use in the manufacture of Vistogard®. The information provided in the application supports the use of all proposed drug vehicles (e.g. soft foods). The proposed drug product specification is deemed adequate to assure identity, strength, purity, and quality of the drug product for this patient population. 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 for the drug product when packaged in the proposed packaging configuration and stored at controlled room temperature, 25°C (77°F) with excursions permitted to 15° to 30 °C (59° to 86°F).

*Biopharmaceutical:*

Uridine triacetate oral granules were classified by the applicant as an immediate release drug product. (b) (4)

(b) (4) the classification as immediate release is satisfactory. The product is a (b) (4) oral granule which varies in size. As a result, the process validation batches demonstrated (b) (4) resulting in significant intra-batch and inter-batch variability in the dissolution of the products. This variability is potentially due to the dissolution dependence on the particle size of the granules which clinically could impact the absorption and availability of the drug. However, due to the tolerable safety profile and no known toxic dose, the life-threatening indication, and the fact that patients will be frequently dosed and monitored, the variability in the drug product dissolution is not likely to have adverse clinical consequences. Therefore, this dissolution testing was deemed acceptable on an interim basis, and to further address these concerns and confirm the dissolution studies submitted to support the manufacturing process, a post-marketing commitment was agreed upon with the applicant (see Section 13).

**Facilities review/inspection**

The Office of Compliance issued an overall acceptable recommendation on November 6<sup>th</sup>, 2015 for all manufacturing and testing facilities that were inspected during the review cycle.

## **4. Nonclinical Pharmacology/Toxicology**

The nonclinical pharmacology/toxicology reviewer, W. David McGuinn, Ph.D., and the team leader, Todd Palmby, Ph.D., state that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval and that no additional nonclinical pharmacology/toxicology studies are needed. The reviewers summarize that the data from animal

studies supports the clinical efficacy of uridine triacetate. The following summary of nonclinical pharmacology and toxicology assessments are abstracted from their reviews.

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. In all these studies, uridine triacetate demonstrated very little toxicity even at high daily doses. In addition, three studies were submitted on the effects of uridine triacetate in mice exposed to fluorouracil as supportive efficacy data.

### **General nonclinical pharmacology/toxicology considerations**

#### *Safety Pharmacology Assessments:*

The pharmacology/toxicology review and referenced nonclinical safety review for NDA 208169 based on safety pharmacology studies demonstrated that *in vitro*, uridine triacetate did not inhibit the slow potassium rectifier channel (hERG) at physiologically relevant concentrations.

#### *Repeat-dose Toxicology Studies:*

Repeat-dose toxicology studies were conducted in both rats and dogs. Uridine triacetate caused no observable cardiac toxicity in dogs or rats. In repeat-dose toxicology studies in rats (3 months and 6 months), animals tolerated doses as high as 2000 mg/kg/day (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.

#### *Genetic-toxicology studies:*

Uridine triacetate was not genotoxic in the Ames test, the mouse lymphoma assay, and the mouse micronucleus test. There were no findings suggestive of tumorigenic potential in the 6-month repeat-dose toxicity study in rats. Long-term carcinogenicity studies were not conducted or required.

#### *Reproductive toxicology:*

Orally administered uridine triacetate did not affect fertility or general reproductive performance in male and female rats at doses up to 2000 mg/kg per day (about one-half the maximum recommend human dose (MRHD) of 40 g per day on a body surface area basis).

### **Other notable issues**

#### *Animal Efficacy Data and timing of uridine administration*

In mice given a sub-lethal dose of fluorouracil, the administration of oral uridine triacetate diminished hematological toxicity as a function of increasing dose, but did not completely prevent hematological toxicity. In mice given a lethal dose of fluorouracil, administration of oral uridine triacetate increased survival to 90% when given within 24 hours. Survival diminished with increasing intervals between the fluorouracil dose and uridine triacetate treatment (20% survival when given at 96 hours) demonstrating that earlier administration of uridine triacetate is more beneficial. However, no definitive conclusions should be made from animal models regarding human prognosis at various times, therefore specific information on percent survival at

time points was excluded from labeling. These animal efficacy results are internally consistent with the clinical efficacy results and clinical results that efficacy of uridine triacetate after 96 hours has not been demonstrated.

