CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208159Orig1s002

Trade Name:	VISTOGARD
Generic or Proper Name:	uridine triacetate
Sponsor:	Wellstat Therapeutics Corporation
Approval Date:	April 8, 2016
Indication:	VISTOGARD is a pyrimidine analog indicated for the emergency treatment of adult and pediatric patients: • following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or • who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

208159Orig1s002

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Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:

208159Orig1s002

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159/S-002

APPROVAL LETTER

Wellstat Therapeutics Corporation
Attention: Michael K. Bamat, Ph.D.
Vice President, Research and Development
930 Clopper Road
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Supplemental New Drug Application (sNDA) dated February 29, 2016, received February 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vistogard® (uridine triacetate) Granules, 10g.

This "Prior Approval" supplemental new drug application provides for a shelf life extension from 24 months to 36 months.

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Kristine Leahy, RPh., Regulatory Project Manager, at (240) 402-5834.

Sincerely,

Anamitro Banerjee -S
Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2016.04.08 16:20:00 -04'00'

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208159Orig1s002

PRODUCT QUALITY REVIEW(S)

NDA Supplement REVIEW
OFFICE OF NEW DRUG PRODUCTS
DIVISION 1, BRANCH 2
CMC REVIEW FOR THE DIVISION OF ONCOLOGY 1

NDA #: 208159	**Submission Type:**	**Date of submission:** 29-Feb-2016
Supplement #: S-002	edr	**Date of FDA's receipt:** 29-Feb-2016
Supplement Type: PAS	Original	**DARRTS SD #:** 64

REVIEWER NAME: Paresma Patel, Ph.D.

REVIEW DATE: 08-Apr-2016
GOAL DATE: 29-June-2016
REVIEW #: 01

NAME & ADDRESS OF APPLICANT: Wellstat Therapeutics Corp
930 Clopper Road
Gaithersburg, MD 20878

PROPRIETARY NAME: Vistogard

NAME OF DRUG: Uridine triacetate

SUPPLEMENT PROVIDES FOR: Shelf life extension

INDICATION: Emergency treatment of adult and pediatric patients following a 5-fluorouracil (5-FU) or capecitabine overdose or who exhibit early-onset, severe to life-threatening toxicity or unusually severe adverse reactions within 96 hours following the end of 5-FU or capecitabine administration

DISPENSED: R_x

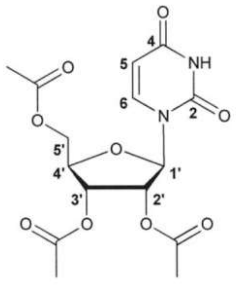
PROPOSED CHANGES: Request for a shelf life extension from 24 months to 36 month based on 48-month supportive stability data of (b) (4) and extrapolation of 24-month stability of (b) (4) registration lots.

DOSAGE FORM: Granules

STRENGTHS: 10 g

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME AND STRUCTURE:



[(2R,3R,4R,5R)-3,4-Diacetyloxy-5-(2,4-dioxopyrimidin-1-yl)-oxolan-2-yl]methyl acetate

Chemical Formula: $C_{15}H_{18}N_2O_9$

Molecular Weight: 370.31

RELATED IND, NDA, DMF: N/A

COMMENTS: In this submission, the applicant is proposing a shelf life extension from 24 months to 36 months. Supportive stability data for [redacted] (b) (4) through 6 months under accelerated conditions (40 °C/75% RH) and 48 months under long term conditions (25 °C/60% RH) are provided in this submission and are within specifications. Stability data for registration lots [redacted] (b) (4) are provided through 6 months under accelerated conditions (40 °C/75% RH) and 24 months under long-term conditions (25 °C/60% RH) and are within specifications. Statistical analysis of the registration lots was used to support the extrapolation of data to 36 months.

The proposed changes are acceptable and have no adverse impact on the drug product quality.

CONCLUSION AND RECOMMENDATION: This submission is recommended for approval from the stand point of chemistry, manufacturing, and controls.

Paresma R. Patel -S (Affiliate)

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DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2001105316, cn=Paresma R. Patel -S (Affiliate)
Date: 2016.04.08 08:05:30 -04'00'

REVIEWER: Paresma Patel, Ph.D.

Anamitro Banerjee -S

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Date: 2016.04.08 09:16:50 -04'00'

BRANCH CHIEF: Anamitro Banerjee, Ph.D.

