

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208159Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 9, 2015
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA/BLA # Supplement #	NDA 208159/S0
Applicant	Wellstat Therapeutics Corporation
Date of Submission	July 10, 2015
PDUFA Goal Date	March 10, 2015
Proprietary Name / Non-Proprietary Name	Vistogard/ Uridine Triacetate
Dosage Form(s) / Strength(s)	Oral granules/ 10 grams in single- ^{(b) (4)} packets
Applicant Proposed Indication(s)/Population(s)	VISTOGARD i ^{(b) (4)} within 96 hours of ^{(b) (4)} administration.
Action/Recommended Action for NME:	<i>Approval</i>
Approved/Recommended Indication/Population(s) (if applicable)	VISTOGARD is indicated for the emergency treatment of adult and pediatric patients: <ul style="list-style-type: none"> • 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.

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Gwynn Ison
Statistical Review	Joyce Chen; Shenghui Tang
Pharmacology Toxicology Review	W. David McGuinn; Todd Palmby
Clinical Pharmacology Review	Runyan Jin, Qi Liu; Anshu Marathe; Yaning Wang
Genomics Review	Sarah Dorff; Rosane Charlab Orbach
CMC Review	Xavier Ysern; Xiao Chen; Olen Stephens
Biopharmaceutics	Ge Bai; Salaheldin S. Hamed; Sandra Suarez-Sharp
DPMH Maternal Health	Tamara Johnson
DPMH Pediatrics	Ethan Hausman
OSE/DMEPA	Grace Jones
OPDP	Nick Senior
OSI	Lauren Iacono-Connors
Patient Labeling	Sharon Mills; LaShawn Griffiths
Associate Director for Labeling	William Pierce
CDTL Review	Julia Beaver

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

1. Introduction

This application seeks to establish the indication for uridine triacetate for the treatment of patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting symptoms of serious toxicity within 96 hours of 5-fluorouracil administration. The application relies on the clinical experience of 135 patients, enrolled in two single-arm, open-access studies, who were treated with uridine triacetate following an overdose (n=117) or after exhibiting severe or life-threatening symptoms consistent with fluorouracil toxicity (n=18). The two studies were controlled by the collective experience of 25 patients reported in the literature to have a documented overdose of fluorouracil and supported by an extensive review of submitted safety reports to the Agency concerning fluorouracil overdose. Of the 135 patients who were treated with uridine triacetate, 130 (96%) survived and five (4%) died. Of the 25 patients reported in the literature to have received a documented overdose of fluorouracil, 21 (84%) died.

The toxicity profile of uridine triacetate can be characterized as mild with the most common reported adverse reactions were vomiting, nausea, and diarrhea. The most important safety concern regarding the administration of uridine triacetate is the potential attenuation of the efficacy of fluorouracil or capecitabine. For this reason, the indication of uridine triacetate is restricted to the emergency use for overdose or for early-onset, severe adverse reactions associated with fluorouracil. (b) (4)

Based on the data submitted in this New Drug Application, uridine triacetate was determined to exhibit a favorable benefit:risk profile for the emergency treatment of fluorouracil overdose and is recommended for approval for the following indication:

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.

2. Background

From the CDTL review:

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.

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. Overdoses of fluorouracil most commonly result from infusion rate overdoses (from pump failures and incorrect programing) as opposed to dose overdoses. In addition, early-onset, severe or life threatening toxicities from these drugs can also result in death.

Product Information

The active ingredient of Vistogard® 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 1st, 2009-** Uridine triacetate received orphan drug designation (b) (4) in the treatment of fluorouracil poisoning.
- **July 5th, 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 (b) (4).
- **May 2014-** FDA recommended (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 (b) (4) to treat patients at risk of excess fluorouracil toxicity due to overdose”.
- **January 15th, 2016-** The first portion of the rolling submission of NDA 208159 was submitted.
- **September 4th, 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

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance.

From the CMC review:

This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has rendered a final “Acceptable” recommendation for the facilities involved in this application (refer to Panorama 6-Nov-2015).

The claim for the Categorical Exclusion for the Environmental Assessment as per 21 CFR 25.31 (b) is granted. The labels/labeling issues have been resolved as of this review through meetings with the clinical division.

