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RESEARCH**

APPLICATION NUMBER:

208159Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 208159
Product Name: Vistoguard® (uridine triacetate)

PMC Description: 3001-1 A retrospective analysis of the drug product manufacturing process development to further examine the relationship between particle size distribution and dissolution. Interbatch and intrabatch variability in dissolution is observed, but the cause has not been established. This analysis will provide data that will lead to more consistent quality in the drug product.

PMC Schedule Milestones: Final Protocol Submission: 02/2016
Final Report Submission: 08/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This product meets an unmet medical need for a potentially life-threatening indication. The drug product has no known toxic dose, so super-therapeutic doses are not a concern. For the 5-fluorouracil overdose indication, patients are dosed 10 grams every 6 hours for 20 doses, so variation in dose is likely to be mitigated by the high dose and frequency of dosing. Clinical data demonstrates that the key determinant in efficacy is early administration relative to the onset of symptoms and that lower doses of Vistogard have demonstrated efficacy. Therefore, the observed variation in dose strength is mitigated by the need to make this product available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Interbatch and intrabatch variability in dissolution is observed. The PMC is proposed to examine the relationship between particle size distribution and dissolution. As a result, the manufacturing process will be updated to improve the consistency of the product quality with regards to the impact of formulation material attributes, manufacturing process parameters, manufacturing unit operations.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

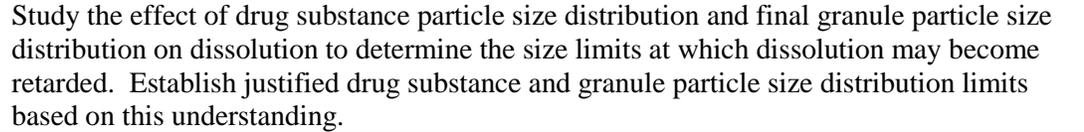
- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

- a)  (b) (4)
- b) 
- 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

JEANNETTE L O'DONNELL
12/09/2015

KATHERINE M FEDENKO
12/09/2015

**Office of Hematology and Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)
Labeling Review**

NDA / BLA #	208159
NDA / BLA Type	Efficacy Supplement
Proprietary Name (nonproprietary name)	VISTOGARD® (uridine triacetate)
Receipt Date	July 10, 2015
PDUFA Goal Date (Internal Goal Date)	January 10, 2016 (December 21, 2015)
Review Classification	Priority (expedited)
Proposed Indication(s)	(b) (4)
Dosing Regimen	Adult: 10 grams (1 packet) orally every 6 hours for 20 doses Pediatric: 6.2 grams/m ² of body surface area orally every 6 hours for 20 doses
From	William Pierce, PharmD, BCPS Associate Director for Labeling (ADL), DOP1

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I. BACKGROUND (*from CDTL Review*)

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.

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/m² 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.

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 (ARs) (> 2%) were vomiting, nausea, and diarrhea. Serious adverse reactions and Grade ≥ 3 ARs were seen in only one patient receiving uridine triacetate (grade 3 nausea and vomiting). No deaths were attributable to uridine triacetate.

II. ADL LABELING REVIEW

To complete this review, the DOP1 ADL met with review team members and attended labeling meetings to negotiate the revisions recorded in the final labeling. Preliminary ADL labeling comments were provided to the Applicant with the Filing Communication (September 8, 2015; see *Comments: W1 - W21*). The previously approved uridine triacetate product (Xuriden®) (NDA 208169) for the treatment of hereditary orotic

aciduria was also reviewed to ensure consistency (when possible) in the applicable labeling sections.

This review identifies key labeling revisions, provides a brief rationale for selected labeling revisions, and includes an annotated comparison of the original and final labeling (USPI and PPI). The labeling revisions in this review were implemented to provide recommendations and edits in the VISTOGARD® labeling to ensure that the prescribing information is a useful communication tool for healthcare providers (HCPs) and uses clear, concise language; is based on regulations and guidance; and conveys the essential scientific information needed for the safe and effective use of VISTOGARD®.

See the NDA 208159 Action Package for all labeling correspondence with the Applicant. Also see the primary reviews from the applicable review discipline for additional rationale and more detailed information.

III. KEY LABELING REVISIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION

- **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)

2. DOSAGE AND ADMINISTRATION

- Added a table and additional directions that provide pediatric doses based on body surface area and the amounts of VISTOGARD® required in grams and graduated teaspoons; this is also consistent with the XURIDEN® USPI.
- Added additional directions to describe how to administer VISTOGARD via a nasogastric (NG) tube or gastrostomy tube (G-tube).

6. ADVERSE REACTIONS

- Revised the safety database description to include the combined population from both trials to better describe the patient experience and remove redundant information.
- Added a statement related to the exposure of patients who were treated with VISTOGARD in the safety database.
- Added a statement to describe the serious adverse reactions and adverse reactions (ARs) that lead to permanent discontinuation observed in the clinical trials.

- Removed unnecessary clarifying information related to limitations in the causality assessment (e.g., “possibly related”) for the labeled ARs and a description of other potential confounding factors.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- The *Risk Summary* was revised to reflect the limited cases of uridine triacetate use during pregnancy.

8.4 Pediatric Use

- Revised to improve the description of the pediatric use database, include an exposure statement, and align with the current pediatric labeling guidance and regulations.

8.5 Geriatric Use

- Revised to change the [REDACTED] (b) (4) statement to “did not include sufficient numbers of subjects aged 65 and over” in accordance with 21 CFR 201.57(f)(10)(ii)(B) and ICH geriatric guidance recommendations.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Reviewer Comment: The review team noted that the available genetic test results do not correlate well with the early-onset of toxicity from fluorouracil, and do not clearly describe the role of DPD deficiency, due to multiple test methods and limitations related to the different types of test kits that were utilized. Therefore, DPD deficiency is not described in the VISTOGARD labeling, and instead, the indication statement describes patients according to unusually early-onset, severe, and life-threatening toxicities.

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 to [REDACTED] (b) (4)
- Removed the [REDACTED] (b) (4)

17. PATIENT COUNSELING INFORMATION (PCI)

- Revised to be consistent with the PCI labeling guidance and to add important dosing instructions that should be conveyed to patients.

PATIENT PACKAGE INSERT (PPI)

- The PPI was extensively revised to ensure consistency with the USPI, remove redundant information, remove promotional language, and ensure that the content is consistent with the Guidance for Useful Written Consumer Information (July 2006).
- No Medication guide was required.

INSTRUCTIONS FOR USE (IFU)

- Given the emergency use setting for VISTOGARD, and expectation that most of the VISTOGARD use will be administered in a hospital or under close observation by HCPs, separate IFU is not required.

IV. ORIGINAL vs. FINAL LABELING (USPI and PPI)

The final version of the labeling (submitted December 7, 2015) is shown below in track changes in comparison to the original version of the labeling submitted with this NDA (July 10, 2015). Extensive format related changes were also made during the labeling review, but are not annotated in the labeling comparison below for better legibility.

