



1 July 2016

As a follow up to earlier discussions with Drs. Benson and Venook and on behalf of Wellstat Therapeutics Corporation, I respectfully request the NCCN Panel on Colon Cancer review the enclosed data for inclusion of VISTOGARD® (uridine triacetate) for the emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine (5-FU) 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.

The incorporation of an important life-saving chemotherapeutic antidote like VISTOGARD® in the NCCN Guideline is rare but not without precedent – for example, the inclusion of VORAXAZE® (glucarpidase for acute renal injury due to methotrexate toxicity). VISTOGARD® has a specific indication for use, and therefore we have provided detailed suggestions (per our discussion with Dr. Benson) below about optimal guideline and template placement. These recommendations are based on how other supportive agents are listed within NCCN Guidelines.

Specific Guideline Changes: Instruct on the emergency use of VISTOGARD® when indicated for overdose or early onset of severe toxicity in conjunction with 5-FU and/or capecitabine.

1. **Pathological Stage and Treatment Sections (Surveillance):** “Assess for signs of early-onset severe 5-FU or capecitabine toxicity for first two cycles” with accompanying footnote detailing the signs (neurologic, cardiac, unusually severe nausea and/or vomiting, etc.) → If yes, treat with uridine triacetate.”
2. **Evidence Blocks:** include a mention of uridine triacetate in evidence blocks that include 5-FU (eg, COL-4A). Include a single row underneath “Evidence Blocks for Adjuvant Therapy” entitled: “Antidotes for Overdose and Early-Onset Severe Toxicities Associated with 5-FU Adjuvant Therapies”
3. **Discussion Section: MS-32/MS-33:** at first appearance of FOLFOX: please add: “Use of 5-FU (or capecitabine) has been associated with early-onset severe toxicities. Uridine triacetate should be used at first signs and/or symptoms of early-onset severe toxicities associated with 5-FU or immediately following 5-FU (or capecitabine) overdose.”
4. **Discussion (page MS-19):** After the paragraph titled “Capecitabine and CapeOx”: *Vistogard (uridine triacetate) should be used for 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.*
5. **Principles of Adjuvant Therapy:** (page 1 of 2, COL-F): Add a final bullet that reads: “Use of 5-FU (or capecitabine) has been associated with early-onset severe toxicities. Uridine triacetate should be used at first signs and/or symptoms of early-onset severe toxicities associated with 5-FU or due to 5-FU (or capecitabine) overdose”.

Chemotherapy Templates: Add a statement as in (3) and (5) above to 5-FU (or capecitabine) as appropriate.

FDA Clearance Status: VISTOGARD® received FDA approval on December 11, 2015 under Fast Track designation and Priority Review and for use as the first and only emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine (5-FU) 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.

Rationale: 5-FU and its oral prodrug capecitabine are two of the most widely prescribed cancer drugs in the US. Approximately 300,000 patients in the US receive 5-FU or capecitabine annually as part of their chemotherapy regimen. 5-FU and capecitabine are highly cytotoxic drugs with a narrow margin of safety. Overdoses due to infusion pump misadventure (malfunctions and programming errors) as well as pharmacy transcription errors can

lead to excessive 5-FU or capecitabine exposures, at a higher than intended infusion rate ($>1.25\times$ the intended rate of infusion). Additionally, $>15\%$ of patients show signs and symptoms of severe 5-FU or capecitabine-related toxicity, which is lethal in 1,300 patients per year (frequency of 0.5% treated patients).

As part of the NDA, the Sponsor provided 42 documented cases of 5-FU overdose that resulted in 38 deaths. All cases received supportive care. Additionally, from its own safety databases FDA identified numerous additional historical 5-FU ($n=58$) or capecitabine ($n=145$) cases, many with early-onset, severe or life-threatening toxicity who received supportive care but ultimately all resulted in death, and confirming a very low survival rate (publication in press).

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 have not been established. There is no published clinical evidence that indicates VISTOGARD[®] reduces the antitumor efficacy of 5-FU or capecitabine.

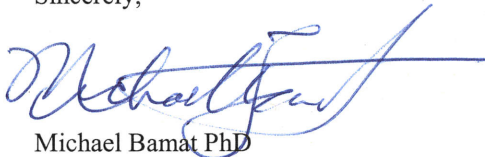
VISTOGARD[®] provides bioavailable uridine, a direct biochemical antagonist of 5-FU toxicity. VISTOGARD[®] delivers 4- to 7-fold more uridine into the systemic circulation compared to equimolar doses of uridine itself. Maximum concentrations of uridine in plasma following oral VISTOGARD[®] are generally achieved within 2 to 3 hours, and the half-life ranges from approximately 2 to 2.5 hours. In normal cells, VISTOGARD[®] stops the process of cell damage and cell death caused by 5-FU, and counteracts 5-FU toxicity. VISTOGARD[®] protects normal cells and allows recovery from damage caused by 5-FU. Uridine derived from VISTOGARD[®] is converted into uridine triphosphate (UTP), which competes with FUTP for incorporation into RNA, preventing further cell death and dose-limiting toxicities.

The following publications and presentations are submitted in support of this proposed change.

1. VISTOGARD[®] approved package labeling.
2. ASCO-GI 2016 Abstract and Poster
3. EAPCCT 2013 Abstract and Deck
4. Ison G, Beaver JA, McGuinn WD, et al. FDA Approval: Uridine Triacetate (Vistogard[®]) for the Treatment of Patients Following Fluorouracil or Capecitabine Overdose or Exhibiting Early-Onset Severe Toxicities Following Administration of These Drugs. Clinical Cancer Research (2016, in press). Will provide a copy when published (**approximately 15 July**).
5. Ma WW, Saif MW, El-Rayes B, et al. Emergency Use of Uridine Triacetate for Prevention and Treatment of Life-Threatening 5-Fluorouracil and Capecitabine Toxicity. Draft manuscript submitted to Cancer (2016).
6. Hematology Oncology Pharmacy Association (HOPA) Presentation (2016).

We would like to thank Drs. Venook and Benson for their time, and also we acknowledge the past and present NCCN panel members who directly contributed to the development of Vistogard, either as investigators or as advisors: Drs. Marwan Fakih, Muhammad Wasif Saif, Thomas Cartwright, Bassel El-Rayes, Wen Wee Ma, and James Posey.

Sincerely,



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