CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209939Orig1s000
209940Orig1s000
PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209939
Review #2

Drug Name/Dosage Form	Letermovir Tablet
Strength	240 mg, 480 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Mar 8, 2017	All
Amendment	May 15, 2017	Quality
Amendment	May 16, 2017	Quality
Amendment	June 22, 2017	Quality
Amendment	July 25, 2017	Quality
Amendment	May 15, 2017	Quality
Amendment	Aug 22, 2017	Container Labeling

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Ben Stevens
Drug Product	Yong Wang	Balajee Shanmugam
Process	Ying Wang	Steven Frisbee
Microbiology	Ying Wang	Steven Frisbee
Facility	Rebecca Dombrowski	Derek Smith
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Environmental Assessment	James Laurenson	Michael (Scott) Furness
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
	Type II	None				
Various	Type III *(if applicable)*	See DP review				
	Type IV *(if applicable)*	None				
	Other	None				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 209940		Letermovir Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Methods Verification	NA	None requested		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the Product Quality perspective. This document (Review #2) contains the final evaluation of all manufacturing facilities, finalized container labels, the Final Risk Assessment, and the summary of all product quality aspects of the NDA (in Section II B, below). See Review #1 (August 18, 2017) for details of other product quality evaluations.

II. Summary of Quality Assessments

A. Product Overview

Letermovir is an NME that inhibits the cytomegalovirus (CMV) DNA terminase complex, which is required for viral DNA replication. It is indicated for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Two dosage forms have been developed: Tablets under NDA 209939 and Injection under NDA 209940. Both NDAs were granted Breakthrough Therapy designation and Orphan Drug status, and are being reviewed under a Priority classification because of unmet clinical need.

Proposed Indication(s) including Intended Patient Population	Adult hematopoietic stem cell transplant recipients who are seropositive for cytomegalovirus infection
Duration of Treatment	From day of transplant (or no later than 28 days post-transplant) through 100 days post-transplant.
Maximum Daily Dose	480 mg per day (240 mg per day for patients being treated with cyclosporine)
Alternative Methods of Administration	Intravenous infusion (see NDA 209940)

B. Quality Assessment Overview

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All sites are found acceptable upon completion of this review, but will result in a post approval inspection recommendation for th (b) (4) facility to address continued process validation efforts for the (b) (4), impurity testing and adherence t (b) (4) and conformance to application commitment/changes post approval. The Overall Manufacturing Facility Status in Panorama is Approve as of Nov 1, 2017. For details, see the Facility evaluation within this review (Product Quality Review #2).

The drug substance is th (b) (4) of letermovir, and all drug substance information is provided in this NDA (b) (4); of letermovir have been

found [redacted] had been used in all stages of formulation development and clinical studie [redacted] stability testing to date. The drug substance specification includes tests and acceptance criteria for description, assay, impurities (related substances), chiral purity, identification, residual solvents, water conten [redacted], bacterial endotoxins and microbiological purity (TAMC/TYMC). No acceptance criteria for particle size are included in the specification since the manufacturing process provides adequate control of the particle size distribution. Stability data support a retest period o [redacted] months when stored a [redacted] RH and packaged i [redacted] For details, see the Drug Substance evaluation within Product Quality Review#1 (Aug 18, 2017).

The drug products are immediate-release tablets with the following appearance:

- 240 mg: Yellow, oval shaped tablet debossed with"591"on one side and the Merck logo on the other side
- 480 mg: Pink, oval, bi-convex, tablet debossed with "595" on one side and the Merck logo on the other side

Three NDA registration batches of each strength were manufactured at the intended commercial site (MSD, Ireland) at a scale o [redacted] tablets. The commercial packaging is in aluminum-aluminum blisters, with 7 tablets per blister card. In one configuration, a 1-month carton holds 4 child-resistant dose packages with days of the week marked off. In a second configuration, designed for in-patient use, a 14-tablet carton holds two 7-tablet blister cards perforated for division into individual 1-tablet blisters. Letermovir tablets showed very little or no change in any quality perameters under long term (30°C/ 75%RH/ 18M) and accelerated (40°C/ 75%RH/ 6M) conditions. An expiration dating period of 30 months is appropriate for both strengths, when stored under USP controlled room temperature conditions. For details, see the Drug Product evaluation within Product Quality Review#1 (Aug 18, 2017).

[redacted] The intended commercial product differs from the Phase 3 formulation (PMF [redacted]
The intended commercial scales will be between [redacted] tablets for the 240 mg strength and between [redacted] tablets for the 480 mg strength. The applicant has conducted extensive manufacturing process development for this drug product. Risk based assessment, prior knowledge, multi-factor designs and one-factor - at-a-time experimental approaches are used in the development. Based on the study results and understanding, control strategies are established consisting of proven acceptable ranges (PARs) for the [redacted] Appropriate microbial quality monitoring is performed

at product release and on stability. For details, see the Process evaluation within Product Quality Review#1 (Aug 18, 2017).

For routine QC testing of the Letermovir Tablets 240 mg and 480 mg for batch release and stability testing, dissolution testing in pH 4.5 acetate buffer with 0.6% Tween-80, Apparatus II (paddle) at 75 rpm is acceptable, with the following (revised) acceptance criteria:

- Q (b)(4)% at 30 minutes for the 240 mg strength
- Q %at 45 minutes for the 480 mg strength

For details, see the Biopharmaceutics evaluation within Product Quality Review#1 (Aug 18, 2017).

After evaluation of requested information, the Categorical Exclusion from an Environmental Assessment per 21 CFR 25.31(b) was determined to be appropriate. For details, see the Environmental Assessment evaluation within Product Quality Review#1 (Aug 18, 2017).

C. Special Product Quality Labeling Recommendations (NDA only)

Appropriate edits to the PI have been made based on product quality recommendations

The How Supplied section of the PI has a single storage statement for all packaging configurations of the tablets:

> Store PREVYMIS tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

See Final Container Labels (within this review) for information on the packaging configurations.

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209939

Stephen Miller

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table Letermovir Tablets (NDA 209939)

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 (solid state)	(b) (4)	**M**	(b) (4)	Acc	
Content uniformity		**L**		Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**	Dissolution method is appropriate; time point for 240mg strength revised to 30 min with adjustment of Q-value.	Acc	
Patient Use Considerations		**L**		Acc	

Stephen Miller

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Recommendation: Approval

NDA 209940
Review #2

Drug Name/Dosage Form	Letermovir Injection
Strength	240 mg/vial and 480 mg/ml (both 20 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Mar 8, 2017	All
Amendment	Apr 26, 2017	Quality
Amendment	May 15, 2017	Quality
Amendment	July 17, 2017	Quality
Amendment	July 19, 2017	Quality
Amendment	July 25, 2017	Quality
Amendment	July 26, 2017	Quality
Amendment	Aug 3, 2017	Quality
Amendment	Aug 18, 2017	Quality
Amendment	Aug 22, 2017	Container Labels

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Ben Stevens
Drug Product	Shrikant (Suresh) Pagay	Balajee Shanmugam
Process	Ying Wang	Steven Frisbee
Microbiology	Jonathan Burgos	Erika Pfeiler
Facility	Rebecca Dombrowski	Derek Smith
Biopharmaceutics	NA	
Environmental Assessment	NA	
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
	Type II	None				
Various	Type III	See DP review				
	Type IV *(if applicable)*	None				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 209939		Letermovir Tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Methods Verification	NA	None requested		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the Product Quality perspective. This document (Review #2) contains the final evaluation of all manufacturing facilities, the Final Risk Assessment, and the summary of all product quality aspects of the NDA (in Section II B, below). See Review #1 (August 18, 2017) for details of other product quality evaluations.