Therefore, from the OPQ perspective, this NDA is recommended for approval. A 24 month shelf life is granted for the drug product when stored in the proposed container configuration and stored at 25°C (77°F), excursions permitted to 15° to 30 °C (59° to 86°F).

There will be one post-marketing commitments for this NDA. In the cross referenced NDA 208-169, the process validation batches demonstrated (b) (4) such that there is significant variability in dissolution of the products intra-batch and inter-batch. Presumably, this is due to dissolution dependence on the particle size of the granules. Because the indication for NDA 208-159 is lifesaving, orphan designated, (b) (4) and there is no toxic dose known for the product, the risk-benefit analysis for this product dictates that the NDA be approved. Furthermore, for the 5- fluorouracil toxicity indication, dosing and monitoring of the patients is frequently enough such that variability in the drug product is not likely to adversely impact the patient. Post-marketing commitments were established for NDA 208-169 that will address the same product quality concerns for NDA 208-159. The new post-marketing commitment for NDA 208-159 is as follows:

(b) (4) retrospective analysis (b) (4) manufacturing process, (b) (4)

(b) (4)

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.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

From the primary pharmacology/toxicology review:

The nonclinical safety package for uridine triacetate included safety pharmacology studies, repeat-dose toxicology studies in dogs (3 month) and rats (3 and 6 months), genetic toxicology studies, and reproductive toxicology studies in rats (Segment 1 fertility and early embryonic development study and Segment 2 embryo-fetal development study). In all these studies, uridine triacetate demonstrated very little toxicity even at high daily doses as one might expect of an acetylated pyrimidine natural product.

The studies of uridine triacetate efficacy reviewed here showed that uridine triacetate and uridine both prevent further damage due to 5-FU over exposure as measured by white cell parameters once they are given, but these treatments do not reverse the damage by day 8. By day 12 white cell parameters remain below historical controls, but show signs of recovery. The antidotal activity of uridine triacetate demonstrates a dose response with a plateau at the highest doses of these experiments. These results suggest that the clinical dose is higher than necessary to achieve the desired clinical response.

When 5-FU is given to mice at a relatively high dose without (b) (4) or at a low dose with (b) (4), uridine triacetate significantly increases survival. Survival decreases as the interval between the administration of 5-FU and the administration of uridine triacetate increases. Administration of uridine triacetate more than 96 hours after the 5-FU dose is ineffective.

Once given, uridine triacetate stops the progressive damage caused by overexposure to 5-FU in the intestines of mice. This antidotal effect can be seen qualitatively as improved tissue health in micrographs and quantitatively as increased two dimensional surface areas of the intestinal villi. The area of the intestinal villi after uridine triacetate treatment was statistically equivalent to that of saline controls.

Though these efficacy experiments are poorly designed and in some places poorly controlled and missing data the total body of evidence indicates that uridine triacetate prevents further damage from high exposures to 5-FU once it is administered. It does not appear to significantly hasten recovery. (b) (4)

(b) (4) *The evidence of efficacy in animals supports the evidence of clinical efficacy for this setting.*

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

From the clinical pharmacology review:

The clinical pharmacology program for uridine triacetate includes 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 following are the major findings of the review:

- The proposed dose is reasonable for adults based on the high survival rate and lack of major safety issues observed in the clinical trials.*
- The proposed dose is reasonable for pediatric patients based on the efficacy and safety findings in WELL 401. The data is however limited to 6 pediatric patients.*
- Food did not impact the pharmacokinetics of uridine and it is recommended to administer uridine triacetate without regard to meals in the labeling.*
- There is no clinically meaningful effect of gender, race, age and body surface area on uridine PK in adults and no dose adjustment is needed based on these intrinsic factors.*

NDA208159 is acceptable for approval from a clinical pharmacology perspective.