#### *Uridine triacetate effect on efficacy of fluorouracil*

As discussed in Section 2, there are two primary mechanisms for fluorouracil (or capecitabine) mediation of toxicity. Uridine triacetate is converted to UTP which clearly competes with FUTP for incorporation in RNA. The role of uridine triacetate on inhibition of thymidine synthesis by inhibition of thymidylate synthase is not as clear. The applicant cited a paper which concluded that uridine does not reverse thymidylate synthase inhibition<sup>3</sup>. However, another publication demonstrated that deoxyuridine monophosphate directly competes with FdUMP at thymidylate synthase sites potentially affecting DNA synthesis<sup>4</sup>. The potential for uridine triacetate to affect deoxyuridine triphosphate levels and impact the thymidylate synthase inhibition by fluorouracil in tumor cells in vivo is unclear. In addition, the relative contributions of RNA toxicity and DNA toxicity of fluorouracil to the anti-tumor activity in various disease settings have not been adequately demonstrated in humans. Therefore, mechanistically the effect of uridine triacetate on the anti-tumor activity of fluorouracil is not known and uridine triacetate has the potential to result in decreased fluorouracil efficacy.

The applicant submitted additional publications detailing preclinical xenograft tumor models in mice treated with standard dose and high dose fluorouracil followed by administration of uridine triacetate or uridine. However, these studies are not conclusive regarding the effect of uridine triacetate on the efficacy of fluorouracil in humans as many were uncontrolled, the studies had small numbers, and no individual animal data was submitted. More importantly, mouse models are not sufficient to demonstrate that uridine triacetate does not have an effect on the efficacy of fluorouracil in humans.

No clinical data was submitted to substantiate the claim that uridine triacetate did not affect the efficacy of fluorouracil. The applicant referenced a clinical publication which studied 57 patients with gastric cancer treated with high-dose fluorouracil, leucovorin, and uridine triacetate<sup>5</sup>. No clinical data was submitted, and literature based survival data is difficult to interpret in cross-trial comparisons, especially with only 57 patients. As no conclusive evidence was provided to support the claim that uridine triacetate does not affect the efficacy of fluorouracil, a limitation of use was added to explain this potential and discourage use of uridine triacetate for non-emergent fluorouracil or capecitabine adverse reactions.

## **5. Clinical Pharmacology/Biopharmaceutics**

The clinical pharmacology/pharmacometrics/pharmacogenomics reviewers (Jeanne Fournie Zirkelbach, Ph.D., Anshu Marathe, Ph.D., and Sarah Dorff, Ph.D.) and team leaders (Qi Liu, Ph.D., Yaning Wang Ph.D., and Rosane Charlab Orbach, Ph.D.) concluded that there are no outstanding clinical pharmacology issues that preclude approval and no additional studies are needed. The following information was abstracted from the Clinical Pharmacology reviews.

### **General clinical pharmacology/biopharmaceutics considerations**

The recommended dose of uridine triacetate in adults is 10 g orally every 6 hours for 20 doses without regard to meals. The recommended dose in pediatric patients is 6.2 g/m<sup>2</sup> orally every 6 hours for 20 doses without regard to meals for patients with body surface area (BSA) up to 1.44 m<sup>2</sup>. For pediatric patients with BSA of 1.44 m<sup>2</sup> and above, the dose is the same as adults.

The clinical pharmacology package included two bioequivalence (BE) studies, a food effect study in healthy subjects, supporting pharmacokinetic (PK) data from Trial WELL401 and Trial 401.10.001, as well as multiple dose PK in patients with solid tumors, patients with diabetic neuropathy and children with mitochondrial disorders. The formulation used in the clinical trials WELL401 and 401.10.001 is the same as the to-be-marketed formulation; the formulation used in the two PK studies contained slightly less active ingredient ((b)<sub>(4)</sub>% vs. 95%). Uridine triacetate delivers 4- to 6-fold more uridine into the systemic circulation compared to equimolar doses of uridine itself. Following a single dose of oral uridine triacetate, the maximum uridine concentrations in plasma is achieved within 2-3 hours and the half-life ranges from approximately 2 to 2.5 hours. Mean uridine concentrations after 20 doses increased approximately 1.5 times in the clinical studies. Uridine does not bind to plasma proteins and is soluble in aqueous media. Circulating uridine is taken up into mammalian cells via specific nucleoside transporters, and also crosses the blood brain barrier. Food did not impact the pharmacokinetics of uridine and uridine triacetate can be administered without regard to meals.

Although only 13 patients received uridine triacetate via nasogastric, gastric, or orogastric tube, the proposed uridine triacetate dose appears to be reasonable for these modes of administration given the totality of the data showing similar uridine concentrations post last dose, high survival rate, and low incidence of adverse events.

### **Drug-drug interactions**

*In vitro* enzyme inhibition data did not reveal meaningful inhibitory effects of uridine triacetate or uridine on CYP3A4, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. *In vitro* enzyme induction data did not reveal an inducing effect of uridine triacetate or uridine on CYP1A2, CYP2B6, or CYP3A4. *In vitro* data showed that uridine triacetate was a weak substrate for P-glycoprotein. Uridine triacetate inhibited the transport of a known P-glycoprotein substrate, digoxin, with an IC<sub>50</sub> of 344 μM. Due to the potential for high local (gut) concentrations of the drug after dosing, the interaction of VISTOGARD with orally administered P-gp substrate drugs cannot be ruled out. *In vivo* data in humans are not available.