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILLIAM F PIERCE
12/09/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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Division of Pediatric and Maternal Health Review

Date: November 27, 2015 **Consult Received:** August 17, 2015

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health, Maternal Health Team
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Team Leader
Maternal Health Team
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Oncology Products 1

Drug: Vistogard (uridine triacetate), NDA 208-159,
IND 39-571, IND 118-931

Applicant: Wellstat Therapeutics Corporation

Proposed Indication: indicated [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED]

Subject: Labeling review

Consult Request: "PLLR labeling format"

INTRODUCTION

Wellstat Therapeutics Corporation submitted this NDA 208-159 on July 10, 2015 for Vistogard® (uridine triacetate) oral granules with the indication to [REDACTED] (b) (4)

[REDACTED] The product for this indication was granted both Fast-track and Orphan designation. Prior to the Vistogard NDA submission, the applicant had submitted an application (NDA 208-169, IND 18-931) for Xuriden® (uridine triacetate) oral granules, as a new molecular entity (NME) and uridine replacement product indicated for the treatment of hereditary orotic aciduria (HOA), an inborn error of metabolism. Xuriden was approved for use on September 4, 2015. Vistogard is the same active pharmaceutical ingredient as Xuriden; however, the indications and indicated populations are different. [REDACTED] (b) (4)

On May 7, 2015 the Division of Pediatric and Maternal Health – Maternal Health Team (DPMH-MHT) provided the Division of Gastroenterology and Inborn Errors Products (DGIEP) with a review of Xuriden with recommendations for the Pregnancy and Lactation subsections of the Xuriden labeling in the Pregnancy and Lactation Labeling Rule (PLLR) format. The Division of Oncology Products 1 (DOP1) now requests the assistance of the DPMH-MHT to review and provide labeling recommendations for the Pregnancy (subsection 8.1) and Lactation (subsection 8.2) for Vistogard in compliance with PLLR format.

Please see the DPMH-MHT Xuriden (NDA 208-169) consult in DARRTS, primary author Carol H. Kasten, M.D. dated May 7, 2015, DARRTS Reference ID: 3496693. Differences from Xuriden in the Vistogard mechanism of action, indicated population and labeling are discussed below.

BACKGROUND

5FU Toxicity and Vistogard

5FU is a prodrug that requires a complex series of biotransformations to produce two active metabolites, fluorouridine triphosphate (FUTP) and fluorodeoxyuridine monophosphate (5-FdUMP), both of which induce cytotoxicity;³ however, 5-FdUMP appears to be less toxic to normal tissue than FUTP. Once absorbed, Vistogard is deacetylated to uridine which is then converted to uridine triphosphate (UTP). The increased concentration of UTP provided by Vistogard competes with FUTP for incorporation into RNA. The more UTP which is incorporated into RNA in the setting of a 5FU overdose, the lower the amount of toxic FUTP incorporated. This competitive binding by Vistogard, is the mechanism by which the drug decreases 5FU cytotoxicity.⁴

¹ 5FU is a fluorinated pyrimidine used as an antineoplastic agent that inhibits thymidylate synthase (TS) and interferes with RNA synthesis and function in all cells.

² Vistogard labeling version of November 23, 2015.

³ Fluorouracil Clinical pharmacology online©, www.clinicalpharmacology-ip.com. Elsevier, Gold Standard. Revision date: July 16, 2015 Accessed November 23, 2015.

⁴ Vistogard labeling Sharepoint version November 23, 2015.

Use of Vistogard during Pregnancy

The indicated population for Vistogard is individuals undergoing treatment with 5FU at risk of serious toxicity following an overdose of 5FU and patients exhibiting serious toxicity within 96 hours of 5FU administration. Patients treated with intravenous 5FU have usually been diagnosed with solid tumors of the breast, gastrointestinal tract, pancreas or head and neck. Animal reproduction studies demonstrate that 5FU administered post-conception is embryolethal and during organogenesis is teratogenic at doses lower than the recommended human therapeutic dose.⁵ Use of 5FU in a pregnant woman could be, depending on the timing of administration, embryo-fetal toxic, embryo or fetal lethal or teratogenic. There are no reports of Vistogard use in a pregnant woman.

Use of Vistogard during Lactation

Please see the DPMH-MHT Xuriden (NDA 208-169) consult in DARRTS, primary author Carol H. Kasten, M.D. dated May 7, 2015, DARRTS Reference ID: 3496693.

PLLR

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁶ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Pregnancy

Although no reports of Vistogard use in a pregnant woman are available, two women with HOA are described in Online Mendelian and Molecular Basis of Inherited Disease (OMMBID) who were treated with *uridine* during pregnancy. Note that the uridine formulation used in these case reports is not clear and the clinical relevance is unknown; however, the drug is unlikely to have been uridine triacetate. Patient (b) (6) was treated with uridine during four pregnancies, all of which were reported to result in healthy infants. Patient (b) (6) was treated with uridine during two pregnancies. She also was reported to have delivered (two) healthy infants.⁸ There are no other human data available to assess teratogenic risk in pregnant women treated with Vistogard. Reports of use of uridine

⁵ See Clinical Pharmacology online.

⁶ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁷ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

⁸ See the DPMH Xuridine consult.

(formulation unknown) in pregnant women with HOA are anecdotal; however, these reports do not describe teratogenicity or other embryofetal toxicity.

Pregnancy Labeling

The Vistogard Pregnancy Risk Summary was modified to reflect that there have been two reports of pregnant women with HOA who were treated with uridine (although not Vistogard).

Lactation Labeling

Please see the DPMH review of Xuriden.

RECOMMENDATIONS

DPMH participated in meetings with DOP1 in October and November, 2015.

DPMH revised subsection 8.1 in the Vistogard labeling for compliance with PLLR.

DPMH recommendations are below and reflect discussion with DOP1 on November 13, 2015. DPMH refers to the final NDA 208-159 action for final labeling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 embryo-fetal development [*see Data*]. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, uridine triacetate was administered orally to pregnant rats during the period of organogenesis at doses up to 2000 mg/kg per day (about one-half the maximum recommended human dose (MRHD) of 40 grams per day on a body surface area basis). There was no evidence of teratogenicity or harm to the fetus and no effect on maternal body weight and overall health.

8.2 Lactation

Risk Summary

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. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for VISTOGARD and any potential adverse effects on the breastfed infant from VISTOGARD or from the underlying maternal condition.

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/s/

CAROL H KASTEN
11/27/2015

LYNNE P YAO
11/28/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 23, 2015

To: Geoffrey Kim, M.D.
Director
Division of Oncology Products 1 (DOP1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Carole Broadnax, RPh, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): VISTOGARD (uridine triacetate)

Dosage Form and Route: oral granules

Application Type/Number: NDA 208159

Applicant: Wellstat Therapeutics Corporation

1 INTRODUCTION

On January 16, 2015, Wellstat Therapeutics Corporation submitted for the Agency's review an original New Drug Application (NDA) 208159 for VISTOGARD (uridine triacetate) oral granules. The proposed indication for VISTOGARD (uridine triacetate) oral granules is to treat patients:

- following (b) (4) overdose (b) (4) or
- who exhibit early-onset severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or certain early-onset unusually severe adverse reactions ((b) (4) gastrointestinal toxicity and/or neutropenia) within 96 hours of 5-fluorouracil or capecitabine administration.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on July 22, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI).