II. Summary of Quality Assessments

A. Product Overview

Letermovir is an NME that inhibits the cytomegalovirus (CMV) DNA terminase complex, which is required for viral DNA replication. It is indicated for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Two dosage forms have been developed: Tablets under NDA 209939 and Injection under NDA 209940. Both NDAs were granted Breakthrough Therapy designation and Orphan Drug status, and are being reviewed under a Priority classification because of unmet clinical need.

Proposed Indication(s) including Intended Patient Population	Adult hematopoietic stem cell transplant recipients who are seropositive for cytomegalovirus infection
Duration of Treatment	From day of transplant (or no later than 28 days post-transplant) through 100 days post-transplant.
Maximum Daily Dose	480 mg per day (240 mg per day for patients being treated with cyclosporine)
Alternative Methods of Administration	Tablets (see NDA 209939)

B. Quality Assessment Overview

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All sites are found acceptable upon completion of this review, but will result in a post approval inspection recommendation for the (b) (4) facility to address continued process validation efforts for the (b) (4) impurity testing and adherence to (b) (4) and conformance to application commitment/changes post approval. The Overall Manufacturing Facility Status in Panorama is Approve as of Nov 1, 2017. For details, see the Facility evaluation within this review (Product Quality Review #2).

All drug substance information is provided by cross-reference to NDA 209939 (letermovir tablets). The drug substance specification includes bacterial endotoxin level and limits on aerobes and yeast/mold, to be applied to batches used to manufacture the injection. The same drug substance specification is reproduced in NDA 209940. For details, see the Drug Substance evaluation within Product Quality Review#1 (Aug 18, 2017).

The drug product is a sterile solution supplied as a 20 mg/mL formulation in two different configurations, 240 mg/Vial and 480 mg/Vial (12 and 24 mL fills, respectively). The product is sterilized by (b) (4)
The applicant corrected a number of data omissions related to control of sterility through responses to information requests sent at the time of filing and during the review. As amended, the application demonstrated adequate sterility assurance and appropriate control on endotoxin levels in the drug product. For details, see the Microbiology evaluation within Product Quality Review#1 (Aug 18, 2017).

The drug product is a liquid (b) (4) for injection. It is administered as an IV infusion after diluting with either normal saline or 5% dextrose solution. Studies were performed to show that both diluents were compatible, and to support labeling recommendations regarding compatible tubing, IV bags and catheters. The container is a Type I glass 30 mL vial for both presentations, with sufficient fill to allow withdrawal of the full dose. The major excipient in the drug product is hydroxypropyl betadex (hydroxypropyl-beta-cyclodextrin) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) . The drug product specifications are appropriate, and include product description, visible particulates, identification by (b) (4), assay, pH, particulate matter, fill volume, sterility and bacterial endotoxin. A 30-month expiration dating period for product stored under USP Controlled Room Temperature is appropriate. This is supported by up to 18 months of stability data (3 NDA registration batches of each strength and 1 batch of each strength at the production scale and site) under the long term storage condition of 25°C/60% RH. Degradation is very slight, even under accelerated conditions (maximum (b) (4) after 6 months at 40°C/75%RH). Additional studies performed which includes in-use study when mixed with diluents for administration, photo-stability study (b) (4) temperature excursion study, freeze-thaw study, and leachable/extractable study. For details, see the Drug Product evaluation within Product Quality Review#1 (Aug 18, 2017).

The drug product manufacturing process consists of (b) (4) (b) (4) (b) (4) The manufacturing process was extensively studied (including studies on (b) (4) is adequately described, and appropriately controlled. For details, see the Process evaluation within Product Quality Review#1 (Aug 18, 2017).

No Biopharmaceutics evaluation was needed for this injection solution. See review of NDA 209939 for information related to the categorical exclusion from the Environmental Assessment.

C. Special Product Quality Labeling Recommendations

No edits to the vial and carton labels were recommended in Review#1. These labels were revised (Aug 22, 2017 amendment) to show the proprietary name "Prevymis" but are otherwise unchanged.

Appropriate edits to the PI have been made based on product quality recommendations.

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209940

Stephen Miller

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Letermovir Injection (NDA 209940)

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**
Sterility		H	See Microbiology review (in Rev-1)	Acc	
Endotoxin Pyrogen		M	See Microbiology review (in Rev-1)	Acc	
Assay, Stability		L		Acc	
Assay (Preservative)	(b) (4)	NA		NA	
Assay (anti-oxidant)		NA		NA	
Uniformity of Dose (fill Vol / deliverable vol)		L		Acc	
Osmolality		L		Acc	
Ph (low)		L		Acc	
Particulate Matter		M	See DP Review and Process Review (in Rev-1)	Acc	
Leachables Extractables		L		Acc	
Appearance (color, turbidity)		L	(b) (4)	Acc	
Patient Use Considerations		L		Acc	

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Recommendation: Pending

NDA 209939
Review #1

Drug Name/Dosage Form	Letermovir Tablet
Strength	240 mg, 480 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Mar 8, 2017	All
Amendment	May 15, 2017	Quality
Amendment	May 16, 2017	Quality
Amendment	June 22, 2017	Quality
Amendment	July 25, 2017	Quality
Amendment	May 15, 2017	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Ben Stevens
Drug Product	Yong Wang	Balajee Shanmugam
Process	Ying Wang	Steven Frisbee
Microbiology	Ying Wang	Steven Frisbee
Facility	Rebecca Dombrowski	Derek Smith
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Environmental Assessment	James Laurenson	Michael (Scott) Furness
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
	Type II	None				
Various	Type III *(if applicable)*	See DP review				
	Type IV *(if applicable)*	None				
	Other	None				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 209940		Letermovir Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Methods Verification	NA	None requested		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

At the present time a recommendation cannot be made from the product quality perspective because the evaluation of the manufacturing facilities is on-going. Specifically, a follow-on inspection is needed for the (b) (4) facility. Additionally, evaluations of results from two pre-approval inspections conducted during this review cycle are on-going at this time.