### **Pathway of elimination**

Uridine can be excreted via the kidneys, but is also metabolized by normal pyrimidine catabolic pathways present in most tissues. Based on a literature review, the urinary excretion of uridine was approximately 24% of the dose following 2 to 12 g/m<sup>2</sup> uridine IV infusion and approximately 1% of the dose following oral uridine 8 to 12 g/m<sup>2</sup>.

### **Evaluation of intrinsic factors potentially affecting elimination**

A two stage PK analysis was conducted by the applicant to determine the effect of various intrinsic factors on the PK of uridine triacetate. There was insufficient data to assess the effect of creatinine clearance on clearance of uridine. There was a trend for increase in clearance with

increasing body surface area (BSA) in adults. However based on the high survival rate and large safety margin, dose adjustment is not needed based on adult BSA or creatinine clearance.

### **Demographic interactions/special populations**

Neither gender nor age (range evaluated: 20 to 83 years) had a substantial effect on uridine PK. There is insufficient data to assess the effect of race on the clearance of uridine. PK data is limited in pediatric patients. However, the proposed pediatric dose of 6.2 g/m<sup>2</sup> (not to exceed 10 g per dose) orally every 6 hours is supported by the efficacy and safety data from pediatric patients (n=6) in trial WELL401.

### **Thorough QT study or other QT assessment**

The effect of uridine triacetate on QT or QTc prolongation has not been studied. The applicant was granted a waiver for conducting a Thorough QT (TQT) study in humans by QT-IRT. The QT-IRT stated that “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.”

### **Exposure-response relationships**

Uridine triacetate is a pro-drug of uridine. Uridine is the active moiety in the plasma, which was determined using a validated HPLC method. The assay to detect uridine triacetate was not validated as the sponsor claimed that uridine triacetate was not stable in biological fluids. The clinical pharmacology team did not conduct an exposure-response analysis because clinical efficacy was demonstrated at the proposed dose. In addition, since the safety profile of uridine triacetate was considered low risk, exposure-response analyses for safety were also not conducted.

### **Other notable issues**

(b) (4)



### *Genomics*

The pharmacogenomics review focused on the reporting of genomic data specifically related to dihydropyrimidine dehydrogenase (DPD) deficiency. DPD is responsible for the breakdown of fluorouracil and capecitabine to inactive metabolites. Approximately 0.2-5% of the population have partial or complete DPD deficiency which could lead to impaired elimination of fluorouracil and capecitabine and therefore potentially early-onset, severe or life-threatening

toxicity. In studies WELL401 and 401.10.001, testing for DPD deficiency and other genetic variations were performed in 19 patients with previously known DPD deficiency or early-onset toxicity. Nine patients had variants in the gene encoding DPD and four had genotypes often associated with complete or partial DPD deficiency. However, the pharmacogenomics team concluded that the available genetic testing results could not definitively account for the early-onset, severe or life-threatening toxicities from fluorouracil or capecitabine administration due to the inconsistencies introduced by the use of different tests with differing methods and allele assays, as well as the unclear functional impact of some of the variants identified. There were also cases of early-onset toxicity which did not have positive DPD testing and cases for which no testing was performed. For these reasons, no specific description of DPD deficiency was included in the label.

## 6. Clinical Microbiology

The microbiology review by Christina Capacci-Daniel, Ph.D. concluded that there were no outstanding microbiology issues that preclude approval and no additional studies were needed. The tests and proposed acceptance criteria for microbial burden were considered to be adequate to assure the microbial quality of the drug product.

## 7. Clinical/Statistical- Efficacy

Gwynn Ison, M.D., was the primary clinical reviewer of efficacy for this application. There were no disagreements between the CDTL and clinical reviewer with respect to efficacy analyses. As the data submitted was descriptive in single-arm trials there was no formal statistical review conducted although the statistical team assisted with description of the overdose rate and dose analysis. This NDA is primarily supported by survival results from two single-arm, open-label, expanded access trials entitled “**An Open-Label Protocol for the Use of Uridine Triacetate as an Antidote to Treat Patients at Excess Risk of fluorouracil Toxicity Due to Overdosage or Impaired Elimination (401.10.001)**” and “**Emergency Use of Uridine Triacetate as an Antidote to Treat Patients at Excess Risk of 5-Fluorouracil Toxicity Due to Overdosage or Rapid Onset of Serious Toxicity (WELL401)**”. Trial 401.10.001 enrolled 60 patients and Trial WELL401 enrolled 75. The data from these 135 patients are used for the primary efficacy analysis of survival at 30 days or the resumption of chemotherapy if prior to 30 days.