2 MATERIAL REVIEWED

- Draft VISTOGARD (uridine triacetate) oral granules PPI received on July 10, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 13, 2015.
- Draft VISTOGARD (uridine triacetate) oral granules Prescribing Information (PI) received on July 10, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 13, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
11/23/2015

CAROLE C BROADNAX
11/23/2015

BARBARA A FULLER
11/24/2015

LASHAWN M GRIFFITHS
11/24/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 23, 2015
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 208159
Product Name and Strength: Vistogard (uridine triacetate) Oral Granules, 10 g
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Wellstat Therapeutics Corporation
Submission Date: July 10, 2015 and November 19, 2015
OSE RCM #: 2015-311
DMEPA Primary Reviewer: Grace P. Jones, PharmD, BCPS
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the New Drug Application approval process for Vistogard, we reviewed the proposed container label, carton labeling, and Prescribing Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Vistogard is proposed as an (b) (4) for patients at risk for toxicity following an overdose of 5-fluorouracil or capecitabine, and is indicated for both adult and pediatric patients. The proposed adult dose is 10 g (1 packet) orally every 6 hours for 20 doses, and the proposed pediatric dose is 6.2 g/m² based on body surface area (BSA) orally every 6 hours for 20 doses. Thus, a pediatric patient may require a dose that is a partial content of the 10 g packet depending on the BSA of the pediatric patient. In response to an information request sent on September 29, 2015, the Applicant revised language in the proposed PI Section 2 to include pediatric dosing by a range of BSA with the dose represented in grams and in teaspoons. They also included instructions on how to measure a pediatric dose using either a scale or a graduated teaspoon (see DARRTS Labeling/Package Insert Draft; Response to Information Request, dated October 2, 2015). Furthermore, in response to an information request sent on October 8, 2015, the Applicant indicated that a graduated teaspoon for pediatric dosing would not be co-packaged with the proposed product since most pharmacies provide graduated teaspoons during dispensing. The Applicant also stated they will be sure to have graduated teaspoons readily available for pharmacies and Vistogard distributors for expedited shipping if necessary (see DARRTS Response to Information Request, dated October 13, 2015). Of note,

this Applicant also markets the (b) (4) formulation of uridine triacetate under the proprietary name Xuriden (NDA 208169) for the treatment of hereditary orotic aciduria of which a dose of Xuriden is also measured using a scale or a graduated teaspoon, which is not co-packaged. Per discussion with DOP1, based on clinical trials, the number of pediatric patients who required Vistogard (b) (4) was small; six pediatric patients received Vistogard primarily due to accidental ingestion of capecitabine (parent's medication) and received Vistogard therapy in hospital. Due to the remote nature of a pediatric patient requiring Vistogard (b) (4), a pediatric patient is likely to receive full course of Vistogard therapy in a hospital setting, be clinically monitored for the duration of therapy and resolution of overdose. Additionally, hospitals stock graduated teaspoons and standard measuring devices. Therefore, because the likelihood of pediatric population usage of Vistogard (b) (4) will be small and will likely receive full course of treatment in a hospital setting, we determined that in this situation, pediatric dosing based on grams and graduated teaspoon is acceptable, and co-packaging of a graduated teaspoon would not be necessary.

The proposed PI that the Applicant submitted on November 19, 2015, addresses recommendations for adding instructions for mixing the granules for nasogastric or gastrostomy tube administrations and the recommendation to change the phrase (b) (4) to "single-dose" throughout the PI (see DARRTS Information Requested, dated November 16, 2015). Our review of this PI determined it appears acceptable from a medication error perspective.

The section in the container label and carton labeling regarding "Directions for use" and "prescribed dosage" can be improved to provide clear information regarding the usual dosage and how the proposed product should be used based on information in the PI Section 2.

4 CONCLUSION & RECOMMENDATIONS

Our review found the proposed pediatric dosing based on grams and teaspoons appears acceptable in this instance because a pediatric patient requiring Vistogard (b) (4) would likely receive full course of Vistogard therapy in a hospital setting. Since hospitals normally stock standard measuring devices, not co-packaging Vistogard with a graduated teaspoon appears acceptable.

The proposed container label and carton labeling can be improved to provide clarity of information and to promote safe use of the product.

4.1 RECOMMENDATIONS FOR WELLSTAT THERAPEUTICS CORPORATION

We recommend the following be implemented prior to approval of this NDA:

Container (packet) Label and Carton Labeling:

- To improve readability of the “Directions for use” information, we recommend revising the current language. For example, revise to:
 - **Directions for use:** Each Vistogard dose should be mixed into a soft food (such as applesauce, pudding, or yogurt) immediately prior to administration. For pediatric administration, see prescribing information. Discard unused portion of granules.
Usual dosage: See prescribing information
- Revise the statement (b) (4) to “single-dose” to remain consistent with changes in the PI.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vistogard that Wellstat Therapeutics Corporation submitted on July 10, 2015.

Table 2. Relevant Product Information for Vistogard	
Initial Approval Date	N/A
Active Ingredient	Uridine Triacetate
Indication	(b) (4)
Route of Administration	Oral
Dosage Form	Oral granules
Strength	10 g packets
Dose and Frequency	Adult: 10 gram taken by mouth every 6 hours for a total of 20 doses Pediatric: 6.2 grams/m ² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses
How Supplied	20 x 10 g packets provided in a carton 4 x 10 g packets provided in a carton
Storage	Store at controlled room temperature, 25°C (77°F); Excursions permitted to 15°C to 30°C (59°F to 86°F)
Container Closure	(b) (4)

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/s/

GRACE JONES
11/23/2015

CHI-MING TU
11/23/2015

Internal Consult

Pre-decisional Agency Information

To: Jeannette O'Donnell, Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Date: November 23, 2015

Re: **Vistogard (uridine triacetate) oral granules**
NDA 208159
Comments on proposed product labeling (PI, PPI, and
carton/container)

In response to the Division of Oncology Products 1 (DOP 1)'s July 22, 2015, consult request, OPDP has reviewed proposed product labeling (Package Insert (PI), Patient Package Insert (PPI), and carton/container) for Vistogard (uridine triacetate) oral granules. The version of the PI used in this review was sent via electronic mail from DOP-1 on November 13, 2015, and is titled, "NDA 208159-substantially complete label.docx."

OPDP's comments for the PI are provided directly in the attached PDF document. OPDP's comments for the proposed PPI were provided in a separate patient labeling review from the Division of Medical Policy Programs dated November 23, 2015.

OPDP does not have comments for the proposed carton/container labels at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
11/23/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 13, 2015

TO: Jeannette O'Donnell, Regulatory Project Manager
Gwynn Ison, M.D., Medical Reviewer
Division of Oncology Products 1

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D., for Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #208159

APPLICANT: Wellstat Therapeutics

DRUG: Vistogard™ (uridine triacetate)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of 5-fluorouracil poisoning

CONSULTATION REQUEST DATE: August 3, 2015
INSPECTION SUMMARY GOAL DATE: November 20, 2015
DIVISION ACTION GOAL DATE: December 17, 2015
PDUFA DATE: March 10, 2016

I. BACKGROUND:

Wellstat Therapeutics Corporation (Wellstat) seeks approval to market uridine triacetate for the

(b) (4)

. This intended indication is based on the efficacy and safety data from two Expanded Access Studies: 401.10.001, an open-label, single arm, multi-center study in adults at risk of serious 5-fluorouracil (5-FU) toxicity following 5-fluorouracil over dosage or patients with rapid onset of serious toxicity (within 1 to 4 days), and Study Well401, an open label, single arm, multi-center study in adult and pediatric patients at risk of serious 5-fluorouracil toxicity following 5-fluorouracil or capecitabine overdosage or patients with rapid onset of serious toxicity (within 1 to 4 days).

Uridine triacetate is an acetylated, orally administered prodrug of the pyrimidine nucleoside uridine. Uridine triacetate is efficiently absorbed and immediately converted to circulating uridine. It is used as an antidote to treat patients who are at risk of excess 5-FU toxicity due to 5-FU over dosage or who are exhibiting rapid (within 96 hours or less) onset of serious toxicity following 5-FU administration.

