FDA Approval: Uridine Triacetate for the Treatment of Patients Following Fluorouracil or Capecitabine Overdose or Exhibiting Early-Onset Severe Toxicities Following Administration of These Drugs

Gwynn Ison, Julia A. Beaver, W. David McGuinn Jr., Todd R. Palmby, Jeannette Dinin, Rosane Charlab, Anshu Marathe, Runyan Jin, Qi Liu, Xiao Hong Chen, Xavier Ysern, Olen Stephens, Ge Bai, Yaning Wang, Sarah E. Dorff, Joyce Cheng, Shenghui Tang, Rajeshwari Sridhara, William Pierce, Amy E. McKee, Amna Ibrahim, Geoffrey Kim, and Richard Pazdur

Authors' Affiliations: Center for Drug Evaluation and Research, U.S. Food and Drug Administration, White Oak, Maryland.

Corresponding Author: Gwynn Ison, OHOP, OND, CDER, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Building 22, Room 2102, Silver Spring, MD 20993-0002. Phone: 301-796-2330; Fax: 301-796-9845; E-mail: Gwynn.Ison@fda.hhs.gov

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Abstract

On December 11, 2015, the FDA approved uridine triacetate (VISTOGARD®, Wellstat Therapeutics Corporation) for the emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, and of those 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. Uridine triacetate 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, and the safety and efficacy of uridine triacetate initiated more than 96 hours following the end of administration of these drugs has not been established. The approval is based on data from two single-arm, open-label, expanded access trials in 135 patients receiving uridine triacetate (10g or 6.2g/m^2 orally every 6 hours for 20 doses) for fluorouracil or capecitabine overdose, or who exhibited severe or life-threatening toxicities within 96 hours following the end of fluorouracil or capecitabine administration. Ninety six percent of patients met the major efficacy outcome measure, which was survival at 30 days or survival until the resumption of chemotherapy, if prior to 30 days. The most common adverse reactions were vomiting, nausea, and diarrhea. This article summarizes the FDA review of this New Drug Application (NDA) and the data supporting approval of uridine triacetate as well as the unique regulatory situations encountered by this approval.

Introduction

Each year, hundreds of thousands of patients in the United States receive treatment with either fluorouracil or capecitabine (a pro-drug of fluorouracil) for a variety of malignancies, including multiple gastrointestinal malignancies and breast cancer (1). Fluorouracil and capecitabine are cytotoxic antimetabolites that interfere with nucleic acid metabolism in both normal and cancer cells. Studies have reported an approximate 0.5% incidence of mortality from fluorouracil toxicity, and an estimated 0.5-1% of incidence of mortality from capecitabine-based regimens (2-7). While overdoses of these drugs are rare, they can result in significant morbidity and mortality. In addition, certain patients have impaired elimination of these drugs and therefore manifest with early-onset, severe or life-threatening toxicities that can result in death. One of the most well-described etiologies for impaired elimination of fluorouracil and capecitabine is a partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPYD, also known as DPD), which is the initial rate-limiting enzyme in the catabolism of fluoropyrimidines (8). DPD activity is subject to wide variability due in part to genetic variation in the sequence of the DPD gene (*DPYD*), which can result in a range of enzymatic deficiency from partial (~3-5% of the population) to complete loss (~0.2% of the population) of enzyme activity (9-10). Unfortunately, prescreening of patients for "impaired" DPD activity prior to initiation of pyrimidine therapy is not routinely performed and is not yet possible with a high level of predictive accuracy using available genotyping and/or phenotyping tests (11). Prior to uridine triacetate, there were no approved therapies for patients experiencing serious or life-threatening toxicities after receiving fluorouracil or capecitabine.

Chemistry

VISTOGARD oral granules contain the active ingredient uridine triacetate, which is a pyrimidine analog. The chemical name for uridine triacetate is (2',3',5'-tri-O-acetyl-ß-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione. Uridine triacetate is supplied as 10g packets for oral administration containing the following inactive ingredients: ethylcellulose (0.309 grams), Opadry® Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.077 grams), and natural orange juice flavor (0.131 grams). During the NDA review, concerns related to intra-batch and inter-batch variability in the dissolution of the products were identified that could impact the absorption and availability of the drug. However, due to the demonstrated favorable benefit-risk and no known toxic dose, the variability was deemed acceptable, and a post-marketing commitment to confirm the dissolution studies and address these concerns was agreed upon.

