CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208627Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208627
Review #1

Drug Name/Dosage Form	Tpoxx (tecovirimat) Capsules
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	SIGA Technologies, Inc
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
CMC Rolling Submission	Aug 3, 2017	Quality
Completion of NDA	Dec 8, 2017	All
Amendment	Jan 12, 2018	Quality
Amendment	Jan 26, 2018	Quality
Amendment	Feb 9, 2018	Quality
Amendment	Feb 23, 2018	Labeling
Amendment	Mar 13, 2018	Labeling/Packaging
Amendment	Mar 20, 2018	Quality
Amendment	Apr 6, 2018	Labeling Exception
Amendment	Apr 17, 2018	Labeling Exception
Amendment	Apr 24, 2018	Container Labeling

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Katherine Windsor	Ben Stevens
Drug Product	Yushi Feng	Balajee Shanmugam
Process	Iwona Weidlich	Arwa El Hagrasy
Microbiology	Iwona Weidlich	Arwa El Hagrasy
Facility	Frank Wackes	Derek Smith
Biopharmaceutics	Yang Zhao	Elsbeth Chikhale
Environmental Assessment	James Laurenson	M. Scott Furness
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Steve Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
Various	Type III *(if applicable)*	See DP review				
	Type IV *(if applicable)*	See DP review				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 69019	IND for Tecovirimat Caps	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the product quality perspective.

A Post-Approval Commitment (PMC) has been established under which the applicant will conduct a risk assessment for elemental impurities when new batches of the drug product are manufactured.

II. Summary of Quality Assessments

A. Product Overview

Tecovirimat is a small synthetic compound that inhibits a viral protein necessary for release of infectious smallpox (variola) virus from cells. It was developed to treat smallpox infection, and has been included in the US Strategic National Stockpile in case a smallpox release should ever occur. There were significant regulatory interactions, and the applicant produced commercial scale batches, during IND development.

Proposed Indication(s) including Intended Patient Population	Treatment of human smallpox disease caused by variola virus in adults and pediatric patients.
Duration of Treatment	14 days
Maximum Daily Dose	Three 200 mg capsules twice a day (1200 mg per day).
Alternative Methods of Administration	Mixing of 200 mg, 400 mg or 600 mg doses with liquids or soft foods

B. Quality Assessment Overview

Drug Substance:

Tecovirimat has low solubility by the BCS criteria, (b) (4) Three polymorphs of tecovirimat have been identified, (b) (4) (b) (4)

Tecovirimat monohydrate drug substance is manufactured by (b) (4)

Following pilot scale manufacture and prior to scale up and commercial process validation, a series of QbD/DoE studies were performed. The results of these studies were used to establish a control strategy – critical process parameters, in-process controls, and specifications for both regulatory starting materials and the final DS – generally aimed at ensuring an acceptable impurity profile, correct polymorph (b) (4)

Since the validation of the commercial scale manufacturing process (b) (4) approximately 20 commercial scale batches of acceptable quality have been produced demonstrating the robustness of the process. The retest period for tecovirimat monohydrate (b) (4) is (b) (4) months when stored at (b) (4) RH. For additional details, see Katherine Windsor's Drug Substance Review, below.

Drug Product:
Tpoxx is supplied as hard gelatin capsules with an opaque orange body imprinted in white ink with "SIGA®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off white powder. Each capsule contains tecovirimat monohydrate equivalent to 200 mg of tecovirimat. All excipients (except the gelatin capsule shell) are compendial, and comply with the specifications defined per USP/NF. For patients unable to swallow capsules, the content of 1-3 capsules can be mixed with (b) (4) (b) (4) of a suitable liquid (e.g., milk, (b) (4), chocolate milk) or soft food (e.g., apple sauce, (b) (4) yogurt), and consumed within 30 minutes. Five food matrices were studied: applesauce, chocolate milk, 2% milk, infant formula, and vanilla yogurt, under storage conditions of 41°F and 77°F. Additional in-use stability data was obtained on suspensions in water across the pH range of (b) (4) When mixed at the full dose, all food-drug and drug-water matrices exhibited acceptable stability over a 24-hour period and a 72-hour period, respectively, and passed the acceptance criteria for both tecovirimat assay and for the absence of related substances. This provides adequate support for the labeling instructions for the preparation of 200, 400 and 600 mg doses in liquids or soft foods.

The drug product specification includes appearance, identification, assay, impurities, dissolution, content uniformity, (b) (4), and microbiological tests. The proposed drug product specification is adequate to ensure the quality of the drug product, and the tests and acceptance criteria are appropriately justified. Considering the manufacturing processes for drug substance and product, the excipients and the oral route of administration, elemental impurities do not pose any significant risk to patients. As a Post-Marketing Commitment (PMC), the applicant will conduct a formal elemental impurity risk assessment when drug product is manufactured, and will submit the assessment as a CBE-30 supplement.

The immediate container is a HDPE bottle containing 42 capsules (one week supply), with a child-resistant closure and an induction seal. Up to 84 months of stability data at the long-term (25°C/60%RH) condition, in (b) (4) and (b) (4)-count bottles (bracketing the commercial packaging of 42-count bottles) are available from 3 registration batches (b) (4) Commercial Scale) and 3 commercial/process validation batches. There was little

change or variability over time for all tested quality attributes (appearance, assay, related substances including (b) (4), dissolution, and microbiological tests). This data supports an expiration dating period of 84 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F). Further extension of the expiration dating period are very likely, given the high stability of this product.

Based on FDA recommendation, the Applicant requests to include expiration date only on the storage configuration of pallets, not on the smaller configurations of bottles (i.e., the immediate container, trays, and shippers). This approach is consistent with the recommendations in the FDA letter to the applicant dated October 31, 2017 and is supported from the product quality perspective.

For additional details, see Yushi Feng's Drug Product review, below.

Process:
Tecovirimat 200 mg capsules are manufactured (b) (4)

(b) (4)

Facilities:
All manufacturing facilities are acceptable based on review of relevant information in conjunction with results from the following inspections:

- Nov 2017 inspection of Catalent Pharma Winchester, KY; DP manufacturing

(b) (4)

An Overall Manufacturing Facility Status recommendation of Approve was entered in Panorama on Apr 2, 2018. For additional details, see Frank Wackes' Facility review, below.

Biopharmaceutics:
The following dissolution method and acceptance criterion are adequate for the routine QC testing of the proposed drug product at batch release and on stability:

Acceptable dissolution method and acceptance criterion for Tecovirimat monohydrate Capsules 200 mg						
Tier	Apparatus	Speed (rpm)	Temperature	Volume (mL)	Medium	Acceptance criterion
I	USP 2 (paddle)	75	37 °C	900	0.05M KH_2PO_4 buffer containing 1% hexadecyltrimethylammonium bromide (HDTMA), pH 7.5	NLT (b)(4)% (Q) of the label claim dissolved in 45 minutes
II	USP 2 (paddle)	75	37 °C	840	0–15 minutes: 0.05M KH_2PO_4 buffer containing pancreatin (≤ 1750 USP units of protease activity/1000 mL, pH 7.5)	NLT (b)(4)% (Q) of the label claim dissolved in 45 minutes
				60	After 15 minutes: 0.05M KH_2PO_4 buffer containing 15% of HDTMA added to the above medium	

In addition, the bridging for the different formulations used in clinical studies is acceptable. For additional details, see Yang Zhao's Biopharmaceutics review, below.