From the genomics reviewer:

The available genetic results cannot account for the rapid onset of serious toxicity in most patients evaluated. The inconsistency introduced by the use of different tests across patients, which could employ different methods and assess different alleles, and the unclear functional impact of some of the variants identified make the results difficult to interpret.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

This application is supported by two single-arm, expanded access studies 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. The following is excerpted from the clinical studies section (14) of the agreed upon text in the uridine triacetate package insert regarding the design and efficacy results of Studies 401.10.001 and WELL401:

The efficacy of VISTOGARD was assessed in 135 patients who were treated in two open-label trials, Study 1 (n=60) and Study 2 (n=75). The patients in both studies had either received an overdose of fluorouracil or capecitabine, or presented with severe or life-threatening toxicities within 96 hours following the end of fluorouracil or capecitabine administration. Overdose was defined as administration of fluorouracil at a dose, or infusion rate, greater than the intended dose or maximum tolerated dose for the patient’s intended regimen of fluorouracil. VISTOGARD was administered at 10 grams orally every 6 hours for 20 doses or at a body surface area adjusted dosage of 6.2 grams/m²/dose for 20 doses for four patients between 1 and 7 years of age. The major efficacy outcome was survival at 30 days or until the resumption of chemotherapy if prior to 30 days.

In Study 1 and Study 2 combined, 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 VISTOGARD 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. The severe or life-threatening toxicities involved the central nervous system (such as encephalopathy, acute mental status change), cardiovascular system, gastrointestinal system (such as mucositis), and bone marrow. A total of six pediatric patients were administered VISTOGARD. Four patients initiated VISTOGARD more than 96 hours following the end of fluorouracil or capecitabine administration. 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.

The survival results are shown in Table 1. Of the 135 patients who were treated with VISTOGARD in Studies 1 and 2 there were five deaths due to fluorouracil or capecitabine toxicity (4%). Of the five patients who died, two were treated after 96 hours following the end of fluorouracil administration. In the patients treated with VISTOGARD for an overdose of fluorouracil or capecitabine in Studies 1 and 2 combined (n=117), survival at 30 days was 97% (n=114). In the patients receiving VISTOGARD for early-onset severe or life-threatening toxicity in Studies 1 and 2 combined (n=18), the survival at 30 days was 89% (n=16). In these studies 33% of patients (n=45) resumed chemotherapy in less than 30 days. Based on retrospective historical case reports of 25 patients who were overdosed with fluorouracil and

received supportive care only, all were overdosed by rate with a range 1.9 to 64 times the planned infusion rate, and 84% died.

Table 1 Combined Efficacy: All Patients in Study 1 and Study 2

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

^a Survival includes patients who survived at 30 days or patients who resumed chemotherapy prior to 30 days.

8. Safety

The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert. Unlike most oncology products, there were no warnings and precautions in the agreed upon package insert.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions and using a wide range of doses, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of VISTOGARD was assessed in 135 patients (median age 59 years, 56% male) treated in 2 single-arm, open-label, multi-center trials. VISTOGARD was administered at 10 grams orally every 6 hours for 20 doses or at a body surface area adjusted dosage of 6.2 grams/m²/dose for 20 doses in four patients between 1 and 7 years of age. The median duration of exposure was 4.8 days, with a median of 20 doses (range 1 to 23). VISTOGARD was discontinued for adverse reactions in two (1.4%) patients. Serious adverse reactions and Grade ≥3 adverse reactions were seen in one patient receiving VISTOGARD (Grade 3 nausea and vomiting). Table 2 summarizes the adverse reactions that occurred in greater than 2% of patients in Studies 1 and 2 combined.

Table 2 Adverse Reactions in > 2% of Patients Receiving VISTOGARD in Studies 1 and 2

Adverse Reaction	N=135 Patients
Vomiting	13 (10%)
Nausea	7 (5%)
Diarrhea	4 (3%)

9. Advisory Committee Meeting

This application was not referred to a meeting of the Oncologic Drugs Advisory Committee.

10. Pediatrics

From the CDTL Review:

Orphan designation for uridine triacetate was granted on May 1st, 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

I concur with the conclusions made by the CDTL as below:

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

The major labeling discussions that took place between the review team and the applicant is summarized in the review performed by the Associate Director for Labeling, Bill Pierce and the following is excerpted from his review:

Established Pharmacologic Classification (EPC): Revised from (b) (4) to “pyrimidine analog”. The review team determined that “pyrimidine analog” was the most scientifically accurate and clinically meaningful EPC without being promotional or misleading.