REVIEW NOTES

Vistogard (uridine triacetate) oral granules (NDA 208159) was approved on December 11, 2015 for the emergency treatment of adult and pediatric patients due to a 5-fluorouracil (5-FU) or capecitabine overdose or who exhibit early-onset, severe to life-threatening toxicity or unusually severe adverse reactions following the administration of 5-FU or capecitabine. Uridine triacetate is an acetylated pro-drug of uridine that competitively inhibits incorporation of fluorouracil metabolites into RNA thereby reducing cell damage. The drug product is composed of (b) (4) granules containing (b) (4) % uridine triacetate and the following inactive ingredients: ethylcellulose, Opadry Clear, and natural orange juice flavor. The drug product is packaged in individual (b) (4) sachets containing 10 g uridine triacetate, and is intended to be mixed with foods that are easily swallowed.

Proposed Changes

Request for a shelf life extension from 24 months to 36 month based on 48-month stability data of (b) (4) *and extrapolation of 24-month stability of* (b) (4) *registration lots* (b) (4)

Summary

In this submission, the applicant is proposing a shelf life extension from 24 months to 36 months for drug product with current packaging and stored at controlled room temperature, 25 °C with excursions permitted to 15° to 30 °C (59° to 86 °F). Supportive stability data for (b) (4) through 6 months under accelerated conditions and 48 months under long term conditions are provided in this submission. Stability data for registration lots (b) (4) are provided through 6 months under accelerated conditions and 24 months under long-term conditions. Statistical analyses of the registration lots are used to support the extrapolation of data to 36 months. The individual parameters of assay, moisture, and degradation for each storage condition were analyzed with a linear regression fit. The approved stability protocol for registration batches is provided below. The stability protocol is the same for (b) (4). The stability specifications for (b) (4) are different from registration lots in acceptance criteria for identification by HPLC, reporting of related substances, and dissolution. The stability data indicate no significant change in the (b) (4) lots of Vistogard oral granules under accelerated or long term conditions.

(b) (4)

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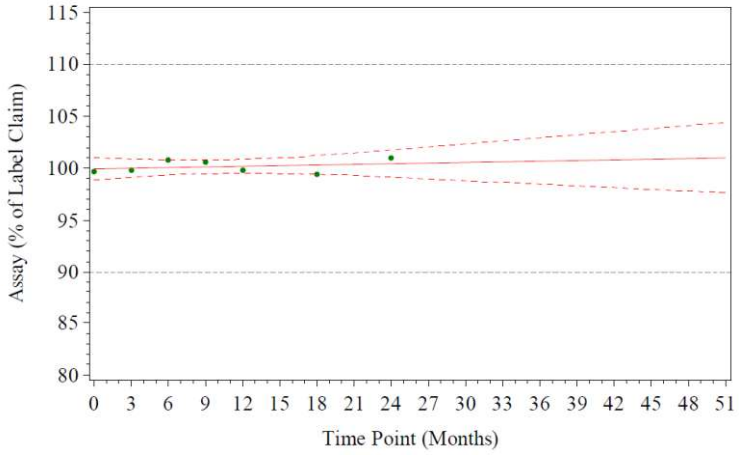
Representative Statistical Analysis (Registration Lot W017891):

Figure 2 Lot W017891 % Assay Shelf Life Estimation at 25°C / 60% RH



Reviewer Comments: ***Adequate***

The proposed shelf life extension of Vistogard granules from 24 months to 36 months is adequately justified in this supplement. Stability data for [redacted] (b) (4) are provided and within specifications. Extrapolation of the available long term stability data (24 months) for the registration batches is used to support the shelf life extension. Statistical analysis of assay, moisture, and impurities with linear regression was used to support the shelf life extension to 36 months.

Recommendation:

This supplement is recommended for approval from the stand point of chemistry, manufacturing, and controls.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208159Orig1s002

OTHER REVIEW(S)

BIOPHARMACEUTICS REVIEW Division of Biopharmaceutics			
Application No.:	NDA 208159/S2	**Biopharmaceutics Reviewer:** Ge Bai, Ph.D.	
Submission Date:	February 29, 2016		
Division:	ONDP Division I	**Acting Biopharmaceutics Lead:** Sandra Suarez, Ph.D.	
Applicant:	Wellstat Therapeutics Corp	**Acting Biopharmaceutics Branch Chief:** John Duan, Ph.D.	
Trade Name:	Vistogard	**Date Assigned:**	April 18, 2016
Generic Name:	Uridine triacetate	**Date of Review:**	June 8, 2016
Indication:	Emergency treatment of adult and pediatric patients following a 5-fluorouracil (5-FU) or capecitabine overdose or who exhibit early-onset, severe to life-threatening toxicity or unusually severe adverse reactions within 96 hours following the end of 5-FU or capecitabine administration	**Type of Submission:** New supplement	
Dosage Form/ strengths	Granules, 10g		
Route of Administration	Oral		
Type of Review	Evaluation of the biopharmaceutics information supporting the proposed extension of shelf life from 24 months to 36 months.		