Nonclinical Pharmacology and Toxicology

Uridine triacetate is a pyrimidine analogue and acetylated pro-drug of uridine. Excess circulating uridine is converted to uridine triphosphate (UTP), which competes with FUTP for incorporation into RNA. Uridine competitively inhibits cell damage and cell death caused by fluorouracil. The effect of uridine triacetate on the anti-tumor activity of fluorouracil is not currently known; for this reason, the product information for uridine triacetate included a limitation of use detailing the potential of uridine triacetate to result in decreased fluorouracil or capecitabine efficacy.

Repeat-dose toxicology studies in rats demonstrated that the maximum feasible dose of 2000 mg/kg/day was well tolerated. Uridine triacetate was not genotoxic, and there were no findings suggestive of tumorigenic potential in the 6-month repeat-dose toxicity study in rats. Reports from rodent carcinogenicity studies were not submitted or required to support this

application. Uridine triacetate did not affect fertility or reproductive performance in male and female rats.

In mice given sub-lethal doses of fluorouracil, uridine triacetate decreased hematologic toxicity as a function of increasing dose, although hematologic toxicity was not completely prevented. In mice given a lethal dose of fluorouracil, uridine triacetate resulted in 90% survival when given within 24 hours. Survival decreased with increasing intervals between fluorouracil dosing and uridine triacetate treatment.

Clinical Pharmacology

Following single dose oral administration, the maximum uridine concentrations in plasma was achieved within 2-3 hours, and the half-life ranged from 2 to 2.6 hours. Mean uridine concentrations after 20 doses increased approximately 1.5 times in the clinical trials. Food did not impact the pharmacokinetics of uridine, and uridine triacetate can be administered without regard to meals. When necessary, uridine triacetate can be administered via a nasogastric or gastrostomy tube.

Uridine can be excreted via the kidneys and can also be metabolized by normal pyrimidine catabolic pathways present in most tissues. In vitro enzyme data did not reveal meaningful effects of uridine triacetate or uridine on cytochrome P450 inhibition or induction. In vitro data showed that uridine triacetate was a weak substrate for P-glycoprotein (ABCB1, also known as P-gp). Due to the potential for high concentrations of uridine triacetate in the gut after dosing, the interaction of uridine triacetate with orally administered P-gp substrate drugs cannot be ruled out. There is no clinically meaningful effect of gender, race and age on uridine PK in adults, and no dose adjustment is needed based on these intrinsic factors. Although there was a trend for increase in clearance of uridine triacetate with increasing body surface area (BSA) in

adults, given the high survival rate and large safety margin, dose adjustment was not thought to be needed based on BSA in adults. A BSA-based dose of 6.2 grams/m^2 orally every 6 hours was considered reasonable for pediatric patients, as there were 6 pediatric patients who received BSA-based dosing, and all of them survived without major safety concerns.

Clinical Trial Design

The approval of uridine triacetate was based on data from two single-arm, open-label trials. The first trial, WELL401 (n=75), was a collection of single patient investigational new drug applications performed according to clinical operations procedures developed to provide emergency access to uridine triacetate. The second trial, 401.10.001 (n=60), was an expanded access protocol that was requested by FDA in order to collect better quality efficacy and safety data. Both trials included adult patients who had either fluorouracil overdose or presented with severe or life-threatening toxicities within 96 hours following the end of fluorouracil administration. WELL401 also included patients treated with capecitabine, pediatric patients, patients treated outside of the 96 hour window post-fluorouracil administration, and patients treated outside of the US. For both trials, an overdose was defined as administration of fluorouracil at a dose, or infusion rate, greater than the maximum tolerated dose (MTD) for the patient's intended regimen of fluorouracil or its oral pro-drug, capecitabine. Patients received uridine triacetate 10 grams orally every 6 hours for 20 doses (or at a body surface area adjusted (BSA) dosage of 6.2 grams/m2/dose for 20 doses for four pediatric patients), and follow-up continued for 30 days. The primary efficacy outcome of both trials was survival at 30 days or until the resumption of chemotherapy if prior to 30 days. Due to similarities between the two trials (n=135), the results from these two trials have been pooled.