### **Study Design:**

Both trials were single-arm, open-label, expanded access protocols for use of uridine triacetate as an antidote to treat patients at excess risk of 5FU toxicity due to overdosage or impaired elimination. WELL401 was conducted as a collection of single patient INDs according to clinical operations procedures which were developed to provide emergency access to uridine triacetate prior to the initiation of protocol 401.10.001 (August 2011), and (after August 2011) for patients who did not meet entry criteria for Trial 401.10.001. The main differences of the two trials were that patients treated with capecitabine, pediatric patients, patients treated outside of the 96 hour window post-fluorouracil administration, and patients treated outside of the US were included on the grouping of single patient INDs in WELL401. In both trials, uridine triacetate was administered at 10 g every 6 hours for 20 doses except for four pediatric patients in WELL401

who were treated at a BSA dose of  $6.2 \text{ g/m}^2$  every 6 hours for 20 doses. Follow-up continued for 30-days.

The primary objectives of both trials were:

1. To provide uridine triacetate as an antidote to treat patients at excess risk of fluorouracil toxicity due to overdosage (defined as administration of fluorouracil at a dose, or infusion rate, greater than the maximum tolerated dosage (MTD) for the patient's intended regimen) or impaired elimination
2. To evaluate survival for 30 days in patients treated with uridine triacetate initiated between 3 and 96 hours after completion of fluorouracil dosing, who are at excess risk of fluorouracil toxicity due to overdosage or impaired elimination

Secondary objects of the both trials were:

1. To assess the occurrence, severity, and duration of neutropenia, thrombocytopenia, and leukopenia, commonly associated with fluorouracil dosing, in patients at excess risk of fluorouracil toxicity due to overdosage or impaired elimination
2. To assess the occurrence, severity, and duration of mucositis, diarrhea, and skin and neurological toxicities, commonly associated with fluorouracil dosing, in patients at excess risk of fluorouracil toxicity due to overdosage or impaired elimination
3. To assess systemic levels of uridine and uracil in treated patients
4. To assess the safety and tolerability of uridine triacetate in treated patients

There were two descriptions of what constituted an overdose in the protocol for each trial. In the overdose description section of the protocol, according to the Institute for Safe Medication Practices (ISMP) guidelines for fluorouracil overdose, a patient could be at excess risk for fluorouracil toxicity if the dose of fluorouracil is at least 10% greater than the intended dose or if the infusion rate was at least 25% greater than the intended rate for the patient. However, the eligibility criteria and what was used for trial inclusion was an overdose defined as administration of fluorouracil at a dose, or infusion rate, greater than the MTD for the patient's intended regimen of fluorouracil or its oral pro-drug capecitabine, or impaired fluorouracil elimination. This inconsistency did not affect the efficacy review as the clinical review team determined all patients were enrolled based on the eligibility criteria. As a result the eligibility criteria were described in Section 14 of the label.

Due to the similarities between the two trials, the efficacy was evaluated in both trials combined (n=135).

### **Protocol Deviations**

There were four major protocol deviations; four patients received uridine triacetate greater than 96 hours following the end of fluorouracil or capecitabine administration. Minor protocol deviations included protocol-specified procedures (vital signs, toxicity assessments, lab draws) not being done in 96% of patients, and protocol-specified procedures being done outside of the specified window (52%). As the primary efficacy outcome was survival these violations did not impact the overall conclusions of the trial. The fact that two of the patients treated outside of the 96 hour window died is supportive of the limitation of use that efficacy was not established outside of 96 hours following the end of fluorouracil or capecitabine administration.

### Patient Demographics and Disease Characteristics

In the combined trials, the median age of the patients was 59 years (range: 1 to 83), 56% were male, 72% were white, 9% were Black/African American, 6% were Hispanic, 4% were Asian, and 95% had a cancer diagnosis. Of the 135 patients, 117 were treated with uridine triacetate following an overdose of 5-fluorouracil (n=112) or capecitabine (n=5), and 18 were treated after exhibiting early-onset, severe or life-threatening 5-fluorouracil toxicities within 96 hours following the end of 5-fluorouracil administration. The severe or life-threatening toxicities involved the central nervous system (e.g. encephalopathy, acute mental status change), cardiovascular system, gastrointestinal system (e.g. mucositis), and bone marrow (e.g. neutropenia). A total of six pediatric patients were administered uridine triacetate. Of the 112 patients overdosed with fluorouracil, 105 (94%) were overdosed by infusion rate only (range 1.3 to 720 times the planned infusion rate), four (4%) were overdosed by dose only, and three (3%) were overdosed by both dose and rate.