SUMMARY:

NDA 208159 was approved on December 11, 2015 for Vistogard oral granules. NDA 208159/S2 was submitted on February 29, 2016 by Wellstat Therapeutics Corp seeking approval of extension of shelf life from 24 months to 36 months. Supportive stability dissolution data for [redacted] (b) (4) through 6 months under accelerated conditions (40 °C/75% RH) and 48 months under long term conditions (25 °C/60% RH) are provided in this submission and are within the approved dissolution acceptance criteria for this drug product. Stability dissolution data for registration lots [redacted] (b) (4) [redacted] (b) (4) are provided through 6 months under accelerated conditions (40 °C/75% RH) and 24 months under long-term conditions (25 °C/60% RH) and are within specifications.

RECOMMENDATION

ONDP-Biopharmaceutics has reviewed NDA 208159/S2 for Vistogard oral granules. From the Biopharmaceutics perspective, APPROVAL is recommended for this supplement.

SIGNATURE BLOCK

Ge Bai, Ph.D.,
Primary Reviewer
Division of Biopharmaceutics
Office of Pharmaceutical Quality

Ge Bai -S
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Date: 2016.06.13 12:16:20 -04'00'

Sandra Suarez Sharp, Ph.D.,
Biopharmaceutics Lead (acting)
Division of Biopharmaceutics
Office of Pharmaceutical Quality

Sandra Suarez -A
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Reviewer's Assessment:

The Applicant requested for a shelf life extension from 24 months to 36 month based on 48-month supportive stability data of (b) (4) and extrapolation of 24-month stability of (b) (4) registration lots (b) (4)

Supportive stability data including dissolution for (b) (4) through 6 months under accelerated conditions and 48 months under long term conditions are provided in this submission. Stability data including dissolution for registration lots (b) (4) (b) (4) are provided through 6 months under accelerated conditions and 24 months under long-term conditions. Statistical analyses for assay, impurities, and moisture content data of the registration lots are used to support the extrapolation of data to 36 months.

The currently approved dissolution acceptance criteria are listed in the table below:

Table 1. Approved dissolution acceptance criteria

Test	Acceptance Criterion
Dissolution	(b) (4)

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According to drug product quality reviewer, the statistical analysis of data conducted for assay, impurities, and moisture content indicates the drug product is projected to stay well within the approved acceptance criteria to support a 36 month shelf life. Statistical analysis was not conducted for dissolution.

Comparison of dissolution profiles for (b) (4) registration batches between release and at 24 months for long term storage are within specifications with no discernable differences. Similarly, dissolution profiles at 6 months under accelerated storage conditions are within specifications with no differences from release.

Based on all available stability data, the Applicant's request for extension of the drug product's shelf life from 24 months to 36 months is reasonable and acceptable from biopharmaceutics perspective.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208159Orig1s002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208159/S-002

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Wellstat Therapeutics Corporation
Attention: Michael K. Bamat, Ph.D.
Vice President, Research and Development
930 Clopper Road
Gaithersburg, MD 20878

Dear Dr. Bamat:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 208159

SUPPLEMENT NUMBER: 002

PRODUCT NAME: Vistogard® (uridine triacetate) 10g granules

DATE OF SUBMISSION: February 29, 2016

DATE OF RECEIPT: February 29, 2016

This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes the following change: to request a shelf life extension from 24 months (as granted in approved NDA 208159) to 36 months. Changes of this kind cannot be put into effect prior to approval of a supplement; we consider this to be a **Prior Approval Supplement**. An approved supplement is required for this proposed change prior to distributing drug product made with this change.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 29, 2016, in accordance with 21 CFR: 314.101(a).

If the application is filed, the user fee goal date will be June 29, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, please call me, at (240) 402-5834.

Sincerely,
Kristine F. Leahy -S

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Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research