“Pyrimidine analog” better describes how this drug acts pharmacologically in humans; is consistent with other products used to treat overdose or reverse life threatening ARs related to drug exposure (e.g., VORAXAZE®; Levoleucovorin Injection); and is consistent with the EPC for the other approved uridine triacetate product (XURIDEN®).

1. INDICATIONS AND USAGE

- *The indication statement was divided into separate clauses for the overdose indication; and for the early onset, severe or life-threatening toxicities indication.*
- *The indication statement was revised to clarify that VISTOGARD is approved for adult and pediatric patients.*
- *The terms “early-onset”, “unusual”, and “emergency use” were used to be consistent with the fluorouracil labeling currently under review; and to better describe the intended population indicated for treatment with VISTOGARD.*
- *A statement describing (b) (4) was removed due lack of evidence to support these claims.*
- *Capecitabine was added to the indications statement to better reflect available case data submitted by the Applicant; with consideration to the uridine triacetate mechanism of action, and the fact that capecitabine is a fluorouracil prodrug.*
- *The early-onset, severe or life threatening toxicities (i.e., cardiac or central nervous system; gastrointestinal toxicity and/or neutropenia) were revised to clarify appropriate use of VISTOGARD and to reflect the patient experience from the clinical trials to support this indication.*
- *A Limitations of Use statement (LOU) was added to increase the prominence of the risks related to non-emergent treatment of adverse reactions (ARs) associated with fluorouracil or capecitabine because VISTOGARD may diminish the efficacy of these drugs. The review team agreed that, given the available data related to this concern, the most appropriate way to disseminate this risk was by using only a LOU statement.*

- (b) (4)
- *The statement regarding the timing (within 96 hours) of VISTOGARD administration after fluorouracil or capecitabine was revised and moved to the Limitations of Use since the safety and efficacy of VISTOGARD has not been established when administered 96 hours after discontinuation of fluorouracil or capecitabine.*
 - (b) (4)

12.1 Mechanism of Action

- *This section was extensively revised to improve accuracy; and to remove (b) (4) Throughout the label, potentially misleading statements, which suggest the Applicant has definitely proven VISTOGARD (b) (4).*

14. CLINICAL STUDIES

- *Revised the description of the two registration trials to better describe the data used to support the efficacy of VISTOGARD, and to remove redundant information.*
- *Added a definition for overdose that is consistent with the patients treated in the registration trials and the indicated population*
- *Added a description of the symptoms present in patients who were treated for severe or life-threatening toxicities within 96 hours following fluorouracil administration.*
- *Added a statement to describe the database, exposure, and incidence of death (84%) from the retrospective historical case reports provided by the Applicant. This information is important to adequately interpret the findings from the two single-arm, open-label, registration trials.*
- *Removed claims related (b) (4)*
- *Removed the (b) (4) .*

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action:
Approval
- Risk Benefit Assessment

I concur with the assessment of the review team that this application should be approved.

This application demonstrates the effectiveness of uridine triacetate as emergency treatment of fluorouracil overdose or relative overdose as manifested by early-onset, severe or life-threatening toxicity. The safety of uridine triacetate as emergency treatment has been established, but the routine use of uridine triacetate in non-emergent situations has not been established. During the course of the review, it was critical to label the drug appropriately (b) (4)

[Redacted]

In addition, the indication was broadened to include the potential overdose of capecitabine and was inclusive of the pediatric population. The single-arm strategy was appropriate for this indication as it would have been unethical to require a randomized trial. This application demonstrated the utility of expanded access protocols as the sponsor collected adequate data to support marketing approval from two expanded access studies, thereby allowing access of this life-saving drug during the course of drug development.

Fluorouracil overdose, whether resulting from a true over-administration of drug or from a relative overdose due to metabolic factors, is an oncologic emergency. The approval of uridine triacetate provides a potential life-saving therapy for patients who are exposed to fluorouracil overdose.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

A REMS is not recommended for this product.

- Recommendation for other Postmarketing Requirements and Commitments

There is one post-marketing commitment for this NDA related to CMC.

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

[Redacted] (b) (4)

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.

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

/s/

GEOFFREY S KIM
12/10/2015