Uridine triacetate was provided for emergency use; the number of patients was not predetermined for either study. For Study 401.10.001 there were 59 investigators in the United States. All patients received uridine triacetate. A total of 60 patients were included in the intent-to-treat (ITT) and safety analyses; 53 patients were included in the per protocol (PP) analysis.

For Study Well401 there were 74 investigators in Australia, Canada, Denmark, France, Germany, Greece, Paraguay, Singapore, Spain, and the United States. All patients received uridine triacetate. A total of 75 patients were included in the intent-to-treat (ITT) and safety analyses; 62 patients were included in the per protocol (PP) analysis.

Two clinical sites were chosen for inspection: Dr. Steven Duffy, Richmond, VA, Subject #OD-134 for Study 401.10.001 and Dr. Yudhish Markan, Glenn Burnie, MD, Subject #OD-092 for Study 401.10.00. The sponsor Wellstat was also inspected for both Study 401.10.001 and Study Well401.

These studies were conducted under IND 039571.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI #1: Steven Duffy Bon Secour Medical Office Bldg. 5875 Bremono Rd. Medical Office Bldg. S Suite G11 Richmond, VA 23226	Protocol: 401.10.001 Site: N/A Subject #OD-134	September 17-21, 2015	Pending Interim classification: NAI
CI #2: Yudhish Markan Tate Cancer Center 305 Hospital Drive Glen Burnie, MD 21061	Protocol: 401.10.001 Site: N/A Subject #OD-092	August 26, 2015 – September 9, 2015	Pending Interim classification: VAI
Sponsor: Wellstat Therapeutics Corporation 930 Clopper Road Gaithersburg, MD 20878	Protocols: 401.10.001 and Well401 Number of Subject Records Audited: 69/135 (including Subjects OD-092 and OD-134)	October 5-7, 2015	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI #1: Dr. Steven Duffy
(Protocol: 401.10.001)

- a. What was inspected:** The site enrolled one subject: OD-134. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 208159, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, and IRB correspondence.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. The primary and secondary endpoints were verified against the source data. There was no evidence of underreporting adverse events. A Form FDA 483 was not issued.
- c. Assessment of data integrity:** The data for Dr. Duffy's site, associated with Study 401.10.001 submitted to the Agency in support of NDA 208159, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI #2: Dr. Markan
(Protocol: 401.10.001)

- a. What was inspected:** The site enrolled one subject: OD-092. All available study records for the subject were reviewed. The site records contained documentation of informed consent, subject eligibility, IRB correspondence, and drug accountability. To the extent possible, the record audit included subject medical records, subject histories, laboratory results, drug accountability, concomitant medications, sponsor correspondence, monitoring and financial disclosure compliance. The FDA investigator compared source documentation to the CRF and data listings submitted to NDA 208159.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be flawed. The site had incomplete records available for the audit. The site provided all the study records they had for the subject including progress notes, laboratory reports and hospital records. A copy of the CRF for Subject OD-092 was not retained by the site. However, the FDA field investigator was able to verify most data points. Subject OD-092 met all eligibility criteria, signed the informed consent form, and was enrolled on December 21-22, 2012. The subject survived and was able to resume chemotherapy treatment on January 11, 2013.

However, there were some discrepancies between the source documents at Dr. Markan's site and the data listings submitted to the application. It appears that the data discrepancies were the result of sponsor activities and not the site activities. While the site did not have a copy of the CRF for Subject OD-092, the FDA field investigator had a copy of the CRF provided in the NDA 208159 submission to use during the inspection. The site source documents were not always consistent with what was recorded in the CRF and reported in the application data listings.

For example,

1. The CRF noted that informed consent was obtained from the study subject on December 22, 2012. However, the informed consent form was signed by the subject on December 21, 2012.
2. The CRF noted that the drug overdose event occurred over a period of one hour on December 21, 2012. However, the source records contain conflicting information; that the overdose occurred over a period of one hour or a period of two hours.
3. The CRF noted that a complete physical exam and vital signs collection were not done during study week 1 (days 8-14). However, the source records contain documentation of a physical exam and recording of vital signs on January 2, 2013 (day 13).

Dr. Markan explained during the inspection that the sponsor collected/copied the source documentation sometime after the subject completed the study. In addition, it was the sponsor/monitor that completed the CRF for Subject OD-092, and not site staff. Dr. Markan stated that he never saw the completed CRF, and did not recall ever signing anything stating that he verified the CRF contents. Since the FDA field investigator also conducted the sponsor [Wellstat] inspection they were able to confirm that all Subject OD-092 source records (i.e. hospital records) found at the site matched the copied source records found at the sponsor during the sponsor inspection of Wellstat. There were a number of compliance issues found during the inspection. A five-item Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection of Dr. Markan. Dr. Markan stated that he planned to respond to the inspectional observations in writing.

Observation 1. A clinical investigator did not report to the IRB, within five days of use, the emergency use of a test article for which the IRB had not reviewed the research proposal.

Specifically, the clinical investigator initiated Protocol 401.10.001 and began treatment of a subject with the investigational drug on December 22, 2012. However, an IRB submission form for emergency use was not sent to the IRB until January 5, 2013.

OSI Reviewer Note: Study Protocol 401-10-001 states, "Treatment may begin prior to IRB approval as per 21 CFR 56.104(c). Accordingly, the Investigator must report use of the investigational drug to the IRB within 5 working days after initial treatment." Although, there appears to be a delay in IRB notification (possibly due to the holidays), the IRB ultimately approved the site's participation in the Study. In addition, the IRB approval letter (dated March 3, 2013) indicates that the IRB was aware of site's "emergency use" of uridine triacetate on December 22, 2012. However, it is not clear who notified the IRB on December 22, 2012, since the IRB Site submission records were not

signed by Dr. Markan until January 5, 2013. This represents a protocol violation, but it did not place the subject at undue risk and has no effect on data integrity.

Observation 2. Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

Specifically, there are no records of the date of receipt of the investigational drug for Protocol 401.10.001 by the clinical investigator, the amount received, or the amount that was dispensed and administered to Subject OD-092.

OSI Reviewer Note: This observation is valid in that the site did not have adequate drug accountability records. However, the FDA field investigator stated that they were able to confirm the amount of drug shipped to this site during the sponsor inspection. In addition, hospital records were available at Dr. Markan's site, which document study drug dispensed to the subject. This protocol violation is valid but did not place the subject at undue risk and has no effect on data integrity.

Observation 3. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, the Case Report Forms for Subject OD-092 that were used to submit study data to the sponsor are inaccurate and incomplete. For example:

- a. The CRFs were not completed by anyone who works at the study site, and they were not signed by the Clinical Investigator (CI).
- b. The Data Clarification Forms were not signed by the CI, or study site staff, in the "Investigator Approval" box, but instead were signed by sponsor-directed personnel.
- c. Inaccurate data were entered into the CRFs:
 - The CRFs note that informed consent was obtained from the study subject on 12/22/2012. However, the Informed Consent form was signed by the subject on 12/21/2012.
 - The CRFs note that the drug overdose event occurred over a period of one hour on 12/21/2012. However, the source records contain conflicting information and state the overdose occurred over a period of one hour or two hours.
 - The CRFs note that the first dose of the investigational drug was administered to the subject at 00:00 on 12/22/2012. However, the source records contain conflicting information and indicate that the first dose was administered at either 11:00 pm on 12/21/2012 or at midnight.