### Patient Disposition

A total of 135 patients were enrolled on the two trials. Most patients (61%) completed the dosing of uridine triacetate and the protocol specified 30-day follow-up. Three subjects discontinued uridine triacetate and five subjects died.

	<b>Overdose N=117 (%)</b>	<b>Early-onset N=18 (%)</b>	<b>Total N=135 (%)</b>
Completed trial through Day 30	71 (61)	12 (67)	83 (61)
Resumed chemotherapy prior to Day 30	41(35)	3 (17)	44 (33)
Discontinued due to AE prior to Day 30	2 (2)	1 (6)	3 (2)
Death prior to Day 30	3 (2)	2 (10)	5 (4)

### Efficacy Results

The table below displays the results of the primary endpoint in Trials WELL401 and 401.10.001 combined. Of the 135 patients who were treated with uridine triacetate, 96% (n=130) survived to day 30 or resumed chemotherapy prior to day 30 and 4% (n=5) died. As shown in the table below, the majority of patients who received fluorouracil or capecitabine overdoses (97%) and the majority of patients who exhibited early-onset, severe or life-threatening toxicity following the end of fluorouracil or capecitabine administration (89%) survived.

### Combined Efficacy: All Patients in WELL401 and 401.10.001

	<b>Overdose</b>	<b>Early-Onset</b>	<b>Overall</b>
<b>Total Enrolled</b>	117	18	135
Survival <sup>a</sup>	114 (97%)	16 (89%)	130 (96%)
Death	3 (3%)	2 (11%)	5 (4%)

<sup>a</sup> Survival includes patients who survived at 30 days or patients who resumed chemotherapy prior to 30 days.

### *Efficacy in patients who were overdosed by fluorouracil*

Out of the 112 patients overdosed by fluorouracil, four patients were overdosed by fluorouracil dose alone, with doses eight to ten times the planned dose, and all patients survived. The remaining patients overdosed by fluorouracil (n=108) were overdosed by infusion rate with a range of 1.3 to 720 times the planned infusion rate. Overdoses occurred most commonly due to

the infusion pump being incorrectly programed (n=47) or pump malfunctions (n=26). The applicant submitted retrospective historical case reports of 25 patients who were overdosed with fluorouracil by infusion rate and received supportive care only. These historical case report patients had comparable fluorouracil overdoses at all rates, ranging from 1.9 to 64 times the planned infusion rate. The majority (84%) of these historical patients died, and deaths occurred over the range of infusion rate overdoses. In contrast, 97% (n=105) of the patients who overdosed by fluorouracil infusion rate and received uridine triacetate survived. Since deaths occurred at a range of fluorouracil overdoses, and patients may have variable expressions of toxicity that should not be awaited prior to dosing, it is not possible to quantify the exact overdose which would result in death. Therefore, the indication will reflect simply “overdose” and eligibility criteria and range of fluorouracil overdoses seen in the trials will be described in the clinical trials section. In addition, after a detailed review of all 112 fluorouracil overdose cases on trials WELL401 and 401.10.001, the review team concluded that in the absence of uridine triacetate, patients would have had substantial mortality. Therefore, there is conclusive evidence to support efficacy of uridine triacetate in subjects overdosed by fluorouracil.

*Efficacy in patients who exhibited early-onset, severe or life-threatening toxicity following the end of fluorouracil administration*

There were 18 patients who exhibited early-onset, severe or life-threatening toxicity following the end of fluorouracil administration. Of these two (11%) died and 16 (89%) survived. The review team examined each case in detail and determined that at least 12 of the 18 had benefited from uridine triacetate. Eight of these 12 met FDA determined criteria for demonstrating undisputable uridine triacetate benefit, including life-threatening symptoms appearing within 96 hours following the end of fluorouracil administration, uridine triacetate administration within 96 hours after symptoms appeared, and survival. Four of these patients were intubated due to fluorouracil toxicity and had recovered and survived at 30 days. Another patient required balloon-pump cardiovascular support and recovered after uridine triacetate treatment. Others had life-threatening mental status changes and encephalopathy. In addition, all cases presented with toxicities affecting the cardiac, central nervous, gastrointestinal, or hematopoietic system, and were severe or life-threatening on initial presentation. Despite the life-threatening morbidity seen in almost all of the patients, all but two patients survived. Of the 16 surviving patients, 14 developed symptoms within 96 hours following administration of fluorouracil. An OSE consult requested by OHOP in June of 2014, unrelated to the current NDA, provided some historical information regarding patients who experienced early-onset, severe or life-threatening toxicity following the end of administration of fluorouracil or capecitabine and died. This consult identified fatal adverse event reports of patients who had impaired elimination after treatment with fluorouracil or capecitabine from the last 50 years. Multiple historical cases (58 cases for fluorouracil and 145 cases for capecitabine) were described; many cases demonstrated a similar presentation of early-onset, severe or life-threatening toxicity which was treated with supportive care but ultimately all resulted in death. Therefore, there is conclusive evidence to support efficacy of uridine triacetate in subjects who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil administration.