II. Summary of Quality Assessments

A. Product Overview

Letermovir is an NME that inhibits the cytomegalovirus (CMV) DNA terminase complex, which is required for viral DNA replication. It is indicated for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Two dosage forms have been developed: Tablets under NDA 209939 and Injection under NDA 209940. Both NDAs were granted Breakthrough Therapy designation and Orphan Drug status, and are being reviewed under a Priority classification because of unmet clinical need.

Proposed Indication(s) including Intended Patient Population	Adult hematopoietic stem cell transplant recipients who are seropositive for cytomegalovirus infection
Duration of Treatment	From day of transplant (or no later than 28 days post-transplant) through 100 days post-transplant.
Maximum Daily Dose	480 mg per day (240 mg per day for patients being treated with cyclosporine)
Alternative Methods of Administration	Intravenous infusion (see NDA 209940)

B. Quality Assessment Overview

At the present time, evaluation of the manufacturing facilities is on-going. Specifically, inspection of (b) (4) is scheduled to occur (b) (4) as follow-up to the inspection of (b) (4) Additionally, evaluations of results from two pre-approval inspections of the following facilities are on-going at this time:

- MSD-Ireland (DS and tablet manufacturing)
- (b) (4)

Three other facilities have been determined to be acceptable based on file review.

The drug substance is the (b) (4) of letermovir, and all drug substance

information is provided in this NDA. [redacted] of letermovir have been found. [redacted] had been used in all stages of formulation development and clinical studies [redacted] stability testing to date. The drug substance specification includes tests and acceptance criteria for description, assay, impurities (related substances), chiral purity, identification, residual solvents, water content, [redacted], bacterial endotoxins and microbiological purity (TAMC/TYMC). No acceptance criteria for particle size are included in the specification since the manufacturing process provides adequate control of the particle size distribution. Stability data support a retest period of [redacted] months when stored at [redacted] RH and packaged in [redacted]

The drug products are immediate-release tablets with the following appearance:

- 240 mg: Yellow, oval shaped tablet debossed with"591"on one side and the Merck logo on the other side
- 480 mg: Pink, oval, bi-convex, tablet debossed with "595" on one side and the Merck logo on the other side

Three NDA registration batches of each strength were manufactured at the intended commercial site (MSD, Ireland) at a scale of [redacted] tablets. The commercial packaging is in aluminum-aluminum blisters, with 7 tablets per blister card. In one configuration, a 1-month carton holds 4 child-resistant dose packages with days of the week marked off. In a second configuration, designed for in-patient use, a 14-tablet carton holds two 7-tablet blister cards perforated for division into individual 1-tablet blisters. Letermovir tablets showed very little or no change in any quality perameters under long term (30°C/ 75%RH/ 18M) and accelerated (40°C/ 75%RH/ 6M) conditions. An expiration dating period of 30 months is appropriate for both strengths, when stored under USP controlled room temperature conditions.

[redacted]. The intended commercial product differs from the Phase 3 formulation (PMF3) [redacted]
The intended commercial scales will be between [redacted] tablets for the 240 mg strength and between [redacted] tablets for the 480 mg strength. The applicant has conducted extensive manufacturing process development for this drug product. Risk based assessment, prior knowledge, multi-factor designs and one-factor - at-a-time experimental approaches are used in the development. Based on the study results and understanding, control strategies are established consisting of proven acceptable ranges (PARs) for the [redacted] Appropriate microbial quality monitoring is performed at product release and on stability.

For routine QC testing of the Letermovir Tablets 240 mg and 480 mg for batch release and stability testing, dissolution testing in pH 4.5 acetate buffer with 0.6% Tween-80, Apparatus II (paddle) at 75 rpm is acceptable, with the following (revised) acceptance criteria:

- Q (b) (4) % at 30 minutes for the 240 mg strength
- Q % at 45 minutes for the 480 mg strength

After evaluation of requested information, the Categorical Exclusion from an Environmental Assessment per 21 CFR 25.31(b) was determined to be appropriate.

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendations were conveyed to the OND PM for consideration as the labeling is finalized:

1) List inactive ingredients in alphabetical order in Section 11.
2) We note (b) (4) We recommend that the following storage condition be used for all three:

Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).
Store in original blister package until use.

3) Add this storage condition to the Dosepak (innercard) label:
Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).
Store in original blister package until use.

From the product quality perspective, we support the DMEPA recommendation to include the expiry date and lot number on each blister cell of the 14-count blister cards (healthcare setting use).

For discussion within NDA review team:

- Is tablet strength included at appropriate points in the Highlights Section?
- How should pharmacological class be expressed in Section 11?

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209939

Date: Aug 18, 2017

Stephen Miller

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Comments: ATL for NDA 209939

ENVIRONMENTAL

IQA Review Guide Reference

R Regional Information

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for letermovir in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. Additional information was requested from the applicant to support the claim. The provided information, as well as other information obtained by FDA, was reviewed. The claim for a categorical exclusion from an EA was found to be acceptable.

Environmental

The applicant submitted a claim for a categorical exclusion from an EA for letermovir in accordance with 21 CFR 25.31(b). The required statement of no extraordinary circumstances was included.

FDA responded that additional information was needed to assist its review of the claim. That is, as part of FDA's screening process for new molecular entities (NMEs), and in light of reproductive/developmental (testicular) toxicities noted in nonclinical studies discussed during pre-Phase 3, which raised concerns about hormonal effects per recent EA guidance (USFDA, 2016), FDA utilized a fish plasma model (per Nallani et al., 2016 and Huggett et al., 2003) to help screen for aquatic environmental risk. In the process, FDA found a wide range of predicted log D values for letermovir, from 1.19 to 4.22 (ACD/Labs v ChemAxon at http://www.chemspider.com/Chemical-Structure.26352849.html), which in turn resulted in a wide range of effects ratios (ERs) using an expected introduction concentration (EIC) of 1 µg/L (the concentration used for the categorical exclusion per 21 CFR 25.31(b)). The lowest ER was less than 1,000, the low end of the acceptable ER level per Huggett et al. (2003). Therefore, FDA asked the applicant to provide (1) the estimated production in kg/year and the EIC for the active ingredient, as described in Section III of the FDA EA guidance (USFDA, 1998), (2) any available data and analysis for this substance's log D and bioconcentration factor, (3) any other readily available information for determining a more realistic expected environmental concentration (EEC) (e.g., metabolism and environmental degradation data), and (4) any readily available aquatic toxicity data, environmental risk assessments, or other relevant information for this or similar substances.

The applicant subsequently provided a production amount of (b) (4) kg/year, which is equivalent to an EIC of (b) (4) The applicant also provided a copy of a European Union (EU) environmental risk assessment (ERA) for letermovir. Briefly, the ERA provides the following results:

1. The predicted environmental concentration in surface water, PEC_{SW}, for letermovir is [redacted] (b) (4) and assumes 365 days/year treatment.

2. The lowest predicted no-effects concentration for surface water, $PNEC_{SW}$, among at least three trophic levels (fish) is [redacted] (b) (4)

3. The PEC/PNEC for surface water is substantially lower [redacted] (b) (4)

4. Similar results are found for other media.

The ERA concluded that letermovir is unlikely to pose a risk to the environment and further testing is not necessary.

