

Uridine Triacetate (Vistogard®) National Drug Monograph May 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action

Uridine triacetate is the first available emergency treatment for overdose or life-threatening toxicities of fluorouracil (5-FU) or capecitabine. Uridine triacetate is an acetylated pro-drug of uridine which competitively inhibits cell damage and cytotoxicity caused by fluorouracil.^{1,2}

Indication(s) Under Review in this document

Uridine triacetate 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:

- 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.
- The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established.

Dosage Form(s) Under Review

Oral granules: 10 gram single-dose packets
Available as 1 carton of 20 single-dose packets or 4 single-dose packets

REMS

REMS No REMS Postmarketing Requirements

Pregnancy Rating

Limited case reports of uridine triacetate use during pregnancy are insufficient to inform a drug-associated risk of birth defects and miscarriage.

Executive Summary

Efficacy

- Efficacy for uridine triacetate was assessed in 135 patients from two single-arm, open-label, multi-center trials of patients who either received an overdose of fluorouracil or capecitabine or exhibited severe or life-threatening toxicities within 96 hours of the end of fluorouracil or capecitabine administration
- In patients with early-onset severe or life-threatening toxicity, survival at 30 days was 96% (n=130)
- Five (4%) died; two patients received uridine triacetate after 96 hours following the end of fluorouracil therapy
- Thirty-three percent of patients (n=45) resumed chemotherapy in less than 30 days (median 20 days post-5FU)
- For comparison, 38 of 47 (81%) historical controls with overexposure died

Safety

- Safety for uridine triacetate was assessed in 135 patients from two single-arm, open-label, multi-center trials
- Main safety concern(s): Vomiting (10%), nausea (5%), and diarrhea (3%) were the most frequently observed adverse reactions in the two clinical trials
- One patient experienced grade 3 vomiting and nausea

Other Considerations	<ul style="list-style-type: none"> • The Institute for Safe Medicine Practices recommends implementing a protocol for fluorouracil overdoses which include guidance on administration of uridine triacetate, the only antidote currently available.⁴ • The British Columbia Cancer Agency Management Guidelines recommend supportive care with a fluorouracil overdose at 2 to 10 times the intended rate of infusion with completed administration of at least 50% of intended total dose. Consideration is given for uridine triacetate if the overdose infusion rate was greater than 10 times the intended rate and at least 50% of the intended dose was administered.⁵
Projected Place in Therapy	<ul style="list-style-type: none"> • Place in therapy should be limited to: <ul style="list-style-type: none"> ○ patients with suspected overdose or ○ patients exhibiting life-threatening fluorouracil or capecitabine toxicities within 96 hours of their dose
Potential Impact	<ul style="list-style-type: none"> • National Institutes of Health estimate 8,000 (3%) patients who receive fluorouracil annually will develop some degree of toxic reaction of which 1,300 (15%) are fatal.⁶ • An international study of medication errors identified fluorouracil as the most common drug related to cytotoxic medication errors between 1996 and 2008.⁷ • Uridine triacetate is currently the only FDA approved drug for fluorouracil or capecitabine overdose or early-onset toxicity.¹ • Veterans with an inherited deficiency of dihydropyrimidine dehydrogenase (DHD), an enzyme involved with the metabolism of pyrimidine, are at risk for 5-FU toxicities following therapeutic doses. The incidence of complete DPD deficiency ~ 0.1%; partial deficiency ~3%. Due to high cost of testing and very low yield, it is not commonplace to routinely test for DPD deficiency.

Background

Purpose for review

FDA-approval 12/2015

Issues to be determined:

- ✓ Evidence of need
- ✓ Does uridine triacetate offer advantages to currently available alternatives?
- ✓ What safety issues need to be considered?
- ✓ Does uridine triacetate have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Best Supportive Care includes close monitoring with the following supportive care as needed: intravenous hydration, electrolyte replacement, antiemetics, treatment of diarrhea, mouth and skin care, continuous cardiac monitoring, granulocyte colony-stimulating factors and antibiotics.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to February 2016) using the search terms uridine triacetate, Vistonuride and Vistogard. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

The following outcomes are commonly evaluated in the setting of fluorouracil or capecitabine overdose:

- Survival at 30 days, compared to historic controls
- Resumption of chemotherapy < 30 days

Summary of Efficacy Findings

Uridine triacetate received priority review designation due to its potential for significant improvement in the safety or effectiveness of a serious condition when compared to standard applications. Due to nature of condition being treated, the clinical studies for uridine triacetate were conducting using an open-label expanded access protocol which is a process that allows manufacturers to provide investigational new drugs to patients who cannot participate in a clinical trial.