Environmental Assessment:

The applicant submitted a claim for a categorical exclusion for tecovirimat from the requirement to prepare an environmental assessment (EA), per 21 CFR 25.31(b). The applicant also submitted the required statement of no knowledge of extraordinary circumstances, per 21 CFR 25.15(a). FDA requested additional information to support the claim, and also conducted additional analysis to confirm whether the claim would be acceptable. These FDA analyses included the use of tecovirmat based on a published smallpox exposure scenario. The CDER Environmental Team plans to continue to work with the applicant after approval to determine whether communication with local sewage treatment facilities would be valuable in the context of a very large smallpox exposure. Based on a review of the information provided by the applicant, and the additional analysis by FDA, the claim for a categorical exclusion from an EA is acceptable. For additional details see James Laurenson's Environmental Review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

Recommendations have been conveyed to the OND PM for consideration as the labeling is finalized. See Yushi Feng's OPQ Labeling review, below.

D. Final Risk Assessment (see Attachment)

65 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ENVIRONMENTAL

IQA Review Guide Reference

R Regional Information

Summary: The applicant submitted a claim for a categorical exclusion for tecovirimat from the requirement to prepare an environmental assessment (EA), per 21 CFR 25.31(b). The applicant also submitted the required statement of no knowledge of extraordinary circumstances, per 21 CFR 25.15(a). FDA requested additional information to support the claim, and also conducted additional analysis to confirm whether the claim would be acceptable. Based on a review of the information provided by the applicant, and the additional analysis by FDA, the claim for a categorical exclusion from an EA is acceptable. FDA is seeking additional information from the applicant, however, to evaluate whether a high release/limited timeframe scenario has the potential to disrupt biological systems within sewage treatment plants (STPs). The response date for this request is May 15.

Environmental

The applicant submitted a claim for a categorical exclusion for tecovirimat from the requirement to prepare an EA, per 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but where the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The expected introduction concentration (EIC) provided by the applicant is (b) (4) (µg/L), based on (b) (4) of tecovirimat being used for 2 million people (600 mg, 2 times/day, for 14 days of treatment), which on its face is consistent with the exclusion requirements of < 1 ppb. In addition, a statement was provided declaring no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment, as required per 21 CFR 25.15(a).

FDA responded to the applicant that while the calculation for the EIC, as described in FDA guidance, is based on an annual national volume of wastewater an actual incident likely would occur during a much shorter timeframe than one year and be concentrated in a more limited geographic area than the entire US. This in turn might result in a higher EIC, possibly ≥ 1 ppb. FDA also conveyed its results of an experimental fish plasma model (FPM; per Nallani et al., 2016 and Huggett et al., 2003) used to help screen for aquatic environmental risk when no environmental toxicity data are available. FDA used the following data in the model: a human Cmax of 2.2 µg/mL (from CTD Section 2.5, Clinical Overview), which is used as a rough estimate of blood plasma levels that would result in biological (though not necessarily adverse) effects in the environment; and a predicted log D value of (b) (4) (www.chemspider.com) and the EIC of (b) (4), which are used to estimate plasma levels in fish for comparison to the Cmax. The result was an effects ratio (ER) of (b) (4) which is lower than the acceptable minimum FPM ER of 1,000 recommended by Huggett et al. (2003) (the higher the number the lower the risk). This

model thus indicates some potential concern for this substance in the aquatic environment, especially if the EIC is indeed an under-estimate.

FDA subsequently asked the applicant to provide the following additional data and analysis to assist the review of the claim for a categorical exclusion: (1) any available information for assessing environmental effects for this or similar substances (e.g., aquatic toxicity assay data, acute/subchronic toxicity data [given the likely short-term exposure scenario], "read across" results); (2) available information for determining a more realistic expected environmental concentration (e.g., using metabolism and environmental degradation data in the estimate), in addition to factors noted above; and (3) any other available information relevant to assessing the environmental impact of this substance, including mixture effects from similar substances. FDA advised that an alternative to the claim for exclusion was to submit an EA.

The applicant responded to the FDA request by stating that the calculation provided in the NDA submission had been presented as a worst-case scenario, using the entire amount (2 million treatment courses) of the drug product stored in the national stockpile as the basis for the calculation, and that the calculation in the NDA was conducted according to the FDA EA guidance document specifications (USFDA, 1998). FDA notes, however, that while the calculation that was used was indeed conducted according to the default calculation in the EA guidance (USFDA, 1998), Section III.A.2 of the guidance also states that an alternative calculation should be used if the drug product is intended for use in a specific geographic location (e.g., by using an alternative value for the amount of liters per day entering sewage treatment plants), or for any other reason (e.g., a shorter release period than one year). Given the limited time available before the drug approval date and the need for specific expertise to address this highly unique issue, FDA conducted additional analysis (see Reviewer's Assessment section below).

The applicant also cited the EA guidance for the purpose of conducting a recalculation of the EIC based on metabolism of the active moiety to less pharmacologically active or inactive compounds. As described in the NDA, the applicant notes that the majority of tecovirimat, once absorbed, is metabolized to three main metabolites (M4, M5, and TFMBA) and glucuronide conjugates, none of which are pharmacologically active. Furthermore, the applicant states, only (b) (4)% of administered tecovirimat is detected in (b) (4) An additional amount of (b) (4)% is unidentified and therefore is considered conservatively by the applicant as pharmacologically active upon leaving the body. Therefore, the applicant estimates, a total of (b) (4)% of administered drug may be introduced to the environment, resulting in a recalculated EIC of (b) (4)ppb. FDA notes, however, that deconjugation of drugs during wastewater treatment and in the environment readily occurs (e.g., Celiz et al., 2009), and this is not addressed in the applicant's analysis. Thus, per FDA guidance (USFDA, 1998), which states that as a default the highest quantity of the active moiety expected to be produced should be used for the EIC, conjugates generally should not be subtracted from estimates of excretion of active ingredients unless there are data to specifically indicate that deconjugation does not occur. As with the EIC recalculation due to a different geographic and timeframe scenario, FDA also conducted additional analysis for metabolism (see Reviewer's Assessment section).

Reviewer's Assessment: ***Adequate with the following additional analysis***

The scenario that the applicant used to estimate an EIC of (b) (4) assumed that the entire stockpile was used over an entire year and across the entire US. While it is not clear exactly how smallpox incidents would play out, it is more likely that an incident would occur in a shorter period of time and in a smaller geographic area. Nevertheless, if the applicant's scenario were to occur, this EIC would be consistent with the categorical exclusion from an environmental assessment as claimed, i.e., is less than 1 ppb, per 21 CFR 25.31(b). In addition, a statement was provided declaring no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment, as required per 21 CFR 25.15(a).

As noted previously, a more likely scenario is a smaller incident within a more limited geographic area and timeframe. Therefore, FDA calculated an alternative EIC based on a likely incident scenario described by the Centers for Disease Control and Prevention (CDC, 1999). In this scenario, 15,000 cases were assumed to be reported over a period of approximately three months in the US. The hypothetical incident began during a stealth attack at an event within a large city of 2.5 million. Ultimately, approximately 8,000 cases were assumed to occur within the hypothetical city, while a remaining 7,000 cases would occur across the US when infected people traveled from the event prior to discovery of the attack. FDA focused on the 8,000 cases with the large city. The remaining 7,000 cases across the US represents a similar, though substantially smaller, scenario than the original proposed scenario of 2 million cases across the US, which would result in a lower EIC, even with a more condensed treatment timeframe of three months rather than a full year.