References:

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. Comparison of Measured and Predicted Bioconcentration Estimates of Pharmaceuticals in Fish Plasma and Prediction of Chronic Risk. Bulletin of environmental contamination and toxicology, 96(5), 580-584.

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. Center for Biologics Evaluation and Research. US Food and Drug Administration, Rockville, MD.

USFDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Biologics Evaluation and Research. US Food and Drug Administration, Silver Spring, MD.

Reviewer's Assessment: ***{Adequate/Inadequate}***

The claim for a categorical exclusion from an EA per 21 CFR Part 25.31(b) is appropriate for the anticipated amount of the drug to be used [redacted] (b) (4) EIC). The calculation provided with the updated exclusion request appears accurate. An adequate statement of no extraordinary circumstances per 21 CFR 25.15 is present.

The applicant did not explicitly respond to the FDA observation regarding reproductive/developmental (testicular) toxicities noted in nonclinical studies discussed during pre-Phase 3. Therefore, FDA examined recent data developed by the applicant in response to information requests from FDA on human safety. In response to those requests, in CTD 2.6.6, Toxicology Written Summary, p. 16, the following biomarkers of testicular toxicity were evaluated in the Phase 3 study in HSCT patients: follicle-stimulating hormone, luteinizing hormone, testosterone and Inhibin B. Preliminary

results indicate that there was no significant change from baseline following treatment with letermovir in this patient population (improvement or worsening of condition). In addition, the preclinical fertility and embryonic development toxicology studies had shown nonreversible testicular degeneration and reduced fertility indices only in rats receiving high doses of letermovir. No testicular toxicity was observed in two other species, so it is possible that this is species-specific toxicity, and only seen at high doses. Thus, no reproductive or developmental toxicity or hormonal effects appear to exist at therapeutic or higher levels.

FDA reanalyzed the FMP results using the applicant's EIC of (b) (4) µg/L. The applicant did not clarify the range of log D values, however. Therefore, using the most conservative available log D, 4.22, with the EIC resulted in an ER of (b) (4) which is substantially greater than the Huggett threshold of 1,000 and thus an indicator of low aquatic risk.

FDA next reviewed the EU ERA, which concluded that letermovir is unlikely to pose a risk to the environment and further testing is not necessary. The ERA used a PEC of (b) (4) µg/L for letermovir , which is more than (b) (4) orders of magnitude higher than the EIC of (b) (4) µg/L. The ERA PNEC is (b) (4) µg/L, which is about (b) (4) orders of magnitude higher than the EIC. Thus, FDA concludes that letermovir would not post a risk to the environment at the expected level of exposure.

In summary, FDA found no data to establish that, at the expected level of exposure, there is the potential for serious harm to the environment from approval of the application, per 21 CFR 25.21(a), and thus FDA finds that the claim for a categorical exclusion for letermovir is adequate and acceptable.

Primary Environmental Reviewer Name and Date: James Laurenson, 5/31/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): M. Scott Furness, 6/2/2017

James Laurenson

Digitally signed by James Laurenson
Date: 5/31/2017 03:26:07PM
GUID: 51dc6bdb0000c62de59b85452e59746f

Michael Furness

Digitally signed by Michael Furness
Date: 6/01/2017 08:20:57AM
GUID: 502e8c7600003dd8331cf6eebf43697a

LABELING

IQA Review Guide Reference

NDA 209939

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADEMARK safely and effectively. See full prescribing information for TRADEMARK.

TRADEMARK (letermovir) tablet, for oral use
TRADEMARK (letermovir) injection, for intravenous use
Initial U.S. Approval: 20XX

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TRADEMARK (letermovir)
Dosage form, route of administration	tablet, for oral use
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	TRADEMARK (letermovir) tablet, for oral use To replace with the following: TRADEMARK (letermovir) tablet, 240 mg and 480 mg, for oral use

For injectable, refer to Dr. Pagay's review.

2. *Section 2 Dosage and Administration*

2 Dosage and administration

2.1 General

TRADEMARK Tablets

- Administer with or without food.

- Swallow tablets whole. (b) (4) (b) (4)

TRADEMARK Injection

- Administer by intravenous infusion via a peripheral catheter or central venous line (b) (4)
- Do not administer as an intravenous bolus injection.

(b) (4)

(b) (4)

Not CMC related

(b) (4)

Not CMC related

(b) (4)

Refer to Dr. Pagay's review for CMC related evaluation of injectable.

(b) (4)

Refer to Dr. Pagay's review for CMC related evaluation of injectable.

(b) (4)

Not CMC related

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)	• Administer with or without food. • Swallow tablets whole (b) (4)

For injectable, refer to Dr. Pagay's review for CMC related evaluation.

3. *Section 3 Dosage Forms and Strengths*

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablet
Strengths: in metric system	240 mg and 480 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	TRADEMARK 240 mg tablet is a yellow oval tablet. Each tablet is debossed with "591" on one side and Merck logo on the other side. TRADEMARK 480 mg tablet is a pink oval, bi-convex tablet. [redacted] (b) (4) debossed with "595" on one side and Merck logo on the other side.

For the evaluation of injectable, refer to Dr. Pagay's review.

4. *Section 11 Description*

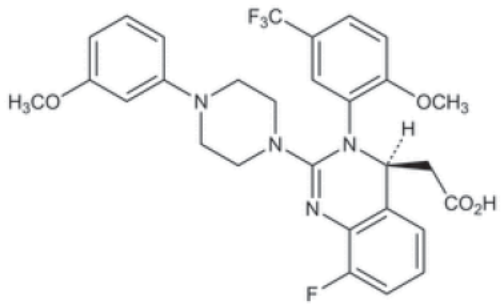
TRADEMARK contains letermovir, an [redacted] (b) (4), and is administered orally or by intravenous infusion.

TRADEMARK is available as 240 mg and 480 mg tablets. TRADEMARK tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: [redacted] (b) (4) [redacted] (b) (4) Carnauba wax is added as a polishing agent.

TRADEMARK is also available as 240 mg and 480 mg injection for intravenous infusion. TRADEMARK injection is a clear, preservative-free sterile solution in single-dose vials of either 240 mg or 480 mg per vial. Each 1 mL of solution contains 20 mg letermovir, hydroxypropyl betadex (150 mg), sodium chloride (3.1 mg), sodium hydroxide (1.2 mg), and Water for Injection, USP. The amount of sodium hydroxide may be adjusted to achieve a pH of approximately 7.5.

Letermovir has a molecular formula of $C_{29}H_{28}F_4N_4O_4$ and a molecular weight of 572.55. The chemical name for letermovir is (4*S*)-2-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid. Letermovir is very slightly soluble in water.