- The CRFs note that a complete physical exam and vital signs collection were not done during week 2 (Days 8 - 14). However, the source records contain documentation of a physical exam and recording of vital signs on 1/2/2013 (Day 13).
- Some hematology and chemistry laboratory data recorded in the CRFs do not match the data found in the source records. Specifically, blood count differentials recorded the CRF and line listings are the percent (%) values, rather than the absolute count in k/mcL as required by the protocol. For example,
 1. The CRF recorded Neutrophils at 5 k/mcL (within normal range: 1.8-7.8 k/mcL) on January 3, 2013. However, the laboratory report showed an absolute Neutrophil count of 0.0 k/mcL (critical low) and Neutrophils at 5% (low). Therefore, the subject was neutropenic; however, the CRF and datalistings reported the subject as normal for neutrophils.
 2. The CRF recorded Neutrophils at 70 k/mcL (High: 1.8-7.8 k/mcL) on January 10, 2013. However, the laboratory report showed an absolute Neutrophil count of 3.0 k/mcL (within normal range: 1.8-7.8 k/mcL) and Neutrophils at 70% (within normal range: 40-74). Therefore, the subject's neutrophils counts were within normal limits, however, the CRF and datalistings reported the subject's neutrophils as extremely high.

OSI Reviewer Note: This observation is valid. However, with the exception of the last bulleted item under 3.c., these discrepancies should not importantly impact subject safety and study outcomes.

Dr. Markan indicated that he did not complete the referenced CRF. It appears that the sponsor completed the CRF for Subject OD-092. Since the FDA field investigator also conducted the sponsor [Wellstat] inspection they were able to confirm that the sponsor completed the CRF for this and all study subjects for Study 401.10.001 and Study WELL401. They were also able to confirm that the laboratory data for hematology for this subject were incorrect. Briefly, based upon the inspection of the sponsor, it appears that hematology data were entered incorrectly for Subject OD-092 into the CFRs and then submitted to the application. These incorrect data resulted in many of the laboratory results being recorded as high or low, when they were actually the opposite, or normal.

Because all source records data were transcribed by the sponsor to CRFs after the subjects had completed the study treatment and participation, the transcribing errors had no impact on subject safety. This protocol violation is valid but did not place the subject at undue risk.

Dataset corrections to the application are discussed under the Sponsor Inspection Summary below.

Observation 4. An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan.

Specifically, the Clinical Investigator (CI) did not follow the protocol and investigational plan. For example:

- a. The CI did not report the investigational drug use to the IRB within 5 working days after initial treatment.
- b. Procedures required by the study protocol were not done. For example:
 - A complete physical exam was not performed during week 3 (Days 15-21).
 - A chemistry blood sample was not collected during week 1 (Days 1 - 8).

OSI Reviewer Note: This observation is valid. With respect to Item 4.a., please refer to OSI Reviewer Notes under Item 1. With respect to Item 4.b., these are missed study-specified procedures. However, hospital records reviewed at the site indicate that vital signs were completed at Weeks 2 and 4. These violations are isolated incidents and have no impact on data integrity. Subject OD-092 did have chemistry blood samples collected prior to dosing (December 21, 2012), during study week 2 (January 3, 2013), and study week 3 (January 10, 2013). This observation should not have placed the subject at undue risk or have significant impact on subject safety.

Observation 5. Investigational records were not retained for a period of two years following approval of a drug's marketing application and discontinuance of the investigation and notification of FDA.

Specifically, the Clinical Investigator (CI) did not maintain all records for Protocol 401.10.001, as required by FDA regulation. For example:

- a. The CI stated that the Case Report Forms (CRFs) were sent to the study sponsor after completion, and he did not keep a copy of them for his study files.
- b. There are no records to document and verify when the overdose event occurred and the amount of medication administered, as recorded on the "Event Information" in the CRFs.
- c. There are no records of investigational drug accountability to verify the amount of investigational drug received by the CI and the disposition of all doses.

OSI Reviewer Note: This observation is valid. Copies of CRFs not retained should have minimal impact on data integrity. Hospital records, including laboratory reports and medical notes, were retained by the site for FDA review. With respect to the lack of records to document and verify the event overdose, the FDA field investigator informed that they were able to confirm the overdose for Subject OD-092 using hospital records that documented the details of the overdose. In addition, hospital records also indicated that Dr. Markan received a phone call at 4 PM on [REDACTED] (b) (6), from the home infusion site indicating that the subject's infusion of 5-FU was mistakenly administered over 1 hour instead of 46 hours. With respect to the lack of investigational drug accountability please refer to the OSI Reviewer Notes provided under Item 2. This records retention violation is valid but did not place the subject at undue risk and has no effect on data integrity.

- c. Assessment of data integrity:** Notwithstanding the inspection observations noted above, the data for Dr. Markan's site associated with Study 401.10.001, submitted to the Agency in support of NDA 208159, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary review of the EIR and communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

3. Sponsor: Wellstat Therapeutics Corporation (Protocols: 401.10.001 and Well401)

- a. What was inspected:** The inspection included but was not limited to overall study conduct, test article accountability records, site monitoring, AEs, and efficacy endpoints. The audit also included Form FDA 1572 and investigator agreements and assessment. The inspection focused on 69 out of a total of 135 subject records enrolled into either Study 401.10.001 or Study Well401.
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the studies. Overall compliance with the investigational plans appeared to be good. No study sites were closed due to GCP non-compliance. The study design and conduct were very unusual. Each clinical site enrolled only one subject with virtually no exceptions. The sponsor used their study monitors to review site source records and complete the CRF's for each study subject. It appears that Wellstat completed the CRFs for all sites in 2014 and 2015. Completions of the CRFs were not done contemporaneously and data queries were handled by e-mail or telephone for the most part. Wellstat documented that all CRFs were sent to the CIs for their review and approval. However, almost half of the sites' records showed that the CIs did not sign off on the CRF verification form provided by Wellstat. However, Wellstat documented several attempts to obtain this form from all the sites, but many did not respond.

Review of the source records for each of the audited subjects, retained and maintained by Wellstat, found that all data transcribed into the CRFs and submitted to the application were accurate with the exception of hematology data. Hematology data were entered incorrectly for 8 out of 69 subjects (11.6%) into the CRFs and then submitted to the application. These incorrect data resulted in many of the laboratory results being recorded as high or low, when they were actually the opposite, or normal. A Form FDA 483 was issued that cited one inspection observation.

Observation 1. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND.

Specifically, for Study Protocols WELL401 and 401.10.001, inaccurate laboratory data were recorded in the study sites' Case Report Forms (CRFs), and these inaccurate data were subsequently reported to FDA by the study sponsor in the NDA submission. For example, 8 of the 69 Subjects' records (11.6%) reviewed during the inspection reported the percent (%) values for blood count differential results, rather than the absolute count in k/mcL as required by the study protocols. This resulted in many of these readings being evaluated by the sponsor as "High" or "Low", when in actuality they were the opposite or normal.