The 8,000 cases were assumed to be distributed across all age groups. Therefore, to calculate the EIC, FDA began with the dosing regimen being considered for tecovirimat of 2 times/day, for 14 days, for the following doses (USFDA, 2018):

1. 600 mg for body weights (BW) > 40 kg;
2. 400 mg for 25 < BW ≤ 40 kg;

(b) (4)

The first (highest) BW group was assumed to represent ages greater than 12 years, which is approximately the age that above which body weights are 40 kg or above (USEPA, 2011). This group corresponds to approximately 84% of the US population (USDOC, 2017), and thus 84% of cases also were assumed to be in this BW (age) group. The remaining cases are distributed evenly among the other BW groups. FDA considered adjusting this distribution based on the assumptions that some adults will maintain some degree of immunity from vaccines last given in the 1970s, and that children will tend to spread the disease more readily and be more susceptible than adults, but based on the literature (e.g., Henderson et al., 1999), these assumptions

could not be substantiated, and therefore FDA used the more conservative approach that would result in a higher EIC.

This analysis resulted in the use of approximately (b) (4) of tecovirimat. When this mass is used within a wastewater treatment system serving 2.5 million over three months, the resulting EIC would be (b) (4) ppb. This EIC is higher than the 1 ppb concentration level required for the categorical exclusion, and therefore FDA also considered using the metabolism information that was provided by the applicant that could reduce the mass excreted to (b) (4)% of the administered dose. As described previously, however, FDA declined to use this value due to the potential deconjugation that could occur. In addition, FDA could not recreate this value from the data provided by the applicant. For example, the claim that only (b) (4)% of administered tecovirimat is detected from (b) (4) appears to come from the CTD section 2.7.2, Summary of Clinical Pharmacology Studies, which states that (b) (4)% of the total radioactive tecovirimat dose—which includes metabolites—was recovered in feces, (b) (4) Therefore, FDA recalculated the metabolism reduction by utilizing data from SIGA (2014). This report indicates that (b) (4)% the parent tecovirimat is excreted without undergoing metabolic biotransformation. The primary tecovirimat glucuronide conjugates, M9 and M8, which accounted for (b) (4)% and (b) (4)% (= (b) (4)%) of the urinary radioactive components, respectively, and (b) (4)% and (b) (4)% (= (b) (4)%) of fecal components, may be hydrolyzed back to the parent compound. Considering a scenario with unchanged tecovirimat (b) (4)%) and hydrolysis of all primary glucuronide conjugates ((b) (4)%), almost (b) (4) the drug ((b) (4)%) could potentially be active in the environment. Using this metabolism value, the final adjusted EIC is (b) (4) ppb, which satisfies the exclusion criterion of < 1 ppb. This value also is likely an overestimate of the EIC given that reductions from the treatment process are not included, including reductions due to the low solubility of tecovirimat, which would tend to increase its affinity to biosolids rather than wastewater.

While the claim for a categorical exclusion based on the < 1 ppb criterion is acceptable based on these analyses, there still is the possibility of the occurrence of a larger incident in a more limited geographic area that could result in an EIC > 1 ppb, even if only for the limited timeframe of the event, such as the three months in the scenario described above. Therefore, FDA considered the short-term toxicity concentration at which adverse effects would likely be experienced. No data could be found on the aquatic toxicity of tecovirimat, however, and therefore FDA used predicted aquatic toxicity data for close structural analogs in the Danish QSAR database website, http://qsar.food.dtu.dk. FDA retrieved data for the four top analogs (one with a similarity index (b) (4) and three with a similarity index (b) (4)) and examined the predictions for short-term aquatic toxicity (LC50s and EC50s) across several species. The lowest aquatic toxicity concentration (highest toxicity) was for analog #2832411, which had a predicted 48-hour EC50 of (b) (4) ppb for *Daphnia magna*. The margin of exposure (MOE; i.e., ratio of the predicted effects concentration to the exposure concentration, with the higher the number indicating lower risk) of the EC50 to the EIC is (b) (4), indicating low short-term risk. Furthermore, this EIC is considered an

overestimate of surface water concentrations because it does not include reductions from wastewater treatment and environmental dilution and degradation. Such effects tend to result in at least a 10-fold reduction of the EIC, which in the CDC scenario would result in a predicted environmental concentration (PEC) of (b) (4) ppb or lower, thus raising the MOE to at least (b) (4). FDA therefore concludes that approval of this drug is not likely to result in a significant impact on the environment under this incident scenario.

FDA then examined how many cases would result in a PEC that is equal to the tentative predicted lowest short-term aquatic EC50 of (b) (4) ppb described above, in order to better understand the size of the scenario that could result in short-term aquatic toxicity or treatment system disruption and thus be a threshold for informing STP managers. A PEC of (b) (4) ppb, however, likely would not actually be reached for the above scenario due to the limitation of the 2 M courses of treatment. That is, 2 M cases in the US would result in about 1.1 M cases in the affected city, assuming the same ratio of cases within the city to cases outside the city used previously (8,000:7,000). In a city of 2.5 million, the PEC would be approximately (b) (4) ppb, thus resulting in an MOE of (b) (4) ppb / (b) (4) ppb = (b) (4) In a scenario where 100 percent of the city/STP area population are considered cases (i.e., ignoring the 8,000:7,000 ratio), which is conceivable (e.g., see O'Toole et al., 2002), up to the 2 million courses of treatment, the PEC would be up to approximately (b) (4) ppb (b) (4) ppb EIC), thus resulting in an MOE of (b) (4) or greater and indicating relatively low, though uncertain risk.

While the above MOEs are all greater than 1, there is some uncertainty in the toxicity values, in particular because they have been derived from analog molecules. This uncertainty, however, is mitigated to some extent by use of the lowest value among the (b) (4) across the four analogs examined. In addition, these latter scenarios, up to millions of cases, are substantially larger than that used by CDC (1999). Furthermore, the percentage of cases, i.e., up to 100 percent within a city/STP area population, also is substantially larger than an estimated 3.5 percent developed by a modeling analysis used to assess various response approaches (Longini et al., 2007). FDA also examined the pharmacological mechanism of action of tecovirimat, noting that this substance specifically inhibits the viral release from cells by targeting protein F13L, which has only been identified in viruses, https://www.uniprot.org/uniprot/?query=f13l&sort=score. Furthermore, the limited nature of impact immediately downstream of a single or small number of STPs due to tecovirimat, given also the effect would be reversible, indicates the impact would not be considered significant.

FDA also considered the possibility that a high concentration of tecovirimat entering a sewage treatment plant during a large incident, such as the (b) (4) ppb EIC scenario above, in addition to likely increases in the use of antibacterials and other drug substances, could disrupt the biological processes (secondary treatment) of the STP (e.g., see Slater et al., 2011). As noted above, tecovirimat targets protein F13L, which reduces the likelihood that tecovirimat would affect bacteria. Furthermore, the limited nature of disruption of a single or small number of STPs, given also the effect would be

reversible, indicates the impact likely would not be considered significant. Nevertheless, this is a substantial area of uncertainty that would benefit from additional research. Therefore, FDA recommends seeking additional information to evaluate whether a high release/limited timeframe scenario has the potential to disrupt biological systems within STPs.