The chemical structure of letermovir is:


F3C
H3CO
N
N
N
H
OCH3
CO2H
N
F

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	TRADEMARK contains letermovir, (b) (4), and is administered orally or by intravenous infusion.
Dosage form and route of administration	TRADEMARK contains letermovir, (b) (4), and is administered orally or by intravenous infusion. TRADEMARK is available as 240 mg and 480 mg tablets.
Active moiety expression of strength with equivalence statement (if applicable)	N/A
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>)	TRADEMARK tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: (b) (4) Carnauba wax is added as a polishing agent. *To list all inactive ingredients in alphabetical order, the following should be used:* TRADEMARK tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone 25, and film-coated with a coating material containing the following inactive ingredients: hypromellose 2910, iron oxide red (only for 480 mg tablets), iron oxide yellow, lactose monohydrate, titanium

	dioxide, and triacetin. Carnauba wax is added as a polishing agent.
Statement of being sterile (if applicable)	Refer to Dr. Pagay's review for injectable.
Pharmacological/ therapeutic class	TRADEMARK contains letermovir, (b) (4), and is administered orally or by intravenous infusion.
Chemical name, structural formula, molecular weight	Letermovir has a molecular formula of $C_{29}H_{28}F_4N_4O_4$ and a molecular weight of 572.55.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Letermovir is very slightly soluble in water.

For the evaluation of injectable, refer to Dr. Pagay's review.

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

16 how supplied/storage and handling

16.1 Tablets

Each TRADEMARK 240 mg tablet is a yellow oval tablet; each tablet is debossed with "591" on one side and Merck logo on the other side. Each TRADEMARK 480 mg tablet is a pink oval, bi-convex tablet; (b) (4) debossed with "595" on one side and Merck logo on the other side. (b) (4)

The 240 mg tablets are packaged into a carton (NDC 0006-3075-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7 count blister card for a total of 28 tablets or into a carton (NDC 0006-3075-04) containing two (2) (b) (4) 7-count blister cards for a total of 14 tablets.

The 480 mg tablets are packaged into a carton (NDC 0006-3076-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 28 tablets or into a carton (NDC 0006-3076-04) containing two (2) (b) (4) 7-count blister cards for a total of 14 tablets.

Store TRADEMARK tablets in the original package until use.

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

16.2 Injection

TRADEMARK is supplied as a sterile, clear solution (b) (4) for intravenous use, (b) (4) of 240 mg (12 mL per vial) or 480 mg (24 mL per vial). The

final solutions for infusion are obtained by dilution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

(b) (4)

A 240 mg single-dose vial (NDC 0006-5003-01) or a 480 mg single-dose vial (NDC 0006-5004-01).

Store TRADEMARK injection vials at 20°C to 25°C (68°F to 77°F); (b) (4) excursions permitted between 15°C to 30°C (59°F to 86°F). Store in the original carton to protect from exposure to light.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Each TRADEMARK 240 mg tablet is a yellow oval tablet; each tablet is debossed with "591" on one side and Merck logo on the other side. Each TRADEMARK 480 mg tablet is a pink oval, bi-convex tablet; (b) (4) debossed with "595" on one side and Merck logo on the other side.
Available units (e.g., bottles of 100 tablets)	The 240 mg tablets are packaged into a carton (NDC 0006-3075-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7 count blister card for a total of 28 tablets or into a carton (NDC 0006-3075-04) containing two (2) (b) (4) 7-count blister cards for a total of 14 tablets. The 480 mg tablets are packaged into a carton (NDC 0006-3076-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 28 tablets or into a carton (NDC 0006-3076-04) containing two (2) (b) (4) 7-count blister cards for a total of 14 tablets.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Each TRADEMARK 240 mg tablet is a yellow oval tablet; each tablet is debossed with "591" on one side and Merck logo on the other side. Each TRADEMARK 480 mg tablet is a pink oval, bi-convex tablet; (b) (4) debossed with "595" on one side and Merck logo on the other side.
Special handling (e.g., protect from light)	Store TRADEMARK tablets in the original package until use.
Storage conditions	Store TRADEMARK tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co.,

	Inc., Whitehouse Station, NJ 08889, USA

For the evaluation of injectable, refer to Dr. Pagay's review.

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

In Highlights of Prescribing Information, use "TRADEMARK (letermovir) tablet, 240 mg and 480 mg, for oral use" instead of "TRADEMARK (letermovir) tablet, for oral use".

All inactive ingredients should be listed in alphabetical order, the following should be used in the second paragraph of Section 11 Description:

> *TRADEMARK tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone 25, and film-coated with a coating material containing the following inactive ingredients: hypromellose 2910, iron oxide red (only for 480 mg tablets), iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin. Carnauba wax is added as a polishing agent.*

Refer to the list of Deficiencies for final comments to be communicated to the applicant.

Patient Information Insert

(b) (4)

Reviewer's Comment:

It is recommended that the following storage condition is used as a standard description in [redacted] (b) (4) as described in the Patient Infoirmation Insert:

[redacted] (b) (4)

Keep TRADEMARK and all medicines out of the reach of children.

All inactive ingredients should be listed in alphabetical order; the following should be used in [redacted] (b) (4) described in the Patient Infoirmation Insert.

[redacted] (b) (4)

II. Labels:

BIOPHARMACEUTICS

NDA: 209939
Drug Product Name/Strength: Letermovir (MK-8228) Tablets/240 mg and 480 mg
Dosage Form: Immediate Release Tablet
Route of Administration: Oral
Applicant Name: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
Intended for use: Prophylaxis of Cytomegalovirus (CMV) Infection
Submission Type: 505b(1) (NME; Priority)

Review Summary:

The Biopharmaceutics review is focused on the evaluation of the adequacy of proposed dissolution method and acceptance criterion.

For the routine QC testing of the Letermovir Tablets 240 mg and 480 mg for batch release and stability testing, the proposed dissolution method and the revised acceptance criteria, shown in the table below, are found acceptable.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp (mL/°C)	Analytical Method	Revised Acceptance Criteria
II (Paddle)	75	25 mM sodium acetate buffer, pH 4.5 with 0.6% Tween-80	900/37 ± 0.5°C	HPLC	Q = (b)(4)% at 30 min for the 240 mg strength; Q = (b)(4)% at 45 min for the 480 mg strength;

Recommendation:

From a Biopharmaceutics perspective, NDA 209939 for Letermovir Tablets 240 mg and 480 mg is recommended for **APPROVAL**.

List Submissions being reviewed (table):

eCTD # (SDN #)	Received date	Document
0001 (4)	3/9/2017	Original submission
0017(20)	6/22/2017	Quality/Response to information request
0023 (26)	7/25/2017	Quality/Response to information request for API PSD

Highlight Key Outstanding Issues from Last Cycle: *Not Applicable. This is the 1st review cycle.*

Concise Description Outstanding Issues Remaining: *None*

BCS Designation

Reviewer's Assessment: *Not Applicable.*

No BCS designation request was submitted. Based on the drug substance physiochemical properties and bioavailability data, the Applicant reported Letermovir as a BCS Class II drug with low solubility and high permeability.