### *Capecitabine*

Only 5 patients (all on trial WELL401) were treated with capecitabine. The capecitabine overdoses were either accidental administration (three pediatric patients), or attempted suicides with overdoses that would be expected to be fatal. All of the patients survived. Additional capecitabine overdose cases submitted in the 120-day safety update (three cases with capecitabine overdoses of greater than 20,000mg or approximately 15 times the approved daily dose) demonstrated survival in situations where in the absence of uridine triacetate the patients would have died. While no cases were initially submitted for capecitabine resulting in early-onset, severe or life-threatening toxicity, the 120-day safety update did include one patient who was treated with capecitabine, experienced severe or life-threatening toxicity within 96 hours of capecitabine administration, was treated with uridine triacetate within 96 hours of symptoms, and survived. Multiple cases from the OSE consult described above also confirm that early-onset, severe or life-threatening toxicity from capecitabine carries a mortality risk. In addition, capecitabine is a pro-drug of fluorouracil, and therefore mechanistically would be expected to have similar overdose and early-onset toxicity effects as well as response to treatment with uridine triacetate. Therefore, the review team recommends inclusion of capecitabine in the indication for both overdose and early-onset, severe or life-threatening toxicity.

### *Efficacy of uridine triacetate initiation more than 96 hours following the end of fluorouracil or capecitabine administration*

Of the 135 patients, 131 were treated within the protocol specified 96 hour window and 98% lived. Four patients were treated outside of the 96 hour window, and 50% died. Additional information from the 120-day safety update (including deaths in which uridine triacetate was administered after 96 hours) was supportive of specifying treatment as soon as possible within 96 hours and that efficacy after 96 hours was not demonstrated. Therefore the review team is recommending inclusion of a limitation of use stating that the safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established. In addition, a specific guidance in the dosing and administration section will specify that patients should be administered uridine triacetate as soon as possible, and the indication will reflect that overdose patients should be treated regardless of symptoms.

### *Pediatrics*

See Section 10 for a full description of efficacy in pediatric patients.

## **8. Safety**

Gwynn Ison, M.D. was the primary clinical reviewer of safety for this application. There were no disagreements between the CDTL and clinical reviewer with respect to safety analyses. The safety database included the two clinical trials WELL401 and 401.10.001 in which all 135 patients received at least one dose of uridine triacetate. The safety data was not typical as there was no control arm for comparison of safety information. In addition, there was considerable confounding of adverse events as all patients treated with uridine triacetate had received an overdose of fluorouracil or capecitabine which was expected to result in substantial toxicity or had already experienced severe or life-threatening toxicity from fluorouracil at the time of uridine triacetate treatment. As evidenced by the protocol deviations, the safety data was also not

rigorously collected. Despite these issues, and given the indication as emergency treatment for a life-threatening condition, the safety information available is adequate to assess the risks and benefits of uridine triacetate. After detailed review by Dr. Ison, the adverse events deemed possibly related to uridine triacetate were separated from those adverse events deemed related to fluorouracil or capecitabine; these adverse events possibly related to uridine triacetate are summarized below.

### **Deaths**

There were no deaths attributable to uridine triacetate. Of the 135 treated patients on both trials, there were five deaths. Three deaths occurred in patients overdosed with fluorouracil and two deaths occurred in patients who exhibited early-onset, severe or life-threatening toxicity after the end of fluorouracil administration. Of the five deaths, two occurred in patients who were treated with uridine triacetate greater than 96 hours following the end of fluorouracil administration (both in patients exhibiting early-onset, severe or life-threatening toxicity).

### **SAEs**

One patient experienced two SAEs (nausea and vomiting) that were deemed at least possibly related to uridine triacetate by the review team due to the temporal association of uridine administration with these reactions.

### **Discontinuations**

Two patients discontinued uridine triacetate due to adverse events of nausea, vomiting and diarrhea.

### **General AEs**

Adverse Events occurring in >2% of patients receiving uridine triacetate included vomiting (10%), nausea (5%), and diarrhea (3%). Of these cases only one patient experienced Grade  $\geq 3$  toxicity of Grade 3 nausea and vomiting; all other cases were Grade 1 and 2. These findings demonstrate that uridine triacetate is very well tolerated and demonstrates an exceedingly acceptable safety profile for the indicated population. Of the six pediatric patients, only two exhibited Grade 1 nausea.

### **Laboratory tests**

Clinical laboratory values did not contribute meaningful data to inform the safety evaluation of uridine triacetate. Because there are no controlled trials of uridine triacetate to support this indication, it is not possible to draw finite conclusions about how uridine triacetate treatment affects the laboratory abnormalities associated with overdose and early-onset toxicity following the end of fluorouracil or capecitabine administration.