Demographics and Disease Characteristics

The majority of patients enrolled in the two trials were White (72%), 9% were Black/African American, 6% were Hispanic, 4% were Asian and 95% had a cancer diagnosis. The median age was 59 years (range: 1 to 83). A total of six pediatric patients were administered uridine triacetate. 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 early-onset, severe or life-threatening toxicities within 96 hours following the end of therapy (see Figure 1). 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. These fluorouracil overdoses occurred most frequently from incorrect programing of the infusion pump (42%) or pump malfunctions (23%). Of the patients who exhibited impaired elimination, the severe or life-threatening toxicities seen 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).

Efficacy Results

Of the 135 patients treated with uridine triacetate in the two trials, 96% (n=130) survived to day 30 or resumed chemotherapy prior to day 30, and 4% (n=5) died. As shown in Table 1, 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. 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 two of these died. The five patients treated with uridine triacetate

after capecitabine ingestion and the six pediatric patients treated with uridine triacetate all survived.

The applicant provided case-reports from 25 patients who were overdosed with fluorouracil by infusion rate (range 1.9 to 64 times the planned infusion rate) and were treated with supportive care alone. These historical case-reports came from various literature sources including reports from the Institute of Safe Medication Practices, US FDA Manufacturers and User Facility Device Experience database, US FDA Adverse Events Database, FDA Medical Product Safety Network, legal documents, and physician or hospital reports. Of these 25 representative historical patients, 84% (n=21/25) died. In comparison, the efficacy results from patients overdosed by fluorouracil and treated with uridine triacetate revealed that 97% survived (n=109/112) (see Figure 2).

Of the 18 patients treated with uridine triacetate after exhibiting early-onset, severe or life-threatening toxicity following the end of fluorouracil administration, two (11%) died and 16 (89%) survived. All cases presented with toxicities affecting the cardiac, central nervous, gastrointestinal, or hematopoietic system, and were severe or life-threatening on initial presentation. Nine patients required intubation due to fluorouracil toxicity and seven of them recovered and survived at 30 days. One patient required balloon-pump cardiovascular support and recovered. Ten patients experienced life-threatening mental status changes or encephalopathy, and eight survived. Of the 16 surviving patients, 14 developed symptoms within 96 hours following administration of fluorouracil. An FDA review of the Adverse Event Reporting System was searched for post-marketing, voluntary adverse event reports of fatalities of patients who experienced early-onset, severe or life-threatening toxicity following the end of administration of fluorouracil or capecitabine. Multiple historical cases from the last 50 years (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.

Safety Results

The primary safety population included 135 patients who received at least one dose of uridine triacetate. Five patients died within 30 days of therapy, although none of the deaths were attributed to uridine triacetate. Three of the deaths occurred in patients who overdosed with fluorouracil and two deaths occurred in patients exhibiting early onset, severe or life-threatening toxicity after fluorouracil administration.

Although the safety review was confounded by adverse events related to fluorouracil or capecitabine, uridine triacetate was overall well tolerated by most patients. Only two patients discontinued uridine triacetate due to adverse reactions (nausea, vomiting, and diarrhea) based on timing of the reaction with uridine triacetate administration. Serious adverse reaction and Grade $\geq$ 3 adverse reactions were seen in only one patient treated with uridine triacetate (Grade 3 nausea and vomiting). Common (Grade 1-2) adverse reactions occurring in >2% of patients treated with uridine triacetate included vomiting, nausea, and diarrhea.