Solubility: Letermovir has two pKa values at 3.6 and 7.1. The solubility of Letermovir in various pH buffer solutions, ranging from pH 1 to pH 12 is displayed in **Figure 1** and **Table 1**. The data showed that the solubility of Letermovir is pH dependent, and Letermovir has low intrinsic solubility of approximately 0.4 mg/mL between pH 4 and 7.

Figure 1: pH-Solubility Profile

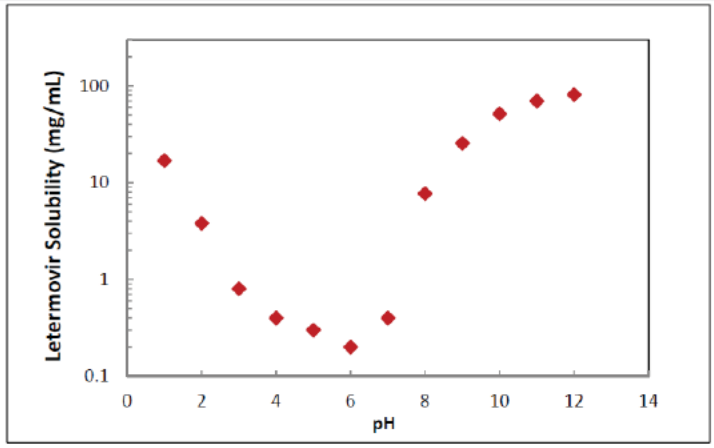


Table 1: Solubility of Letermovir Drug Substance in Aqueous Media

Media	Solubility, mg/mL
Water	0.3
0.1N HCl	19.0
pH 2.4	1.9
pH 4.0	0.4
pH 5.4	0.3
pH 6.8	0.4
pH 7.6	2.8
pH 9.4	38.9
pH 10.8	58.2
pH 12.0	78.1

Permeability: The absolute bioavailability of Letermovir in healthy volunteers has been estimated to be 94 % (89.8 - 97.6) based on population PK analysis. Moderate permeability (9 × 10^{-6} cm/sec) was seen in LLC-PK1 cells.

Dissolution: At least (b) (4)% drug release in 30 min and 45 min from the proposed Letermovir Tablets for the 240 mg and 480 mg strengths, respectively, is reported, using the proposed QC

dissolution method. Of note, the proposed QC dissolution medium contains 0.6% Tween-80. Refer to the section "Dissolution Method and Acceptance Criteria" below.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: *Adequate*

Proposed Dissolution Method and Acceptance Criterion: The dissolution method and dissolution acceptance criterion originally proposed by the Applicant for the proposed drug product are presented below.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp (mL/°C)	Analytical Method	Originally Proposed Acceptance Criterion
II (Paddle)	75	25 mM sodium acetate buffer, pH 4.5 with 0.6% Tween-80	900/37 ± 0.5°C	HPLC	**Q = (b) (4)% at 45 min**

Dissolution Method Development

(b) (4)

7 pages have been withheld in full as b4 (CCI/TS) immediately following this page

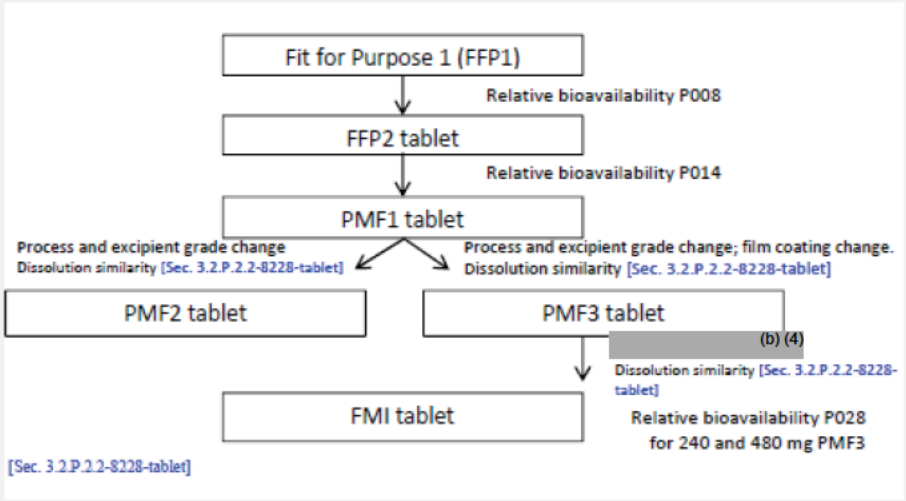
Bridging of Formulations

Reviewer's Assessment: Adequate

A total of six oral formulations of letermovir (FFP1, FFP2, PMF1, PMF2, PMF3, and FMI) were studied at various stages of drug product development (**Table 6**). The proposed formulation bridging strategy among the six formulations is illustrated in **Figure 10**. FMI and PMF3 were used in Phase 3 clinical studies, and the only difference between PMF3 (used in the initial stage of the Phase 3 trial), and FMI is the (b) (4) FMI stands for "Final Market Image" and is the proposed commercial drug product formulation. The manufacturing site of the Phase 3 clinical batches is also the proposed commercial site. Therefore, bridging between the Phase 3 clinical and the proposed commercial drug products is not needed.

Relative BA studies were conducted for FFP1 vs. FFP2 at a 20 mg dose, and FFP2 vs. PMF1 at a 240 mg total dose. Dedicated relative BA studies were not conducted among the PMF1, PMF2, and PMF3 Tablets. However, there appears to be adequate *in vivo* PK data within the NDA for these PMF formulations to support bridging; refer to the Clinical Pharmacology Review for the final determination of the adequacy of PK bridging among PMF1, PMF2 and PMF3. Additionally, these PMF formulations have similar compositions and only differ in terms of the (b) (4) It is acknowledged that the Applicant provided limited comparative in vitro dissolution profile data to support formulation bridging between PMF1 vs. PFM2 (in 0.1 M HCl with 0.2 SDS), and PMF1 vs. PMF3 (in various pH media and water without surfactant); additional comparative in vitro dissolution profile data were not deemed necessary, and so were not requested from the Applicant.

Figure 10: Schematic Diagram of Oral Formulations Used in the Letermovir Development Program and Formulation Bridging Strategy



(b) (4)

[redacted]

Biowaiver Request

Reviewer's Assessment: ***Not Applicable***

A biowaiver was not requested nor required. Both the 240 mg and 480 mg strengths of the proposed to-be-marketed tablets were used in the Phase 3 clinical studies. In addition, the Applicant reported that the clinical study MK-8228-028 (Phase I comparative BA study) demonstrated the bioequivalence between one 480 mg tablet and two 240 mg tablets.