OSI Reviewer Note: Wellstat concurred with the inspection observation in a written response, dated October 27, 2015. Wellstat stated that immediately following the FDA inspection they conducted a review of 100% of the laboratory data from all patients in Studies WELL401 and 401.10.001. They did find additional instances of the same type of error found during the FDA inspection but no other errors in laboratory data entry were identified. Because all source records data were transcribed to CRFs after the subjects had completed the study, the transcribing errors had no impact on subject safety. Wellstat also conducted A Root Cause Analysis (ICAR-WT-15-001) in order to identify the root cause(s) of the data transcription errors and subsequent reporting of the incorrect data to FDA. This analysis identified the root cause to be inadequate training of data transcription, data monitoring, data quality assurance, and data management team member with regard to recognizing the correct differential blood cell count values and units (percent vs absolute counts) to be reported and recorded in the study CRFs. Wellstat stated that the opportunity for such errors was exacerbated by the fact that laboratory source documents were received from 130 different clinical laboratories (instead of one central laboratory) and the need for manual transfer of all data points to CRFs.

Wellstat also provided a robust corrective action plan that included the 100% review of all hematology laboratory data to document any additional errors, obtain guidance from FDA review division (DOP1) to determine any agency-

required actions related to the application, and retrain data transcribers, clinical research associates, data quality assurance, and data management team members. Finally, in the future, Wellstat plans to use a central laboratory and electronic data transfer whenever possible.

This inspectional finding was communicated in an email sent to clinical reviewer Gwynn Ison on October 27, 2015, and discussed with the clinical reviewer Gwynn Ison and CDTL Julia Beaver on October 28, 2015. An IR was sent to Wellstat on October 28, 2015 requesting, in part, that Wellstat include corrected laboratory data and corrected shift tables affected by the transcription errors in the 120 Day Update for Studies 401.10.001 and WELL401 to NDA 208159. Wellstat agreed and planned to provide the corrected information requested in the 120 Day Update to the application. The 120 Day Update was submitted to the application (NDA 208159 SN0037) on November 10, 2015, and includes the corrected hematology datasets.

The inspectional observation is a significant finding that does affect hematology data reliability in the original submission datasets. However, the corrective actions taken by the sponsor, as described in the written response dated October 27, 2015, and the submission of corrected datasets and shift tables, as requested in the IR dated October 28, 2015, should eliminate the hematology data errors submitted to the agency in NDA 208159 (SN0001). As such, with the inclusion of the 120 Day Update, the data may be considered reliable.

- c. Assessment of data integrity:** The data, to include the 120 Day Update, from this sponsor submitted to the Agency associated with Study 401.10.001 and Study Well401 in support of NDA 208159 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Yudhish Markan (Subject OD-092; Study 401.10.001) and Dr. Steven Duffy (Subject OD-134; Study 401.10.001), and the sponsor Wellstat, Study 401.10.001 and Study Well401 data to include the 120 Day Update submitted to the Agency in support of NDA 208159, appear reliable and can be used in support of the application.

The inspection of Dr. Markan identified a number of compliance violations. Briefly, the site failed to notify the IRB within 5 days of the start of emergency use investigational product, the investigational drug disposition records were not adequate, the Case Report Forms for Subject OD-092 contained inaccurate and/or incomplete information, the subject missed a physical exam at study week 3 and a chemistry blood sample was not collected during study week 1.

Finally, the site failed to maintain all records for Protocol 401.10.001, as required by FDA regulation, for a period of not less than 2 years after the investigational product was approved for marketing in the United States. The data submitted to the application for Subject OD-092 was verifiable using available records at this site including, progress notes, laboratory reports and hospital records. However, there were some discrepancies between the source documents at Dr. Markan's site and the data listings submitted to the application. However, the data discrepancies, specifically periodic hematology laboratory tests, were the result of sponsor activities and not the site. Briefly, it was the sponsor that completed the CRF for Subject OD-092, and not site staff. The sponsor's transcription errors between source documentation and CRFs for this subject were, in part, the result of untrained personnel that did not recognize the difference between absolute neutrophil counts, and percent neutrophils, as reported by a clinical laboratory. As such, Wellstat personnel transcribed reported laboratory results to the CRF without consideration of the associated units. A detailed review of these inspectional observations concludes that these conduct issues did not place Subject OD-092 at undue risk or importantly impact study outcome.

The inspection of the sponsor Wellstat revealed that hematology data were entered into the CFRs incorrectly for 8 out of 69 subjects (11.6%) audited. These data were included in the datasets submitted to the application. These incorrect data resulted in many of the laboratory results being recorded as high or low, when they were actually the opposite or normal. An IR was sent to Wellstat on October 28, 2015 requesting, in part, that Wellstat include corrected laboratory data and corrected shift tables affected by the laboratory data transcription errors in the 120 Day Update to NDA 208159. The 120 Day Update was submitted to the application (SN0037) on November 10, 2015, and included the corrected laboratory data and shift tables. Corrective actions taken by Wellstat should eliminate the hematology data errors submitted to the agency in NDA 208159 (SN0001).

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Susan D. Thompson, M.D., for Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

LAUREN C IACONO-CONNORS
11/13/2015

SUSAN D THOMPSON
11/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Medical Team Leader
Linda Lewis, MD, Acting Deputy Director
DPMH

NDA Number: 208,159

Sponsor: Wellstat Therapeutics

Drug: Vistogard (uridine triacetate) oral granules

Indication:  (b) (4)

Proposed Pediatric Regimen: 6.2 grams/m² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses

Labeling Consult Due Date: November 20, 2015

Division Consult Request: The Division of Oncology Products 1 (DOP1) requests DMPH participation in pediatric labeling and conformance of labeling with PLLR format.

Background

Uridine triacetate under NDA 208,159 is undergoing premarket review for [REDACTED] (b) (4)

[REDACTED] The sponsor intends to market the product for use in pediatric and adult patients.

The NDA was submitted with data from one open-label trial in 129 adults (up to 83 years) and a second open-label trial of adult and pediatric patients, which included six pediatric patients (1 to 16 years). Since the drug is being approved for all patients, pediatric information will be distributed throughout labeling.

This pediatric labeling review will focus on labeling sections 1 (Indication), 2 (Dosing and Administration), and 8.4 (Pediatrics). For each section, the suggested labeling is presented first and is followed by suggested revisions which are noted in *bold italics*. Conformance with PLLR labeling will be discussed in a separate Maternal Health review (pending). Additionally, the recommendations in this review are based on the draft labeling document in SharePoint electronic work-room as of October 25, 2015 and may not reflect intervening label revisions by other disciplines.

Note: On September 4, 2015, FDA approved uridine triacetate (same formulation) under the trade name Xuriden (NDA 208,169) for treatment of patients with hereditary orotic aciduria. NDA 208,169 has the same sponsor.

Note: The highlights section of labeling has been reviewed. Comments relating to the summary of dosing are discussed in the review of section 2 (Dosing and Administration). DPMH agrees that there are no safety-related issues that need to be included in the highlights section of labeling and that the highlights section of labeling is consistent with Xuriden labeling.

Note: Section 6 (Adverse Reactions) was reviewed in its entirety. The most common adverse reactions reported in patients (1 to 83 years) were diarrhea (28 of 135 patients), vomiting (23 of 135 patients), and nausea (20 of 135 patients). No differences in safety between pediatric and adult patients are described in labeling. According to the DOP1 reviewer at the labeling meeting of November 3, 2015, review of the safety data in the NDA showed no meaningful difference in safety or efficacy between pediatric and adult patients. The data supporting sections 6 and 14 are undergoing review by the DOP1 and review of those sections of labeling is deferred to the DOP1 clinical reviewer.