### **Immunogenicity**

Not applicable as immunogenicity was not studied.

### **120-Day Safety Update**

Data submitted in the 120-day Safety Update included 25 additional patients treated with uridine triacetate and did not change the conclusion that uridine triacetate was well tolerated with an acceptable safety profile.

## **9. Advisory Committee Meeting**

This application was not referred to an advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

## **10. Pediatrics**

Orphan designation for uridine triacetate was granted on May 1<sup>st</sup>, 2009. There was no PERC review of uridine triacetate. There were six pediatric patients studied on trial WELL401, three accidentally ingested capecitabine and three were either incorrectly given fluorouracil, received fluorouracil at an increased infusion rate, or exhibited early-onset, severe or life-threatening toxicity. All of these patients survived. In addition, according to section 505B(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, a drug may be considered to be effective in the pediatric population when it has been demonstrated to be effective in adults, if the disease process and the benefits of the drug are expected to be the same as is the case for this application. The safety profile is acceptable with a low risk to pediatric patients. Therefore, due to the cases studied, supportive non clinical safety information, adult clinical data, and a strong biologic and clinical rationale, the pediatric indication was included.

## **11. Other Relevant Regulatory Issues**

### **Application Integrity Policy (AIP)**

Based on the review of the Case Report Forms (CRFs) and narratives, the primary data submitted to this application was found to be reliable for the primary analyses of safety and efficacy except for issues identified by OSI. The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

### **Financial Disclosures**

Disclosure of financial interests of the investigators who conducted the clinical trials was submitted in the FDA form 3454. No investigators had any disclosures.

### **Good Clinical Practice**

According to the applicant, the trials were conducted in compliance and accordance with Good Clinical Practice (GCP). Institutional Review Board (IRB) notification was required within 5 days of enrolling and initiating treatment for each patient, per 21 CFR 56.104(c). The IRBs met the requirements of the International Conference of Harmonization (ICH) Harmonized Tripartite Guideline for GCP.

### **OSI audits**

The Office of Scientific Investigations inspected the sponsor Wellstat Therapeutics, Inc., as well as two clinical sites, one from WELL 401 and one from 401.10.001. As the trials were conducted using expanded access emergency treatment procedures, OSI noted that the sponsor assembled the CRFs from the source data. OSI concluded that after an assessment of the source records that the data were generally acceptable except for hematology data. During the transcription of the source data, eight out of 69 audited records had incorrect units of hematology data entered into the CRFs resulting in incorrect assignments of high, low or normal values. For this reason, the sponsor site was given a preliminary outcome of voluntary action indicated. The sponsor submitted updated and corrected hematology laboratory data in the 120-day safety update addressing this concern. One of the clinical sites inspected, Dr. Markan's site in Glen Burnie, MD also received a preliminary outcome of voluntary action indicated due to trial conduct issues including failure to obtain IRB approval within the appropriate timeframe, data inconsistencies, incomplete drug accountability records, and failure to maintain study reports. The review team did not feel the specific violations had impact on the overall results of the trial, only one subject was treated at this site, and most of the violations were due to the emergency nature of the treatment. The preliminary outcome of other inspected site was no action indicated.

### **Other discipline consults**

The follow FDA Offices and Divisions supplied subject matter expertise by consulting on this application; DMPP/OPDP, DMEPA, DRM, Maternal Health, Pediatrics, and Patient Labeling. No issues were identified that precluded recommendations for approval for this application.

## **12. Labeling**

### **Proprietary name**

The proposed proprietary name for uridine triacetate is Vistogard<sup>®</sup>. DMEPA notified DOP1 that the name Vistogard<sup>®</sup> was acceptable from a look-alike and sound-alike perspective. No objections to the name Vistogard<sup>®</sup> were identified by OPDP or the clinical review team during the review cycle.

### **Physician labeling**

The review team did not agree with the applicant's initial approach to the label. This CDTL agreed with the recommendations made by the review teams that are described below. Labeling changes made in agreement with the applicant in the course of the review include the following high-level changes by Section:

- Section 1 Indications and Usage:
  1. The indication statement was split up to include separate clauses for overdose indication and early-onset of severe or life-threatening toxicities.
  2. The explanation of the early-onset toxicities was made more detailed.
  3. The terms early-onset and unusual were used to mirror the fluorouracil label which is currently under revision.
  4. The indication was amended to include capecitabine.
  5. The indication was written inclusive of both adult and pediatric patients.