Overall Recommendation

From a Biopharmaceutics perspective, NDA 209939 for Letermovir Tablets 240 mg and 480 mg is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

8/4/2017
Qi Zhang, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

8/4/2017
Gerlie Gieser, PhD ***(for Elsbeth Chikhale, PhD)***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Qi Zhang

Digitally signed by Qi Zhang
Date: 8/04/2017 11:52:42AM
GUID: 547e178000007695c91eb10380b07939

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 8/04/2017 11:56:27AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table Letermovir Tablets (NDA 209939)

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 (solid state)	(b) (4)	M	(b) (4)	Acc	
Content uniformity		L		Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV		M	Dissolution method is appropriate; time point for 240mg strength revised to 30 min with adjustment of Q-value.	Acc	
Patient Use Considerations		L		Acc	

Stephen Miller

Digitally signed by Stephen Miller
Date: 8/18/2017 11:55:03AM
GUID: 508da7210002a000609476bbecd040f0
Comments: ATL for NDA 209939

Recommendation: Pending

NDA 209940
Review #1

Drug Name/Dosage Form	Letermovir Injection
Strength	240 mg/vial and 480 mg/ml (both 20 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Mar 8, 2017	All
Amendment	Apr 26, 2017	Quality
Amendment	May 15, 2017	Quality
Amendment	July 17, 2017	Quality
Amendment	July 19, 2017	Quality
Amendment	July 25, 2017	Quality
Amendment	July 26, 2017	Quality
Amendment	Aug 3, 2017	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Ben Stevens
Drug Product	Shrikant (Suresh) Pagay	Balajee Shanmugam
Process	Ying Wang	Steven Frisbee
Microbiology	Jonathan Burgos	Erika Pfeiler
Facility	Rebecca Dombrowski	Derek Smith
Biopharmaceutics	NA	
Environmental Assessment	NA	
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
	Type II	None				
Various	Type III	See DP review				
	Type IV *(if applicable)*	None				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 209939		Letermovir Tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Methods Verification	NA	None requested		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

At the present time a recommendation cannot be made from the product quality perspective because the evaluation of the manufacturing facilities is on-going. Specifically, a follow-on inspection is needed for the (b) (4) facility. Additionally, evaluations of results from two pre-approval inspections conducted during this review cycle are on-going at this time.

II. Summary of Quality Assessments

A. Product Overview

Letermovir is an NME that inhibits the cytomegalovirus (CMV) DNA terminase complex, which is required for viral DNA replication. It is indicated for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Two dosage forms have been developed: Tablets under NDA 209939 and Injection under NDA 209940. Both NDAs were granted Breakthrough Therapy designation and Orphan Drug status, and are being reviewed under a Priority classification because of unmet clinical need.

Proposed Indication(s) including Intended Patient Population	Adult hematopoietic stem cell transplant recipients who are seropositive for cytomegalovirus infection
Duration of Treatment	From day of transplant (or no later than 28 days post-transplant) through 100 days post-transplant.
Maximum Daily Dose	480 mg per day (240 mg per day for patients being treated with cyclosporine)
Alternative Methods of Administration	Tablets (see NDA 209939)

B. Quality Assessment Overview

At the present time, evaluation of the manufacturing facilities is on-going. Specifically, inspection of (b) (4) is scheduled to occur (b) (4), as follow-up to the inspection of (b) (4) Additionally, evaluations of results from two pre-approval inspections of the following facilities are on-going at this time:

- MSD-Ireland (DS manufacturing)
- (b) (4)

Two other facilities have been determined to be acceptable based on file review.

All drug substance information is provided by cross-reference to NDA 209939 (letermovir tablets). The drug substance specification includes bacterial endotoxin level and limits on aerobes and yeast/mold, to be applied to batches used to manufacture the injection. The same drug substance specification is reproduced in NDA 209940.

The drug product is a sterile solution supplied as a 20 mg/mL formulation in two different configurations, 240 mg/Vial and 480 mg/Vial (12 and 24 mL fills, respectively). The product is sterilized by (b) (4)
The applicant corrected a number of data omissions related to control of sterility through responses to information requests sent at the time of filing and during the review. As amended, the application demonstrated adequate sterility assurance and appropriate control on endotoxin levels in the drug product.

The drug product is a liquid (b) (4) for injection. It is administered as an IV infusion after diluting with either normal saline or 5% dextrose solution. Studies were performed to show that both diluents were compatible, and to support labeling recommendations regarding compatible tubing, IV bags and catheters. The container is a Type I glass 30 mL vial for both presentations, with sufficient fill to allow withdrawal of the full dose. The major excipient in the drug product is hydroxypropyl betadex (hydroxypropyl-beta-cyclodextrin) (b) (4) (b) (4) (b) (4) , (b) (4) The drug product specifications are appropriate, and include product description, visible particulates, identification by (b) (4) assay, pH, particulate matter, fill volume, sterility and bacterial endotoxin. A 30-month expiration dating period for product stored under USP Controlled Room Temperature is appropriate. This is supported by up to 18 months of stability data (3 NDA registration batches of each strength and 1 batch of each strength at the production scale and site) under the long term storage condition of 25°C/60% RH. Degradation is very slight, even under accelerated conditions (maximum (b) (4) % after 6 months at 40°C/75%RH). Additional studies performed which includes in-use study when mixed with diluents for administration, photo-stability study (b) (4) temperature excursion study, freeze-thaw study, and leachable/extractable study.

The drug product manufacturing process consists of (b) (4) The manufacturing process was extensively studied (including studies on (b) (4) is adequately described, and appropriately controlled.

No Biopharmaceutics evaluation was needed for this injection solution. See review of NDA 209939 for information related to the categorical exclusion from the Environmental Assessment.

C. Special Product Quality Labeling Recommendations

The following recommendations were conveyed to the OND PM for consideration as the labeling is finalized:

1) List inactive ingredients in alphabetical order in Section 11.

For discussion within NDA review team:

- Is tablet strength included at appropriate points in the Highlights Section?
- How should pharmacological class be expressed in Section 11?
- How should the label recommend (b) (4)

(b) (4)

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209940

Date: Aug 18, 2017

Stephen
Miller

Digitally signed by Stephen Miller
Date: 8/18/2017 01:40:07PM
GUID: 508da7210002a000609476bbecd040f0
Comments: ATL for NDA 209940

LABELING
NDA 209940

I. Package Insert

TRADEMARK™ (letermovir) injection, for intravenous use

- Injection: 240 mg/12 mL or 480 mg/24 mL in a single-dose vial (b) (4) (b) (4)

1. *Highlights of Prescribing Information*

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

2. *Section 2 Dosage and Administration*

Section 2.1: Important Dosing and Administration Information

TRADEMARK™ Injection

- Administer by intravenous infusion via a peripheral catheter or central venous line (b) (4) (b) (4)
- Do not administer as an intravenous bolus injection.[5]

Section 2. : (b) (4)

This section also includes a list of IV bags for infusion, infusion sets, plasticizers, and catheters tested for compatibility with letermovir diluted solution in normal saline or 5% dextrose for infusion.