- The FDA approval of uridine triacetate was based on two single-arm, open-label, multi-center trials of patients who 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.
- An 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.
- A total of 135 patients at risk for 5-FU toxicity were included. These include patients expected to experience toxicity due to 5-FU or capecitabine overdose (n=117; 5-FU, n=112; capecitabine, n=5) and those with early-onset toxicity (n=18).
 - Study population demographics:

Median age	59 yrs (range, 1-83)
Male	56%
Caucasian	72%
Black/African American	9%
Hispanic	6%
Asian	4%
 - Ninety-four percent of 112 patients were overdosed by an excessive infusion rate only range (1.3 to 720 times the ordered infusion rate).
 - Four (4%) were overdosed by dose only; Three (3%) overdosed by both dose and infusion rate
- Intervention: Patients were treated with uridine triacetate 10 grams orally every 6 hours for 20 doses up to 96 hours following termination of 5-FU therapy. A total of 6 pediatric patients (1 to 16 years of age) were treated with uridine triacetate.
- Results: refer to Table 1.

Table 1. Combined Efficacy of Both Studies

	Overdose	Early-Onset Symptoms	Overall
Total patients	117	18	135
Survival at 30 days*	114 (97%)	16 (89%)	130 (96%)
Death	3 (3%)	2 (11%)	5 (4%)**

* Survival data includes patients surviving at 30-days or those who resumed chemotherapy within 30-days

** Death resulted in 2 patients who were treated 96-hours following the end of 5-FU administration

- Four patients initiated uridine triacetate more than 96 hours following the end of fluorouracil or capecitabine administration, two of which died.
- Thirty-three percent of patients (n=45) resumed chemotherapy in less than 30 days (median 20 days post-5FU)
- Overall adherence was 92.5% (mean 18.3/20 doses)
- Retrospective historical case control reports (n=25) of 5-FU overdoses by infusion rates ranging from 1.9-64x the planned dose, indicate that 84% resulted in death.
- A study abstract presented in 2009 on 17 patients overdosed with fluorouracil were treated with uridine triacetate at a dose of 10 grams orally every 6 hours for 20 doses beginning between 8 to 96 hours after overdose. The abstract cites an additional 13 patients who experienced a fluorouracil overdose with similar dose and infusion rate characteristics who were treated with supportive care. Eleven of the 13 patients treated with supportive care died of complications from fluorouracil overdose, while all 17 patients treated with uridine triacetate fully recovered.⁸
- A continuing study from the 2009 abstract reported in 2013 described 98 patients overexposed to fluorouracil, mostly due to infusion pump errors, received treatment with uridine triacetate at a dose of 10 grams orally every

6 hours. Of those 98 patients, 96 recovered fully. Infrequent and mild adverse events to uridine triacetate were noted with limited detail.⁹

- A case report of a colorectal cancer patient who experienced Grade 3 and 4 gastrointestinal and hematologic toxicities following a 96-hour infusion of fluorouracil 1000mg/m², was found to be dihydropyrimidine dehydrogenase (DPD) deficient. Subsequent low doses of fluorouracil were tolerated. An accidental infusion of 1000mg was given over 1 minute during the second cycle. In anticipation of severe toxicities, within 8 hours, uridine triacetate was started as 10 g PO every 6 hours for 20 doses. As a result, patient experienced no mucositis or additional cytopenia, compared to their first exposure.¹⁰

Potential Off-Label Use

- Uridine triacetate is also approved for hereditary orotic aciduria as Xuridine® which is available in 2 gram oral packets.

Safety

	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• None

Safety Considerations²

- The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration have not been established.
- Not recommended for non-emergent treatment of adverse reactions related to fluorouracil or capecitabine as uridine triacetate may reduce chemotherapy efficacy.
- Due to potential for nausea and vomiting, recommend that an oral antiemetic regimen is provided prophylactically and as needed during therapy (eg. Ondansetron 8 mg PO, given 20 minutes prior to each uridine triacetate dose)
- Missed doses should be taken as soon as possible
- Ensure patient/caregiver education about dosing preparation, schedule, taking a complete course of therapy (20 doses) and avoiding potential drug-drug interactions that may affect uridine triacetate and the clearance of fluorouracil

Adverse Reactions

Common adverse reactions	Vomiting (13%), nausea (5%), and diarrhea (3%)
Death/Serious adverse reactions	One patient (<1%) had Grade 3 nausea and vomiting
Discontinuations due to adverse reactions	Two patients (1.4%) discontinued therapy for adverse reactions

