



NDA 208627

NDA APPROVAL – ANIMAL EFFICACY

SIGA Technologies, Inc.
Attention: Annie Frimm
Vice President, Regulatory, Clinical and Quality
4575 SW Research Way
Suite 110
Corvallis, OR 97333

Dear Ms. Frimm

Please refer to your New Drug Application (NDA) dated December 8, 2017, received December 8, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TPOXX[®] (tecovirimat) capsules, 200 mg.

This new drug application provides for the use of TPOXX[®] (tecovirimat) 200 mg capsules for the treatment of patients with human smallpox disease caused by variola virus.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, under the provisions of 21 CFR 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible), effective on the date of this letter, for use as recommended in the enclosed agreed upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced animal efficacy regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, instructions for use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABEL

Submit a final printed container label that is identical to the enclosed immediate container label as soon it is available, but no more than 30 days after it is printed. Please submit this label electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Container Label for approved NDA 208627.**” Approval of this submission by FDA is not required before the labeling is used.

MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a material threat medical countermeasure priority review voucher (PRV), as provided under section 565A of the FDCA. This PRV has been assigned a tracking number, PRV NDA 208627. All correspondences related to this PRV should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This PRV may be transferred by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher. The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application.

FDA has published a draft guidance, *Material Threat Medical Countermeasure Priority Review Vouchers*, at <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm592548.pdf>. This guidance, when finalized, will represent the current thinking of the FDA on this topic.

MARKET PACKAGE

Please submit one market package (one bottle) of the drug product when it is available to the following address:

Andrew Gentles, PharmD, BCPS, AQ-ID
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 6211

10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code **20903** if shipping via United States Postal Service (USPS).

Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

SUBPART I APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that TPOXX[®] (tecovirimat) can be safely used without restrictions on distribution or use.
2. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We conclude that the FDA-Approved Patient Labeling and Instructions For Use for TPOXX (tecovirimat) meets the requirements of this subsection. We remind you that the patient labeling and instructions for use must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.
3. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

Therefore, you are required to conduct the following postmarketing study, when feasible and ethical, to meet the Subpart I approval requirements:

- 3417-1 Conduct a Field Study to evaluate the clinical response, drug concentrations, and safety profile of tecovirimat when used in the treatment of subjects with variola virus infection.

We refer to your submission dated April 25, 2018, outlining your plan to conduct this field study to meet the postmarketing requirement and your submission, dated June 8, 2018, stating that you will submit a protocol according to the following schedule:

| | |
|----------------------------|---------|
| Draft Protocol Submission: | 02/2019 |
| Final Protocol Submission: | 06/2019 |

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart I Postmarketing Requirements.**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3417-2 Conduct a human factors validation study to demonstrate that representative users (e.g. healthcare providers and lay users) can safely and effectively prepare and administer tecovirimat to pediatric patients requiring less than a 200 mg dose (i.e. less than 1 full capsule) under simulated use conditions that are representative of realistic use conditions.

The timetable you submitted on June 18, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/2020
Study/Trial Completion: 06/2020
Final Report Submission: 12/2020

- 3417-3 Conduct cell culture studies to characterize tecovirimat antiviral activity against an expanded panel of variola virus isolates and recombinant vaccinia viruses. These studies should capture the known VP37 amino acid heterogeneity in variola viruses, as well as a common orthopoxvirus VP37 polymorphism, and should also include multiple independent isolates with identical VP37 amino acid sequences, when feasible.

The timetable you submitted on May 23, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2019
Final Protocol Submission: 05/2019
Study/Trial Completion: 09/2020
Final Report Submission: 12/2020

- 3417-4 Conduct a study to determine the pharmacokinetics of tecovirimat in subjects with body weight greater than 120 kilograms (>120 kg) and to further determine if a change in dosing regimen is needed in these subjects.

The timetable you submitted on June 1, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2019
Final Protocol Submission: 07/2019
Study/Trial Completion: 08/2020
Final Report Submission: 02/2021

- 3417-5 Conduct an in vitro study to determine the potential for a drug interaction between tecovirimat and phosphate binders. If the results of the study are inconclusive or indicate binding of phosphate binders to tecovirimat is significant, conduct an in vivo study to determine the magnitude of interaction to inform the dosing regimen in patients who concomitantly take phosphate binders.

The timetable you submitted on June 1, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2019
Final Protocol Submission: 07/2019
Study/Trial Completion: 08/2020
Final Report Submission: 02/2021

**POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING
REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

- 3417-6 Conduct and submit a risk assessment for elemental impurities when new batches of the drug product are manufactured. This information should be submitted as a Changes Being Effected-30 Supplement.

The timetable you submitted on April 20 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: NA
Study/Trial Completion: To be determined when new drug product batches are to be manufactured.
Final Report Submission: To be determined when new drug product batches are to be manufactured.

Submit clinical protocols to your IND 069019 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this

NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

Under 21 CFR 314.640, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.640, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/default.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, at (240) 402-5708 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Container Label

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EDWARD M COX
07/13/2018