Decision:

FDA does not anticipate a significant environmental impact from approval of this application, and thus agrees with the claim for a categorical exclusion from an EA. FDA also recognizes uncertainties regarding exposure and toxicity of tecovirimat, particularly within the context of a larger, more concentrated incident than that anticipated here for the categorical exclusion scenario. The concerns primarily involve the potential for disruption of STP microbial communities due to the introduction of tecovirimat, which could be addressed via available data or literature or, if needed, conducting laboratory studies such as OECD 209 (Activated Sludge, Respiration Inhibition Test) and biological nitrification inhibition studies. If disruption risks are likely in the event of a large concentrated incident, FDA would initiate communications with responsible parties (e.g., CDC, Emergency Planning and Community Right-to-Know Act (EPCRA), State or Local Emergency Response Commissions (SERCs/LEPCs), and/or STP representatives) to determine next steps. A request has been submitted to the applicant for a response by May 15 stating their agreement to this approach to provide additional data.

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Primary Environmental Reviewer Name and Date: James P. Laurenson, April 28, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): M. Scott Furness, April 30, 2018

James Laurenson

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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert (SDN 12, eCTD Sequence 0011, Submitted on 2/23/2018)

1. *Highlights of Prescribing Information*

TPO XX (tecovirimat) capsules for oral use

----------DOSAGE FORMS AND STRENGTHS----------

(b) (4).

Revise to:
Each capsule contains tecovirimat monohydrate equivalent to 200 mg of tecovirimat

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Adequate
Dosage form, route of administration	Adequate
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Changes recommended

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 (b) (4)

(b) (4)

2.2 Dosage for Pediatric Patients

The recommended dosage for pediatric patients is based on weight starting at (b) (4) as shown in Table 1. The dose should be given twice daily orally for 14 days and should be taken within 30 minutes after a full meal of moderate or high fat. (b) (4) (**Error! Reference source not found.**)]

2.3 Preparation for Administration to Pediatrics and Those Who Cannot Swallow Capsules

TPOXX capsules are administered by carefully opening the capsule and mixing the entire contents in (b) (4) of liquid (e.g., milk, (b) (4) chocolate milk) or soft food (e.g., apple sauce, (b) (4) yogurt). The entire (b) (4) mixture should be administered within 30 minutes of its preparation.

Table 1: (b) (4)

Body Weight (b) (4)	(b) (4)		**Drug-Food Preparation**
	200 mg twice daily	Contents of 1 Capsule twice daily	Mix 1 capsule of tecovirimat (b) (4) of liquid or soft food. Administer the whole mixture.
	400 mg twice daily	Contents of 2 Capsules twice daily	Mix 2 capsules of tecovirimat (b) (4) of liquid or soft food. Administer the whole mixture.
	600 mg twice daily	Contents of 3 Capsules twice daily	Mix 3 capsules of tecovirimat (b) (4) of liquid or soft food. Administer the whole mixture.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

TPOXX capsules are hard gelatin with an opaque orange body imprinted in white ink with "SIGA" followed by the SIGA logo followed by the "ᴓ®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off-white powder. (b) (4) Each capsule contains tecovirimat monohydrate equivalent to 200 mg of tecovirimat.

Recommended revisions are highlighted

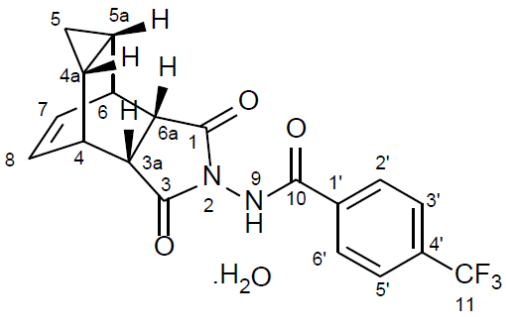
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Changes recommended
Active moiety expression of strength with equivalence statement (if applicable)	Changes recommended
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Changes recommended

4. *Section 11 Description*

11 DESCRIPTION

TPOXX capsules for oral use contain tecovirimat (as tecovirimat monohydrate), (b) (4)

Tecovirimat monohydrate is a white to off-white crystalline solid with the chemical name Benzamide, N-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6 ethenocycloprop[f]isoindol-2(1H)-yl]-4-(trifluoromethyl), rel-(monohydrate). The chemical formula is $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ representing a molecular weight of 394.35 g/moL. The molecular structure is as follows:



Tecovirimat monohydrate is practically insoluble in water and across the pH range of 2.0-6.5 (< 0.1 mg/mL).

TPOXX is available as immediate release capsules containing (b) (4) The capsules are imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®" on an orange body, and a black cap imprinted in white ink with "ST-246®."

(b) (4) colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is composed of gelatin, (b) (4) FD&C blue #1, FD&C red #3 (b) (4) FD&C yellow #6, and titanium dioxide.

Recommended revisions are highlighted

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Changes recommended
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Adequate
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Adequate
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Adequate

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

TPOXX capsules are hard gelatin with an opaque orange body imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off white powder.

(b) (4)

20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Manufactured by:

Catalent Pharma Solutions
1100 Enterprise Drive
Winchester, KY 40391

Distributed by:
SIGA Technologies, Inc.
4575 SW Research Way
Corvallis, OR 97333

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	Adequate
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

(b) (4)