Drug Interactions

Drug-Drug Interactions

- No reported meaningful inhibitor or induction effects of uridine triacetate on cytochrome P450 enzymes
- In vitro data did show that uridine triacetate was a weak substrate for P-glycoprotein (P-gp) and inhibited transport of digoxin, a known P-gp substrate; therefore, the interaction with orally administered P-gp substrate drugs cannot be ruled out.
- Bismuth subsalicylate was originally excluded from the earlier version of the Expanded Access Protocol due to the potential of interfering with uridine triacetate absorption. This caution was included on a conceptual basis as there were no data indicating that this drug slowed absorption. Since that time, formal drug-drug interaction studies were performed and no interference with absorption was noted. This interaction was excluded from the Protocol and not included in the Prescribing Information.¹³

Drug-food Interactions

- None.
- A study of health adult subjects who took 6 grams of uridine triacetate showed no difference in overall rate and extent of uridine exposure under fed or fasted conditions.

Risk Evaluation

As of February 2016

	Comments				
Sentinel event advisories	• None				
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Uridine Triacetate 10g oral packet	None	None	None	Xuriden (2gm pkt) Floxadine Idoxuridine
	Vistogard	None	None	None	Vistoril Vistide
• (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)					

Other Considerations

- The Institute for Safe Medicine Practices recommends implementing a protocol for fluorouracil overdoses which include guidance on administration of uridine triacetate, the only antidote currently available.⁴
- The British Columbia Cancer Agency Management Guidelines recommend supportive care that includes administration of glutamine, colony stimulating factor, and antibiotics for a fluorouracil overdose at 2 to 10 times the intended rate of infusion with completed administration of at least 50% of intended total dose. Consideration is given for uridine triacetate if the overdose infusion rate was greater than 10 times the intended rate and at least 50% of the intended dose was administered.⁵
- The FDA approved Xuriden (uridine triacetate) in 09/2015, packaged in 2 gram oral granule packets for uridine replacement indicated for the treatment of hereditary orotic aciduria.

Dosing and Administration

Recommended Dosage²

- Adults: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals.

Preparation and Administration²

- Measure the dose using either a scale accurate to at least 0.1 gram, or a graduated teaspoon, accurate to the fraction of the dose to be administered.
- Administer each dose with three to four ounces of soft foods (applesauce, pudding or yogurt) or in milk or infant formula and ingest within thirty minutes of mixing. See full prescribing information for preparation and administration instructions.

- Do not chew the granules.
- If a patient vomits within two hours of taking a dose, initiate another complete dose as soon as possible after the vomiting episode. Administer the next dose at the regularly scheduled time.
- Administer via nasogastric tube (NG tube) or gastrostomy tube (G-Tube) when necessary (e.g. severe mucositis or coma).

Storage and Stability

- Store at USP controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F).
- Use within 30 minutes of preparation with soft food.

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • Of the 135 patients in clinical studies with uridine triacetate, 30% were 65 and over, including 11% that were 75 and over. Clinical studies of uridine triacetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.
Pregnancy	<ul style="list-style-type: none"> • Limited case reports of uridine triacetate use during pregnancy are insufficient to inform a drug-associated risk of birth defects and miscarriage. When administered orally to pregnant rats during the period of organogenesis, uridine triacetate at doses of one-half the maximum recommended human dose (MRHD) of 40 grams per day was not teratogenic and did not produce adverse effects on embryofetal development.
Lactation	<ul style="list-style-type: none"> • There are no data on the presence of uridine triacetate in human milk, the effect on the breastfed infant or the effect on milk production. Risk of potential negative effects to the nursing infant as well as the positive effects of breastfeeding should be considered along with the mother's need for use of uridine triacetate.
Renal Impairment	<ul style="list-style-type: none"> • No data identified
Hepatic Impairment	<ul style="list-style-type: none"> • No data identified
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified

Projected Place in Therapy

- Uridine triacetate is currently the only FDA approved drug for fluorouracil or capecitabine overdose or early-onset toxicity. National Institutes of Health estimate 3% of patients who receive fluorouracil will develop some degree of toxic reaction of which 15% are fatal.⁶ An international study of medication errors identified fluorouracil as the most common drug related to cytotoxic medication errors between 1996 and 2008.⁷
- Prior to uridine triacetate's approval, management of fluorouracil or capecitabine toxicities were limited to symptom management and supportive care.
- The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established. The Institute for Safe Medicine Practices recommends implementing a protocol for fluorouracil overdoses which include guidance on administration of uridine triacetate, the only antidote currently available.⁴

References

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized studies essential • Blinding not essential 	<ul style="list-style-type: none"> • Universally accepted direct measure of benefit • Easily measured • Precisely measured 	<ul style="list-style-type: none"> • May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized blinded studies 	<ul style="list-style-type: none"> • Patient perspective of direct clinical benefit 	<ul style="list-style-type: none"> • Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.