6. As detailed in Section 5 of this review, (b) (4) which the applicant had included in labeling was deleted from Section 1.
  7. A Limitations of Use detailing a risk of the non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs was added.
  8. A statement regarding (b) (4) a limitation of use as efficacy after 96 hours is not known.
- Section 6: Adverse Reactions were edited to include a combined population from both trials and only to include adverse reactions attributable to uridine triacetate.
  - Section 11 Description: (b) (4) was removed as this term does not fully explain the effect of uridine triacetate. In the highlights section (b) (4) was replaced with pyrimidine analog.
  - Section 14 Clinical Studies: This section was edited to combine the two trials, include information regarding the historical controls and simplified with respect to data presentation.
  - Throughout the label, including Section 12 (Mechanism of Action), statements which could be misleading regarding (b) (4) were removed.

#### **Carton and immediate container labels**

The carton and immediate container labels were revised for clarity and understandability in conjunction with CMC and DMEPA.

#### **Patient labeling/Medication guide**

The PPI was revised for clarity, brevity, and understandability in conjunction with OPDP and recommendations. No Medication guide was required.

### **13. Recommendations/Risk Benefit Assessment**

#### **Recommended Regulatory Action**

The recommendation of this Cross Discipline Team Leader is for approval of NDA 208159. All review teams recommended approval or reported that there were no findings that would preclude approval. The recommended indication is as follows:

VISTOGARD is indicated for the emergency treatment of adult and pediatric patients:

- following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or
- who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration

Limitations of use:

- VISTOGARD is not recommended for the non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs.
- The safety and efficacy of VISTOGARD initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established.

**Risk Benefit Assessment**

Overdose of fluorouracil or capecitabine, and early-onset, severe or life-threatening toxicity due to fluorouracil or capecitabine, although rare, are commonly fatal and have no approved therapies outside of supportive care. Treatment of patients in this setting constitutes an oncologic emergency. The recommendation for approval of uridine triacetate is based on the primary efficacy analyses from two single-arm trials, WELL401 and 401.10.001. Patients (n=135) were treated with uridine triacetate following a fluorouracil or capecitabine overdose, or after exhibiting early-onset, severe or life-threatening toxicities following the end of fluorouracil or capecitabine administration. These trials demonstrated survival at 30 days or a resumption of chemotherapy prior to 30 days of 96% (n=130). Limitations of the trials included the single-arm and non-randomized design. Due to the life-threatening nature of the conditions, a concurrent control arm would not have been ethical. A detailed evaluation of all uridine triacetate treated patients, and comparisons to historical case reports, demonstrated a clear survival benefit and definitive efficacy in patients receiving fluorouracil or capecitabine overdose and patients exhibiting early-onset severe or life-threatening toxicities. In addition, despite small numbers in certain subgroups such as capecitabine treated patients, and pediatric patients, due to mechanism of action, supportive adult fluorouracil data, and additional information in the 120-day update, uridine triacetate is also effective in these populations. Supportive nonclinical data and consistent recommendations for approval from all disciplines added to the confidence of these conclusions.

The safety profile of uridine triacetate was acceptable and the toxicities were mild and infrequent. Most common adverse reactions (> 2%) were Grade 1 and 2 vomiting, nausea, and diarrhea. Only one patient experienced Grade 3 adverse reactions or serious adverse reactions (grade 3 nausea and vomiting). No deaths were attributable to uridine triacetate.

There is a potential risk that using uridine triacetate in a non-emergent setting for patients who experience usual toxicities of fluorouracil or capecitabine might result in decreased efficacy of fluorouracil or capecitabine. To address this concern, the timing of early-onset toxicities (within 96 hours), and a detailed description of the expected affected organ systems with potential severe or life-threatening toxicities, are described in the indication statement. In addition, a limitation of use was added to further highlight this potential risk.

In conclusion, uridine triacetate for the emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or of patients who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or

capecitabine administration demonstrates a favorable benefit: risk profile with enough evidence to recommend approval.

**Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No post-market risk management activities are necessary at this time (other than those required for all NDAs such as described in 21 CFR 314.81). The proposed label contains patient counseling information for trained prescribing physicians.

**Recommendation for other Postmarketing Requirements and Commitments**

One postmarketing commitment (PMC) from CMC was agreed upon with the applicant to address issues with the process validation batches which demonstrated intra- and inter-batch variability in dissolution of the products. The PMC is as follows:

As part of the dissolution method revision, perform retrospective analysis and confirm the dissolution studies submitted to support this manufacturing process, including:



c) Study the effect of drug substance particle size distribution and final granule particle size distribution on dissolution to determine the size limits at which dissolution may become retarded. Establish justified drug substance and granule particle size distribution limits based on this understanding.

PMC Schedule Milestones

Final Protocol Submission: 2/2016

Final Report Submission: 8/2016

## 14. References

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JULIA A BEAVER  
12/07/2015