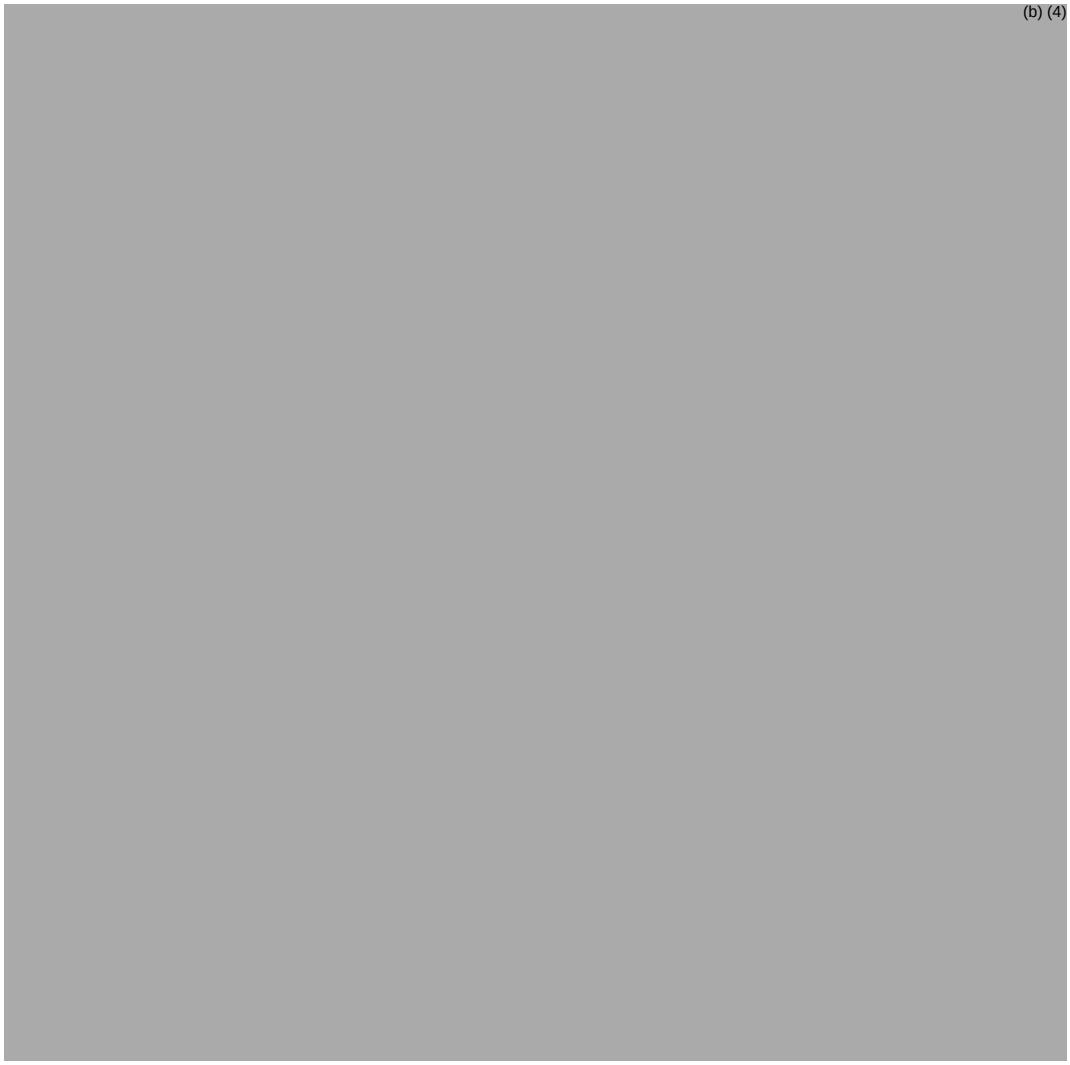
(b) (4)

Reviewer's Assessment of Package Insert: ***Adequate***

II. Labels:

1. *Container and Carton Labels*

(b) (4)



2. *Carton Label*

No additional secondary packaging component (e.g., a carton) is described for this product. The container closure labeling submitted in Section 1.14.1.1 Draft Carton and Container Labels includes only a draft bottle label, no carton label.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ADEQUATE	N/A
Dosage strength	ADEQUATE	N/A
Net contents	ADEQUATE	N/A
"Rx only" displayed prominently on the main panel	ADEQUATE	N/A
NDC number (21 CFR 207.35(b)(3)(i))	ADEQUATE	N/A
Lot number and expiration date (21 CFR 201.17)	ADEQUATE (see section below on the expiration date)	N/A
Storage conditions	To be updated	N/A
Bar code (21CFR 201.25)	ADEQUATE	N/A
Name of manufacturer/distributor	ADEQUATE	N/A
And others, if space is available	N/A	N/A

3. ***Request for Exception to Labeling Requirements for Tecovirimat for the Strategic National Stockpile Post-NDA Approval (SDN 3, eCTD Sequence 0003, Submitted on 12/08/2017)***

SIGA has supplied tecovirimat drug product to the Strategic National Stockpile (SNS) for possible distribution prior to NDA approval under IND 69019 or Emergency Use Authorization (EUA). Since the tecovirimat NDA is not yet approved, commercial product labeling has not yet been approved.

As part of the IND review, SIGA received FDA approvals of label exceptions for 33 lots of tecovirimat drug product on 19 October 2012 (Ref ID: 3205654), for an additional 6 lots of drug product in a letter from Dr. Janet Woodcock dated 22 April 2015 and for 33 additional lots of drug product on 22 April 2016 (Ref ID: 3921220).

As part of the NDA, SIGA requests a label exception as per §21CFR 201.26 for the relabeling of drug based on NDA approval of tecovirimat. This pertains to drug currently stockpiled in the SNS, as well as future drug to be delivered to the SNS. These exceptions would be implemented upon NDA 208627 approval.

Due to operational difficulties and potential risks to product quality and security in re-labeling up to (b)(4) million immediate containers, and based on FDA recommendations (Attachment B—Correspondence A. Gentles to A. Frimm dated 31 October 2017) SIGA proposes to label the pallet packaging only with the expiration dating. The Unit of Use bottles already delivered to the SNS would not be relabeled. Labeling of the pallet is much less laborious and time-consuming,

and involves fewer operations than re-labeling of the Unit of Use bottles. Note, each full pallet contains (b) (4) Unit of Use bottles. It will also facilitate relabeling for future extensions of product expiry. Lastly, labeling of the pallet does not require any specialized equipment and will not compromise the availability of tecovirimat during an emergency.

(b) (4)

(b) (4) The proprietary name "TPOXX®" is conditionally approved by FDA, so it will be included on the labeling submitted with the original NDA for FDA review.

Inclusion of "Rx Only"on Drug Already in the SNS

As noted in the 31 October 2017 correspondence, the current labels on the individual bottles of tecovirimat currently in the SNS do not contain the "Rx Only" statement since these bottles were provided to the SNS prior to NDA approval. As the "Rx Only" statement is not subject to a waiver under §21CFR 201.26, SIGA asks that the Agency exercise enforcement discretion regarding the requirement of this statement for drug already in the SNS. Any new lots of drug provided to the SNS after NDA approval will include the "Rx Only" statement.