Note: Per discussions at the labeling meetings of November 3 and 13, 2015, DOP1 indicated that use of uridine triacetate for pediatric cancer patients would be uncommon and that the virtually all use in cancer patients would commence in-hospital. DOP1 also indicated that virtually all use in patients under "several" years of age would be restricted to treatment of children who unintentionally ingest 5FU and that such exposure would necessitate admission to a hospital or emergency room to commence treatment with uridine triacetate.

Section 1 (Indications)

Proposed:

“VISTOGARD ^{(b) (4)} is indicated ^{(b) (4)}

[Redacted content]

^{(b) (4)}

(b) (4)



Reviewer comment:

DPMH agrees with the indication "VISTOGARD" (b) (4)

Per discussions during the labeling meeting of November 3, 2015, the Indications section is undergoing "substantial revisions to tighten up the indication section of labeling"; therefore, further comment on this section is deferred to DOP1. DOP1 should consider if any information in the above draft language should be included in other sections of labeling.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Adults: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals.
- Pediatric: 6.2 grams/m² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals. The VISTOGARD dose to be administered at 6.2 grams/m² is presented in Table 2.

VISTOGARD Pediatric Dose Based on Body Surface Area (m²)

Patient Body Surface Area m ²	Table 2: VISTOGARD 6.2 grams/m ² /dose [§]	
	Dose in Grams	Dose in Teaspoons
0.34 to 0.44	2.1 to 2.7	1
0.45 to 0.55	2.8 to 3.4	1 ¼
0.56 to 0.66	3.5 to 4.1	1 ½
0.67 to 0.77	4.2 to 4.8	1 ¾
0.78 to 0.88	4.9 to 5.4	2
0.89 to 0.99	5.5 to 6.1	2 ¼
1.00 to 1.10	6.2 to 6.8	2 ½
1.11 to 1.21	6.9 to 7.5	2 ¾
1.22 to 1.32	7.6 to 8.1	3
1.33 to 1.43	8.2 to 8.8	3 ¼
1.44 and above *	10.0	1 full packet *

[§] Dose by body surface area category in this table was rounded to achieve the approximate dose. Each dose is administered every 6 hours for 20 doses.

* May use 1 entire 10 g packet without weighing or measuring. Do not exceed 10 grams/dose.

Reviewer comment: Per discussions during the labeling meeting of November 3, 2015, initial dosing for pediatric patients will be in the hospitalized population and will likely employ mass-based dosing. Spoon-based dosing may be provided to non-hospital scenarios.

In general, DPMH recommends that mass-based dosing instructions for age appropriate formulations (e.g., pills, capsules, tablets, or unit dose sachets) be provide in labeling. For uridine triacetate granules, where the product will be marketed in (b) (4), DPMH recommends mass-based dosing (using a scale) as reflected in table above.

Use of the term “teaspoon” is problematic. For liquid formulations FDA recommends not using the term teaspoon in labeling because definitions of the volume of a teaspoon vary (e.g., 2.5 cc, 5 cc, other).¹ Therefore, existing FDA guidance (Guidance for Industry Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products) and pediatric professional practice associations recommend dosing of orally ingested liquid medications as metric units (mL).^{2,3} While similar recommendations have not been promulgated for powdered or nonencapsulated granule formulations, one may logically infer that the same issue applies for such products

Therefore, while labeling states that a graduated teaspoon should be used, DPMH recommends that the term ‘teaspoon’ be deleted from labeling. Additionally, for the scenario of non-health care facility use, DPMH recommends that the sponsor provide a calibrated measuring device that accurately reflects the corresponding mass based dose recommendation (such as a calibrated measuring cup or calibrated spoon).

At the labeling meetings of October 8 and 15, and November 3, 2015, DOP1, Clinical Pharmacology, and Pharmacotoxicology stated that the safety margin of the product is wide and double or triple doses were not apparently associated with serious or severe adverse effects. While, DPMH recognizes that a wide safety margin of uridine triacetate may reduce the criticality of the preceding recommendation for overdose situations, accurate dosing is needed to avoid under-dosing since the adverse consequences of 5FU fluorouracil may be severe and lethal.

DPMH and DOP1 agree that use of the term “pharmacy provide graduated spoon” or “pharmacy provide graduated teaspoon” which mirrors Xuriden labeling may be a reasonable option.

2.2 Preparation and Administration

¹ Falagas ME, Vouloumanou EK, Plessa E et al. Inaccuracies in dosing drugs with teaspoons and tablespoons. International Journal of Clinical Practice, 64 Issue 9: 1185 – 1189.

² Guidance for Industry Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products; <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM188992.pdf>. Website accessed: October 23, 2014

³ American Academy of Pediatrics, Committee on Drugs. Metric Units and the Preferred Dosing of Orally Administered Liquid Medications. Pediatrics Vol. 135 No. 4 April 1, 2015. pp. 784 -787

(b) (4)

- Mix each VISTOGARD dose with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt and ingest within 30 minutes. Do not chew the VISTOGARD granules. Drink at least 4 ounces of water.

Reviewer comment: DPMH requests that labeling includes instructions on administration of drug in milk or formula if such data are available.

- If a patient vomits within 2 hours of taking a dose of VISTOGARD, initiate another complete dose as soon as possible after the vomiting episode. Administer the next dose at the regularly scheduled time.
- Administer VISTOGARD via a nasogastric tube (NG tube) or gastrostomy tube (G-Tube) when necessary (e.g., severe mucositis or coma).

Reviewer comment: See above comment regarding use of the word 'teaspoon.' Also, DPMH has requested labeling provide instructions for mixing and administration via G-tube and NG-tube.

8.4 Pediatric Use

The safety and effectiveness of VISTOGARD have been established in pediatric patients. Use of VISTOGARD is supported by a single open-label clinical study which included 6 pediatric patients ranging in age from 1 to 16 years (Study 2). (b) (4) of these patients were between 1 to (b) (4) years of age and received a body-surface area adjusted dosage of 6.2 grams/m²/dose × 20 doses. (b) (4) clinical response between adults and pediatric patients treated with VISTOGARD. [see *Clinical Studies (14)*]

Reviewer comment: Per the labeling meetings of November 3 and November 9, 2015, safety and effectiveness was demonstrated by partial extrapolation of efficacy data from adults (Study 1) and data from a second study which included six children. Pediatric dosing was modelled based on allometric scaling and is supported by a lack of enzyme effect (i.e., low likelihood increased or decreased activity or toxicity). The results of both safety and effectiveness were similar in adult and pediatric patients. Additionally, no new juvenile toxicology data will be included in labeling.

Therefore, DPMH recommends the following modification to section 8.4.

*“The safety and effectiveness of VISTOGARD have been established in pediatric patients. Use of VISTOGARD **in pediatric patients** is supported by **an open-label clinical study of adults (Study 1) and second open-label clinical study** which included 6 pediatric patients ranging in age from 1 to 16 years (Study 2). (b) (4) of these **pediatric** patients were between 1 to 2 years of age and received a body-surface area adjusted dosage of 6.2 grams/m²/dose × 20 doses. The **clinical response and safety** in adult and pediatric patients treated with VISTOGARD were similar; however, **clinical** data are limited. [see *Clinical Studies (14)*]*

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/s/

ETHAN D HAUSMAN
11/16/2015

HARI C SACHS
11/16/2015
I agree with these recommendations.