Discussion

The approval of uridine triacetate was based on two open-label, single arm trials and highlights the ability of FDA to approve a drug based on data obtained from expanded-access protocols. As described above, FDA recommended the initiation of trial 401.10.001 in order to conduct a more formal expanded-access trial to allow for the potential of regulatory submission based on clinical data. Due to the life-threatening nature of fluorouracil or capecitabine overdose, and early-onset severe or life-threatening toxicity, it would not have been ethical to conduct a

randomized trial; therefore, FDA viewed the non-randomized design and use of historical controls as acceptable. Despite the lack of concurrent control, efficacy was clearly demonstrated with a survival benefit (96%) in 135 patients who would have otherwise been expected to have substantial mortality. Further, based on the trial results where 50% (n=2/4) of patients treated beyond 96 hours of overdose died as well as supportive nonclinical results, there was compelling rationale to specify a 96-hour timeframe for uridine triacetate administration. As a result, a limitation of use was included in the product labeling, which specifies that the safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine has not been established.

Although there were only six pediatric patients studied on one of the trials, all of the patients survived. The safety profile demonstrated a low risk to pediatric patients with only mild toxicities seen. 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. Similarly, only five capecitabine treated patients were studied on the trials. However, all of these patients survived, and based upon the 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 included capecitabine.

The patients with early-onset, severe or life-threatening toxicity from fluorouracil were closely examined, as 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 were described in the indication statement. In addition, a limitation of use was added to further highlight this potential risk.

The subset of patients studied with early-onset, severe or life-threatening toxicity from fluorouracil was further examined in relation to DPD deficiency. Although 19 patients in the two trials were tested for DPD deficiency (nine patients had variants in *DPYD*, with four having genotypes often associated with complete or partial DPD deficiency), the available genetic testing results could not definitively account for the early-onset, severe or life-threatening toxicities from fluorouracil or capecitabine administration. This may be in part due to the inconsistencies introduced by the use of different tests with differing methods and alleles assayed, as well as the unclear functional impact of some of the variants identified. In addition, there were also cases of early-onset toxicity which did not have a *DPYD* variant identified and cases for which no testing was performed. For these reasons, no specific description of DPD deficiency was included in the label.

In conclusion, uridine triacetate demonstrated efficacy 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. In addition, there were supportive nonclinical data and 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 was favorable to support approval. The approval demonstrates FDA's

commitment to regulatory flexibility through use of available clinical trial data from expanded access protocols to advance the treatment of life-threatening conditions.

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Table 1: Combined Efficacy: All Patients in WELL401 and 401.10.001

	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.

Figure 1: Distribution of Study Participants

Figure 2: Outcome of Fluorouracil Overdose Historical Control Cases vs. Uridine Triacetate Treated Cases

Figure 1:

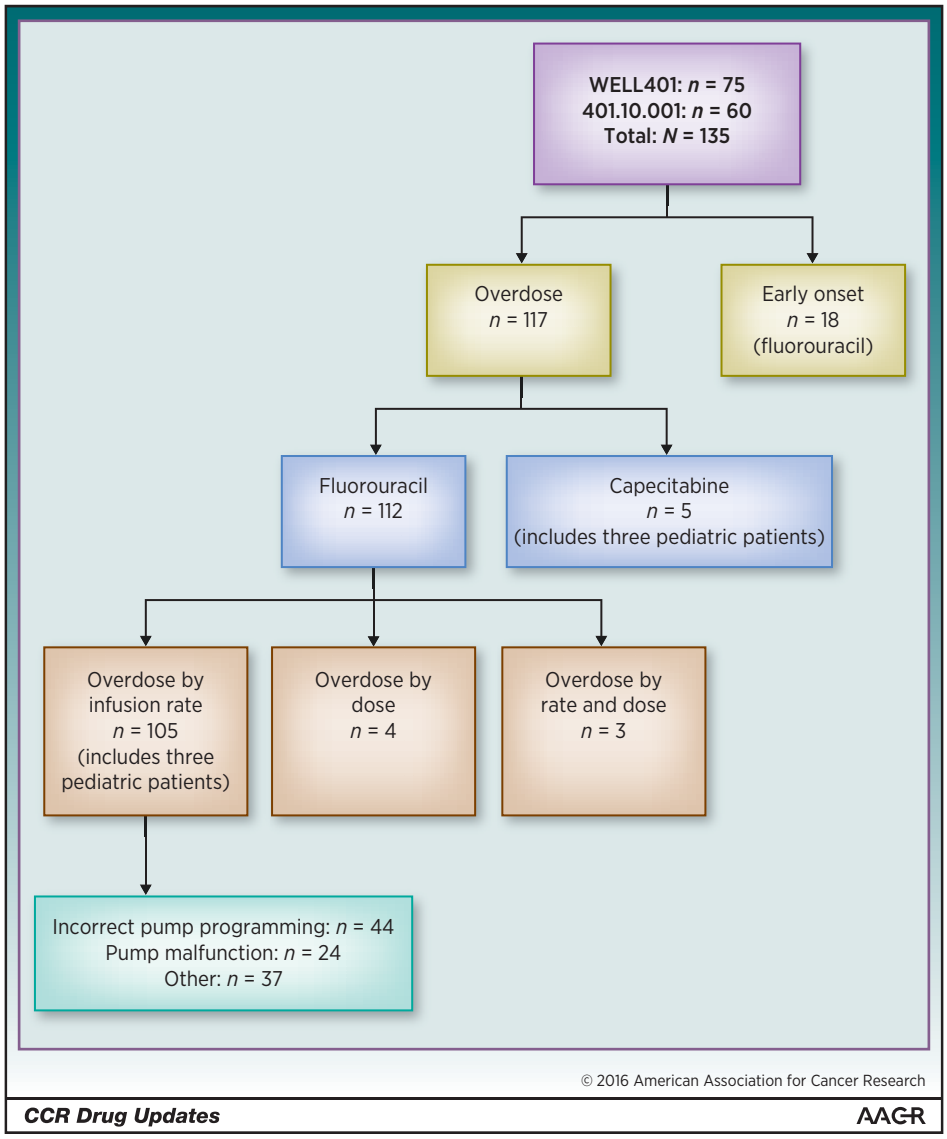
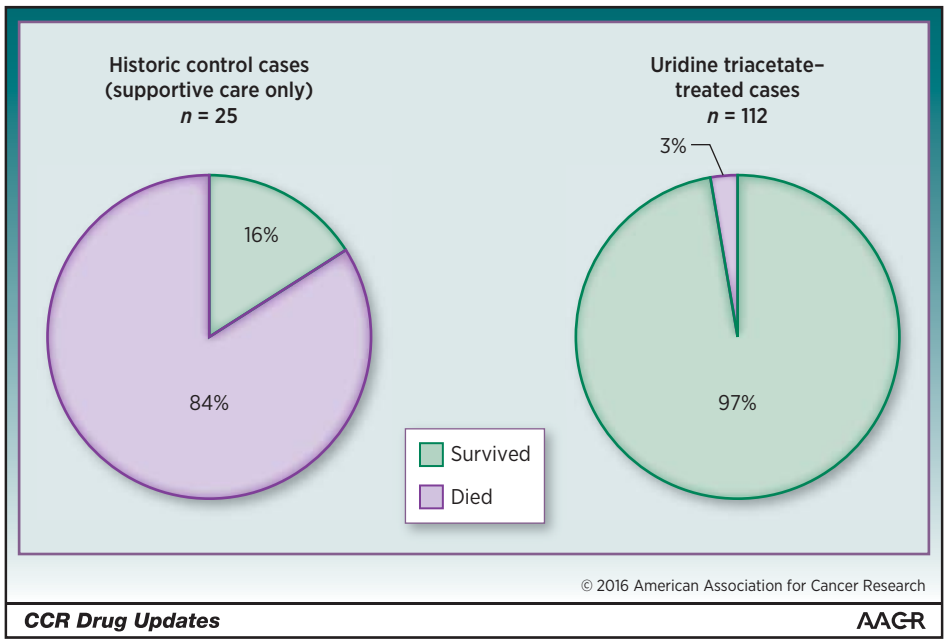


Figure 2:



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Clinical Cancer Research

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