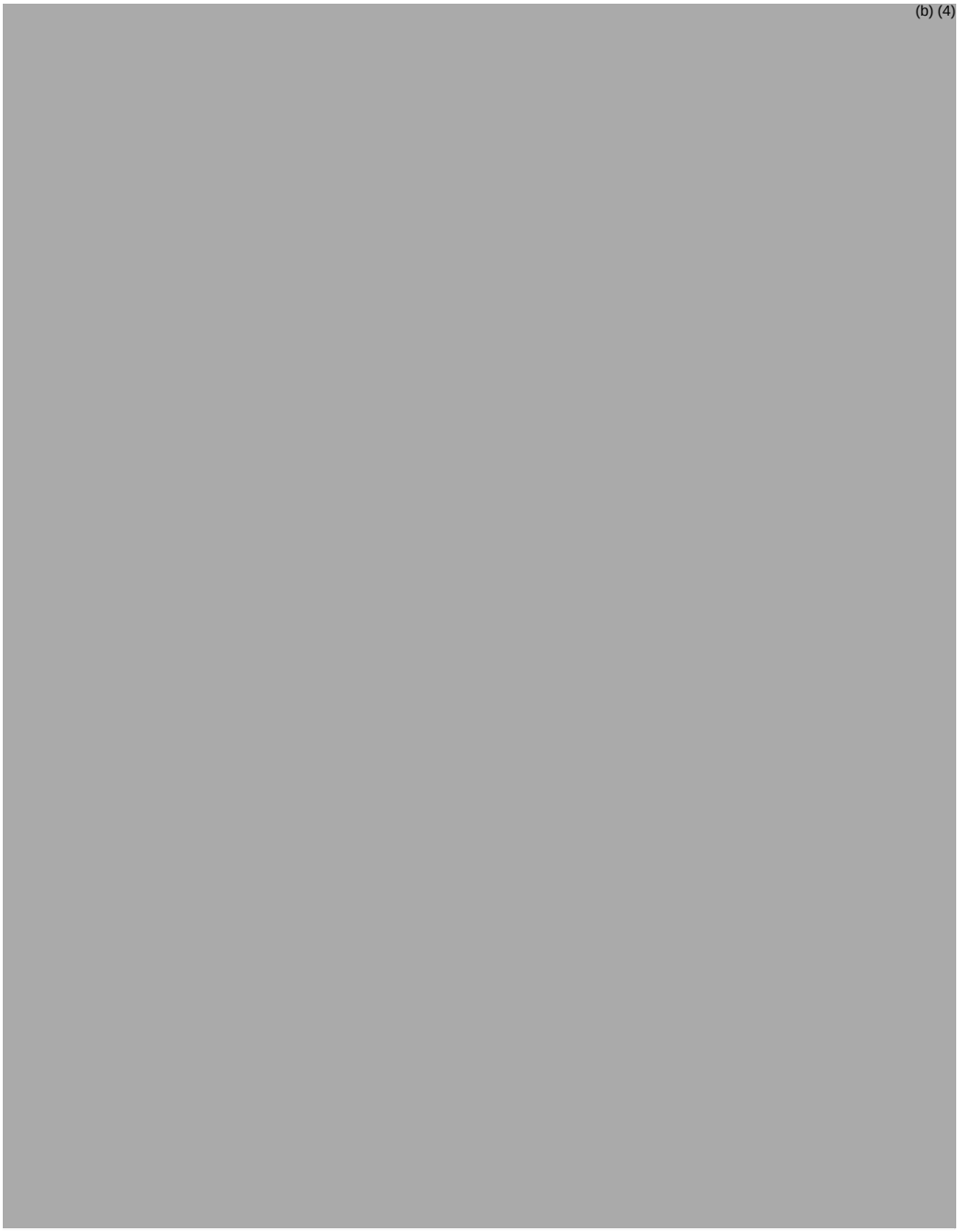
(b) (4)

Proposed Packaging Configuration

SIGA plans to continue to use the unit of use (UoU) bottle and packaging configuration outlined below for any future approved drug product:

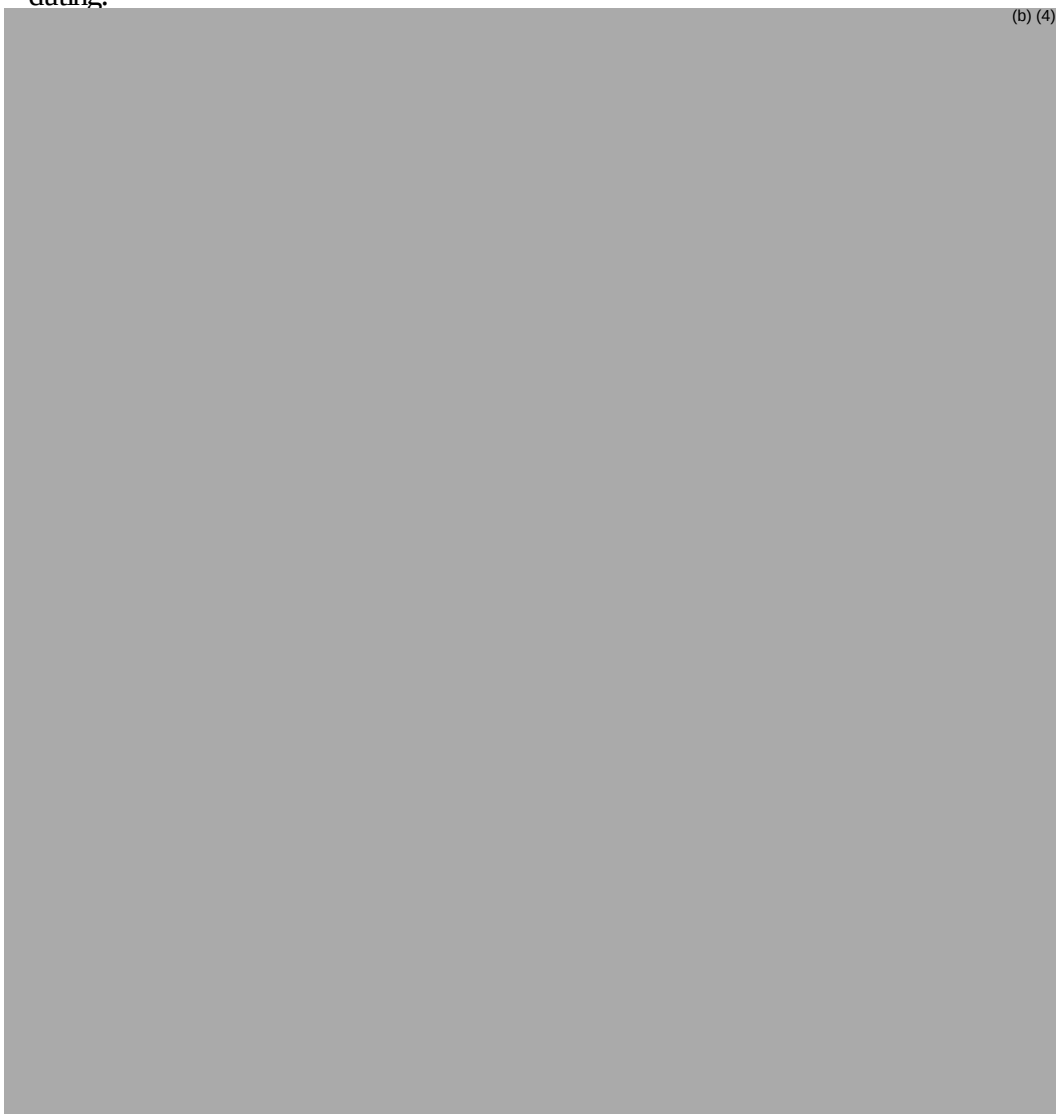
- Immediate container (i.e., Unit of Use bottle): 42 capsules in 75 cc HDPE bottle with product label; (b) (4) child resistant closure with induction seal, with bottle label
- (b) (4) bottles (b) (4) together to form a bundle, with tray label
- Secondary packaging/master shipper - (b) (4) bundles in (b) (4) shipper ((b) (4) bottles per full shipper), with shipper label
- Pallet ((b) (4) bottles per full pallet), with pallet label

A schematic of the packaging configuration is shown below:



Proposed Container Labels for Future Lots for SNS (NDA-Approved Product)

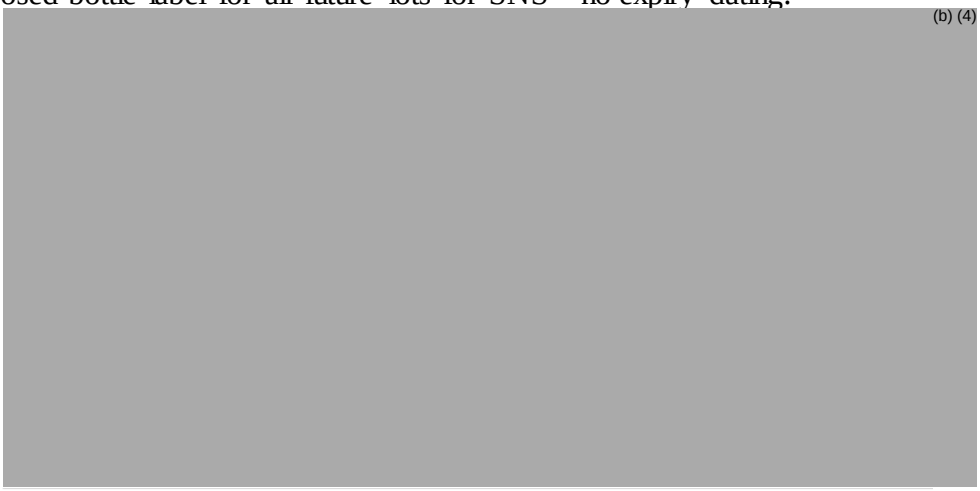
Schematic for tray and shipper labels for all future lots for SNS—no expiry dating:



Schematic for pallet label for all future lots for SNS—includes expiry dating:

Current bottle label on products currently in the SNS (not to be relabeled)—no expiry dating:

Proposed bottle label for all future lots for SNS—no expiry dating:



Reviewer's Assessment of Labels: ***Adequate***

The proposed labeling request on expiration date (only on pallets, not the smaller storage configurations: bottles, trays, and shippers) is appropriate per FDA's recommendation in the MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE dated 10/31/2017 and can be granted.

List of Deficiencies:

Draft IR for container labels:

- For *relabeling* current stockpile products:
  - Please verify that your plan is to relabel pallet labels only, not lower level labels (b) (4)
  - Add storage conditions statement on pallet label (for post-NDA approval relabeling only)
- For *future* products (post-NDA approval):
  - Bottle label (based on label proposed in SDN 12, eCTD Sequence 0011, Submitted on 2/23/2018): Remove (b) (4) from print area
  - Tray and Shipper labels (based on label proposed in SDN 3, eCTD Sequence 0003, Submitted on 12 /08/2017): revise storage condition statement, revise hydrate equivalency statement
  - Pallet label (based on label proposed in SDN 3, eCTD Sequence 0003, Submitted on 12 /08/2017): add storage condition statement

Applicable for Package Insert (b) (4) and the container labels:

- Update the hydrate equivalency statement to read:
  Each capsule contains tecovirimat monohydrate equivalent to 200 mg of tecovirimat
- Update the storage condition statement to read:
  Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Additional considerations:

- Current stockpile bottle label does not bear "Rx Only". Potentially exercise enforcement discretion. To be covered in the exception letter. New product label will have "Rx Only".
- (b) (4)
- Defer to DMEPA regarding the NDC numbers

Overall Assessment and Recommendation:

Deficiencies to be communicated to the Applicant, see above

Primary Labeling Reviewer Name and Date:

Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
Apr 2, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Balajee Shanmugam Ph.D., DNDP1, Branch 3.

Yushi Feng

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Balajee Shanmugam

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BIOPHARMACEUTICS

NDA: 208627-ORIG-1

Drug Product Name/Strength: Tecovirimat monohydrate Capsules/200 mg

Route of Administration: Oral

Applicant Name: SIGA Technologies, Inc.

Product Background: Tecovirimat monohydrate Capsules, 200 mg is indicated for the treatment of orthopoxvirus infections. The recommended dose is 600 mg twice daily for 14 days.

Tecovirimat monohydrate is formulated as capsules containing 200 mg of tecovirimat active pharmaceutical ingredient (API) and is being developed for provision to the Strategic National Stockpile (SNS) as a biodefense agent. The drug substance used is tecovirimat monohydrate in the (b) (4) The inactive ingredients in Tecovirimat drug product include (b) (4) (microcrystalline cellulose, lactose monohydrate), (b) (4) (hypromellose), (b) (4) (croscarmellose sodium), (b) (4) (colloidal silicon dioxide), (b) (4) (sodium lauryl sulfate (b) (4) The excipients chosen for tecovirimat capsules are all compendial (USP/NF), conventional, GRAS, and used as capsule excipients by the pharmaceutical industry.

The proposed drug product is an immediate release orange/black opaque hard gelatin capsule, size "0", containing 200 mg of tecovirimat as white to off-white powder. The capsules are imprinted in white ink with "SIGA®" on an orange body, and a black cap imprinted in white ink with "ST-246®". The capsules are packaged in HDPE bottles.

Review Recommendation: **Adequate**

Submission: Siga Technologies Inc. submitted this NDA seeking approval for Tecovirimat monohydrate Capsules 200 mg under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Reviewer's Assessment: The Biopharmaceutics Review evaluates the adequacy of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability. The following Tier I and Tier II dissolution methods and dissolution acceptance criterion are acceptable. In addition, the bridging for the different formulations used in clinical studies is acceptable.

Acceptable dissolution method and acceptance criterion for Tecovirimat monohydrate Capsules 200 mg						
Tier	Apparatus	Speed (rpm)	Temperature	Volume (mL)	Medium	Acceptance criterion
I	USP 2 (paddle)	75	37 °C	900	0.05M KH_2PO_4 buffer containing 1% hexadecyltrimethylammonium bromide (HDTMA), pH 7.5	NLT (b) (4)% (Q) of the label claim dissolved in 45 minutes
II	USP 2 (paddle)	75	37 °C	840	0–15 minutes: 0.05M KH_2PO_4 buffer containing pancreatin (≤ 1750 USP units of protease activity/1000 mL, pH 7.5)	NLT (b) (4)% (Q) of the label claim dissolved in 45 minutes
				60	After 15 minutes: 0.05M KH_2PO_4 buffer containing 15% of HDTMA added to the above medium	

Recommendation: From the Biopharmaceutics perspective, NDA-208627 for Tecovirimat monohydrate Capsules 200 mg, is recommended for **APPROVAL**.

Review Summary:

List of submissions being reviewed (table):

Original NDA-208627 submitted on August 3, 2017
IND 69019

Highlight key outstanding issues from last cycle: None, this is the first review cycle.

Concise description outstanding issues remaining: None

BCS Designation

Reviewer's Assessment: The Applicant has not requested an official BCS designation.

Solubility: The Applicant stated that tecovirimat monohydrate exhibits low solubility in water and buffers within the gastrointestinal pH range (approximately 2 µg/mL at pH (b) (4) at 37 °C).

Permeability: The Applicant reported that tecovirimat monohydrate is a high permeability drug, per Caco-2 cell study results (study no.: 11SIGAP2 and 12SIGAP1).

Dissolution: See below.

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: ADEQUATE

REVIEW:

1. Drug development rationale and efficacy/safety evaluation:

The Applicant developed tecovirimat for the treatment of orthopoxvirus infections and it is currently being provided to the Strategic National Stockpile as a bioterrorism countermeasure. The Applicant stated that tecovirimat is also active against other members of the orthopoxvirus genus (e.g., vaccinia virus [VACV], cowpox virus [CPXV], and monkeypox virus [MPXV]).

The Applicant evaluated the efficacy of tecovirimat in the non-human primate (NHP) and rabbit lethal challenge models (Animal Rule), and predicted efficacy against human smallpox. Four pivotal studies in NHPs and two pivotal studies in rabbits have been conducted, including dose-down and pharmacokinetic (PK) studies in both animal models as well as treatment initiation delay and treatment duration studies in NHPs. PK and PK/pharmacodynamic (PD) models have been developed for both animal models allowing a direct comparison of the tecovirimat exposure-response relationship.