LINDA L LEWIS
11/16/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208159 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Vistogard™ Established/Proper Name: Uridine Triacetate Dosage Form: Granule Strengths:		
Applicant: Wellstat Therapeutics Agent for Applicant (if applicable):		
Date of Application: July 10, 2015 Date of Receipt: July 10, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: March 10, 2016		Action Goal Date (if different): December 21, 2015
Filing Date: September 8, 2015		Date of Filing Meeting: August 11, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): <div style="background-color: #cccccc; height: 40px; width: 100%;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>		
The efficacy of Vistogard™ initiated more than 96 hours following the end of administration of 5-fluorouracil has not been established.		
Type of Original NDA: AND (if applicable)		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)

Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>	

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	

Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	

Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
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Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 039571, IND 118931

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		DARRTS and Panorama currently have PDUFA date as January 10, 2015. This should update

				after the filing letter goes out
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>):			
	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
	Payment of other user fees:			
	<input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			

<p><u>User Fee Bundling Policy</u></p> <p><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</p>	<p>Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i></p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? <i>(Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>	<input type="checkbox"/>	<input type="checkbox"/>		

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 7 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Orphan drug
NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD

	<input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index : Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only : Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>				Orphan Drug Designation
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels			

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL)			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): EOP2 - July 6, 2010 EOP2 - August 15, 2013 CMC EOP2 meeting – August 21, 2013 Type A meeting – August 27, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 11, 2015

BLA/NDA/Supp #: NDA 208159

PROPRIETARY NAME: Vistogard™

ESTABLISHED/PROPER NAME: Uridine Triacetate

DOSAGE FORM/STRENGTH: Oral Granules

APPLICANT: Wellstat Therapeutics

PROPOSED INDICATION(S):

[REDACTED] (b) (4)

[REDACTED]

BACKGROUND: NME with Fast-track and Orphan Designation. Drug is currently under review in ODE3, if approved their first it will no longer be an NME but will remain in the PDUFA V program.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeannette O'Donnell	Y
	CPMS/TL:	Alice Kacuba Christy Cottrell	N Y
Cross-Discipline Team Leader (CDTL)	Julie Beaver		Y
Division Director/Deputy	Geoffrey Kim		Y
Office Director/Deputy			
Clinical	Reviewer:	Gwynn Ison	Y
	TL:	Julia Beaver	Y

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		N/A
	TL:		N/A
Clinical Pharmacology	Reviewer:	Runyan Jin Covering- Jeanne Fourie Zirkelbach	N Y
	TL:	Qi Liu	N
• Genomics	Reviewer:	Sarah Dorff	Y
	TL:	Rosane Charlab Orbach	Y
• Pharmacometrics	Reviewer:	Anshu Marathe	Y
		Yaning Wang	Y
Biostatistics	Reviewer:	Joyce Cheng	Y
	TL:	Shenghui Tang	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	David McGuinn	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:		N/A
	TL:		N/A
	ATL:	Xiao Chen	N
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Xavier Ysern	Y
• Drug Product	Reviewer:	Donghau (Robert) Lu	Y
• Process	Reviewer:	Jean Tang	N
• Microbiology	Reviewer:	Jean Tang	N
• Facility	Reviewer:	Christina Cappaci-Daniel	Y
		Steven Hertz	N
• Biopharmaceutics	Reviewer:	Salaheldin Hamid	Y
		Sandra Suarez	Y
• Immunogenicity	Reviewer:		N/A
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	BC:	Olen Stephens	Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Mills and Rowe Medina	Y Y
	TL:	Barbara Fuller	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Carole Broadnax	Y

	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Davis Mathew Grace Jones	Y Y
	TL:	Chi-Ming (Alice) Tu	Y
	OSE RPM	Frances Fahnbulleh	Y
OSE/DRISK (REMS)	Reviewer:	Mona Patel	Y
	TL:	Naomi Redd	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	Y
Controlled Substance Staff (CSS)	Reviewer:		N/A
	TL:		N/A
Other reviewers/disciplines			
• Safety	Reviewer:	Christina Marshall Susan Jenny	Y N
	TL:	Katherine Fedenko	N
Other attendees	ORA:	Paul Perdue Jr., John Duan	Y N
		William Pierce, Tracy Salaam, Steven Bird	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments: labeling issues to communicate Some review issues with secondary indication</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: issues for 60 day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO The product came in as an NME but will not retain NME status once approved in ODE3. However, it will remain in the program
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none">• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: Geoffrey Kim

PDUFA Date: 3/10/2016

Expedited review plan

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):
TBA – Target date 10/27/15

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: Milestone target dates as follows:

Labeling meetings to start **early October**: Labeling meeting 1 will be CMC/DMEPA
Total of 6 labeling meetings

Primary Reviews: Friday, November 20, 2015
Secondary Review: Tuesday, December 1, 2015
CDTL Review: Monday, December 7, 2015

Wrap-up meeting: TBA: Target date - Friday, December 4, 2015
Division Director Review: Thursday, December 17, 2015

Action letter circulation: December 17, 2015

ASCO Burst and Press Release

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

JEANNETTE L O'DONNELL
09/08/2015

CHRISTY L COTTRELL
09/08/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: NDA 208159

Application Type: New NDA

Name of Drug/Dosage Form: Vistogard™ (uridine triacetate), Oral granules

Applicant: Wellstat Therapeutics

Receipt Date: July 10, 2015

Goal Date: March 10, 2015

1. Regulatory History and Applicant's Main Proposals

Wellstat Therapeutics submitted NDA 208159, for Vistogard™ (uridine triacetate), as a 505(b)(1) application on July 10, 2015. NDA 208159 references IND 039571 and IND 118931.

The proposed indication for Vistogard™ is:



Vistogard™ (uridine triacetate) is currently designated as an NME with both Fast-track and Orphan Designation. As the drug is already under review for a different indication in ODE3, if it is approved prior to DOP1's action, it will no longer be classified as an NME but will remain in the PDUFA V program.

The following table lists the key regulatory meetings held with the Applicant.

Meeting Type	Meeting Date
End-of-Phase 2 Meeting	July 6, 2010
End-of-Phase 2 Meeting	August 15, 2013
CMC End-of-Phase 2 Meeting	August 21, 2013
Type A Meeting	August 27, 2014

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

RPM PLR Format Review of the Prescribing Information

In addition, the following labeling issues were identified:

1. In the HIGHLIGHTS section, the Applicant needs to center all section titles in the center of the horizontal line.
2. The Applicant needs to add white space before DOSAGE AND ADMINISTRATION and DOSAGE FORMS AND STRENGTHS.
3. The Applicant needs to de-capitalize the dosage form "Oral Granules."
4. The Applicant needs to provide Contact information for Incidence rate for the listed adverse reactions.
5. The Applicant needs to remove the additional word "information" following the verbatim statement, "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."
6. The Applicant needs to add appropriate cross-references and revise the single cross-reference listed to the appropriate format.
7. See attached label for additional labeling review issues.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The Applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 18, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Upon review most section titles were not in the center of the horizontal line.*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There was no white space before DOSAGE AND ADMINISTRATION and DOSAGE FORMS AND STRENGTHS.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: Year currently XX as the product is not approved.

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- NO** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Only one dosage form. However, dosage form "Oral Granules" should not be capitilized.*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Contact information for the company not yet provided. Incidence rate for the listed adverse reactions needs to be included.

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: Remove additional word "information" following the verbatim statement, "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: To be updated at the time of approval

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: The label is missing most cross-references. The single cross-reference found in the FPI is not bracketed.

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, 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.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JEANNETTE L O'DONNELL
09/08/2015

CHRISTY L COTTRELL
09/08/2015