Based on the exposures required for efficacy in NHPs, and using exposure modeling data, the Applicant conducted a human clinical trial to evaluate safety and plasma drug exposures at a dosage predicted to provide several-fold exposure over the effective exposures established in NHP studies but below the No Observed Effect Levels (NOEL) established in toxicological studies. Human dose modeling based on NHP efficacy supports a dose of 600 mg twice daily for 14 days for achievement of efficacious exposure levels in humans, but exceed efficacious exposures in NHPs. The Applicant claims that, based on the data available, tecovirimat is safe in humans.

2. Solubility of tecovirimat monohydrate:

The Applicant stated that tecovirimat monohydrate exhibits low solubility in water and buffers within the gastrointestinal pH range (approximately 2 µg/mL at pH (b) (4) at 37°C).

3. Dissolution method and dissolution acceptance criterion:

The proposed Tier I and Tier II dissolution methods and dissolution acceptance criteria for Tecovirimat monohydrate Capsules 200 mg are as follows:

Tier I Test:

Apparatus:	USP 2 (paddle)
Speed:	75 rpm
Medium:	900 mL of 0.05M KH_2PO_4 buffer containing 1% Hexadecyltrimethylammonium bromide (HDTMA), pH 7.5
Temperature:	37 °C
Acceptance criterion:	NLT (b) (4)% (Q) dissolved in 45 minutes

Tier II Test:

Apparatus:	USP 2 (paddle)
Speed:	75 rpm
Medium:	0–15 minutes: 840 mL of 0.05M KH_2PO_4 buffer containing pancreatin (≤ 1750 USP units of protease activity/1000 mL, pH 7.5); After 15 minutes: 60 mL of 0.05M KH_2PO_4 buffer containing 15% of HDTMA added to the above medium
Temperature:	37 °C
Acceptance criterion:	NLT (b) (4)% (Q) dissolved in 45 minutes after addition of surfactant.

The Applicant reported that Tier I test is the primary dissolution method for batch release testing and Tier II test is conducted for stability samples that failed Tier I due to cross-linking within the capsule shell. The Applicant stated that all dissolution results in this document are reported using the Tier I method.

The Applicant reported that several dissolution method selection criteria were used during the dissolution method development: (1) The dissolution medium should provide tecovirimat solubility that allows complete dissolution of one 200 mg capsule; (2) The dissolution method should provide low variability in the data; (3) The dissolution method should have adequate discriminating power to detect changes in the differences in API particle size and drug product manufacturing process; (4) The dissolution method should not be over-discriminating and reject batches that have been produced using the target manufacturing process.

(b) (4)

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(b) (4)

REVIEWER'S OVERALL ASSESSMENT:

- **Dissolution Method:** The proposed dissolution methods [Tier I: *USP apparatus II (Paddle)/75 rpm/900 mL of 0.05M KH_2PO_4 buffer containing 1% HDTMA, pH 7.5*; Tier II: *USP apparatus II (Paddle)/75 rpm/840 mL of 0.05M KH_2PO_4 buffer containing pancreatin (≤ 1750 USP units of protease activity/1000 mL, pH 7.5) (0–15 minutes) and additional 60 mL of 0.05M KH_2PO_4 buffer containing 15% of HDTMA (after15 minutes)*] for the quality control of the proposed immediate release drug product, Tecovirimat Capsules 200 mg are acceptable.
- **Dissolution Acceptance Criterion:** The dissolution acceptance criterion of "NLT (b) (4) % (Q) in 45 minutes" for the proposed Tecovirimat Capsules 200 mg is acceptable and supported by the provided dissolution data.
- **Formulation Bridging:** Tecovirimat Capsules (b) (4) are bridged by a clinical pharmacokinetic study (study No. SIGA-246-PO-005). In addition, the registration batches and commercial batches (that differ (b) (4)) have similar dissolution profiles. The bridging is acceptable.

Biowaiver Request

Reviewer's Assessment: N/A

A Biowaiver is not requested nor required.

R Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: N/A

List of Deficiencies: None

Primary Biopharmaceutics Reviewer: Yang Zhao, Ph.D., 4/16/2018
Secondary Reviewer: Elsbeth Chikhale, Ph.D., 4/20/2018

APPENDIX

Table. Summary of in vitro dissolution data

Studies Where Used/Location	Product ID/ Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times - Mean % Dissolved (range)
SIGA-246-001 SIGA-246-002 (Section 5.3.3.1)	(b) (4)				
SIGA-246-001 SIGA-246-002 (Section 5.3.3.1) SIGA-246-PO-005 (Section 5.3.1.2)					
SIGA-246-PO-005 (Section 5.3.1.2)	8F076	200 mg capsule (b) (4)	1% (b) (4) HDTMA in 900 mL of 0.05M phosphate buffer pH 7.5 at 37°C USP Apparatus 2 at 75 rpm	(b) (4)	15 (min) - 49 30 (min) - 67 45 (min) - 75 60 (min) - 79 (b) (4)
SIGA-246-004 (Section 5.3.3.1)	0910434	200 mg capsule (b) (4)	(b) (4)		15 (min) - 90 30 (min) - 98 45 (min) - 100 60 (min) - 101 (b) (4)
			1% (b) (4) HDTMA in 900 mL of 0.05M phosphate buffer pH 7.5 at 37°C USP Apparatus 2 at 75 rpm		15 (min) - 69 30 (min) - 92 45 (min) - 97 60 (min) - 99 (b) (4)
Studies Where Used/Location	**Product ID/ Batch No.**	**Dosage Form**	**Conditions**	**No. of Dosage Units**	**Collection Times - Mean % Dissolved (range)**
SIGA-246-009 SIGA-246-010 SIGA-246-018 (Section 5.3.3.1) SIGA-246-012 SIGA-246-013 (Section 5.3.3.3) SIGA-246-015 (Section 5.3.3.4) SIGA-246-008 (Section 5.3.5.1)	24601010	200 mg capsule (b) (4)	1% (b) (4) HDTMA in 900 mL of 0.05M phosphate buffer pH 7.5 at 37°C USP Apparatus 2 at 75 rpm	(b) (4)	15 (min) - 67 30 (min) - 88 45 (min) - 95 60 (min) - 98 (b) (4)
SIGA-246-015 (Section 5.3.3.4)	24601049	200 mg capsule (b) (4)	1% (b) (4) HDTMA in 900 mL of 0.05M phosphate buffer pH 7.5 at 37°C USP Apparatus 2 at 75 rpm		15 (min) - 68 30 (min) - 87 45 (min) - 93 60 (min) - 95 (b) (4)

KEY: HDTMA = hexadecyltrimethyl-ammonium bromide ; ID = identification; min = minute(s); No.= number; USP = United States Pharmacopeia.

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Elsbeth Chikhale

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Tpoxx (tecovirimat) Capsules, 200 mg

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**		Acc	
Physical stability (b) (4)		**M**	(b) (4)	Acc	
Content uniformity		**L**		Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**	Appropriate dissolution methods and AC. (b) (4)	Acc	
Patient Use Considerations	Instructions for administering doses of 200, 400 or 600 mg in liquids or soft foods	**L**	Acceptable stability behavior during in-use studies with liquids and soft-foods.	Acc	

Stephen Miller

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