(b) (4)

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)	Yes included 'Do not administer as a bolus dose'; provided a list of approved drugs which can be combined with letermovir in normal saline and in 5% dextrose. Also provided a list of drugs which cannot be combined with letermovir. A separate list is provided of the plastic material used for IV bags and IV sets compatible with letermovir.

(b) (4)

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

4. *Section 11 Description*

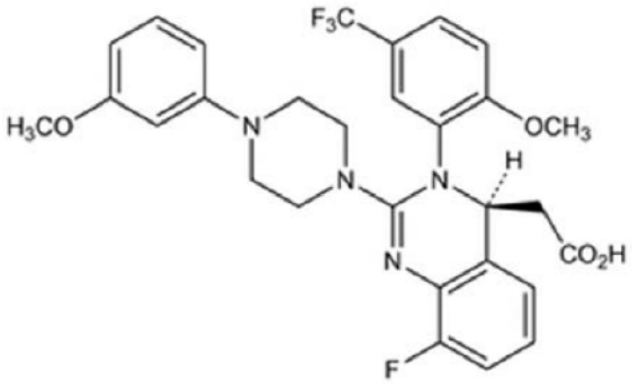
TRADEMARK contains letermovir, (b) (4) and is administered orally or by intravenous infusion.[144,145]

TRADEMARK is available as 240 mg and 480 mg tablets.[146] TRADEMARK tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: (b) (4) (b) (4) (b) (4) Carnauba wax is added as a polishing agent.[147]

TRADEMARK is also available as 240 mg and 480 mg injection for intravenous infusion.[148] TRADEMARK injection is a clear, preservative-free sterile solution in single-dose vials of either 240 mg or 480 mg per vial.[149] Each 1 mL of solution contains 20 mg letermovir, hydroxypropyl betadex (150 mg), sodium chloride (3.1 mg), sodium hydroxide (1.2 mg), and Water for Injection, USP. The amount of sodium hydroxide may be adjusted to achieve a pH of approximately 7.5.[150]

Letermovir has a molecular formula of $C_{29}H_{28}F_4N_4O_4$ and a molecular weight of 572.55.[151] The chemical name for letermovir is (4*S*)-2-{8-Fluoro-2-[4-(3- methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid.[152] Letermovir is very slightly soluble in water.[153]

5. The chemical structure of letermovir is:[154]



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	yes
Dosage form and route of administration	yes
Active moiety expression of strength with equivalence statement (if applicable)	na
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>)	yes
Statement of being sterile (if applicable)	yes
Pharmacological/ therapeutic class	abbreviated
Chemical name, structural formula, molecular weight	yes
If radioactive, statement of important nuclear characteristics.	na
Other important chemical or physical properties (such as pKa or pH)	yes

Comment:
The pharmacological/therapeutic class is abbreviated. Please include the complete title.
For tablets, include all inactive ingredients in alphabetical order.

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

TRADEMARK is supplied as a sterile, clear solution injection for intravenous use, (b) (4) (b) (4) of 240 mg (12 mL per vial) or 480 mg (24 mL per vial).[309] The final solutions for infusion are obtained by dilution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.[310]

(b) (4)

A 240 mg single-dose vial (NDC 0006-5003-01) or a 480 mg single-dose vial (NDC 0006-5004-01).
Store TRADEMARK injection vials at 20°C to 25°C (68°F to 77°F); (b) (4) excursions permitted between 15°C to 30°C (59°F to 86°F).[311] Store in the original carton to protect from exposure to light.[312]

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

Reviewer's Assessment of Package Insert: Adequate after revision.
Also as noted in Section 2 of the PI, (b) (4) storage time and temperature after dilution in IV bags for infusion is provided. Adequate.

Comment:
The pharmacological/therapeutic class is abbreviated (b) (4) *Please include the complete title.*

For tablets, include all inactive ingredients in alphabetical order.

- (b) (4)

MICROBIOLOGY

Product Background:

NDA: 209940

Drug Product Name /Strength: Letermovir Injection, 20 mg/mL

Route of Administration: Injection

Applicant Name: Merck Sharp & Dohme Corp.

Manufacturing Site: MSD Ireland (Carlow)
Dublin Road,
Carlow, Ireland

Method of Sterilization: (b) (4)

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
03/08/2017	03/08/2017	N/A	03/14/2017
04/19/217	04/19/217		04/19/2017
05/15/2017	05/15/2017		05/15/2017
07/17/2017	07/17/2017		07/17/2017
07/26/2017	07/26/2017		07/26/2017
08/03/2017	08/03/2017		08/03/2017

Highlight Key Outstanding Issues from Last Cycle: N/A
Concise Description Outstanding Issues Remaining: N/A
Supporting/Related Documents:

Remarks Section: Recommended for Approval

This ANDA was submitted in E-CTD format.

The applicant did not provide necessary information in the original submission dated 08 March 2017 (GSR Seq. 0000). Two information requests were submitted. The first Information Request was submitted by the Agency on 07 April 2017, and was necessary to make the application fileable. The applicant responded on 19 April 2017, and the application was determined to be acceptable for filing. A second IR was submitted by the Agency on 09 May 2017. The applicant responded on 15 May 2017.

Unless otherwise indicated, information was provided by the applicant on the original submission.

S Drug Substance

N/A, drug substance is nonsterile, and is sterilized as part of the drug product manufacturing process.

P.1 Description of the Composition of the Drug Product

The drug product is a sterile solution supplied as a 20 mg/mL formulation in two different configurations, 240 mg/Vial and 480 mg/Vial (12 and 24 mL fills, respectively). Both presentations are filled in 30 mL vials. Exact formulation is described in the table below.

Ingredient	Quality Standard	Function	Quantity, mg/Vial	
			240 mg/Vial	480 mg/Vial
Letermovir	In-House	Active Ingredient	240	480
Hydroxypropyl Betadex	USP-NF	(b) (4)	1800	3600
Sodium Chloride	USP-NF		37.2	74.4
Sodium Hydroxide	USP-NF		14.4	28.8
Water for Injection	USP-NF		(b) (4)	

- **Description of container closure system**

Configuration	Component	Description	Manufacturer
240 mg/Vial and 480 mg/Vial*	Vial	(b) (4) Clear Type I (b) (4) Vial	(b) (4)
	Stopper	(b) (4)	
		(b) (4)	

*, The same container closure system was used for both configurations.

The information provided by the applicant was adequate.

Acceptable

P.2 Pharmaceutical Development

N/A

30 pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

P.7 Container Closure

Summary table of the container closure system proposed

See P.1.

P.8 Stability

N/A

P. 8.1 Stability Summary and Conclusion

Proposed Expiry: 30 Months. The expiry date is based on Long Term Storage (25°C/60% RH) conditions of the 240 mg/Vial configuration. Since both configurations are generated from the same formulation, the same proposed expiration applies to both 240 mg/Vial and 480 mg/Vial drug products. Sterility (per USP <71>) and endotoxin (per USP<85>) analyses were conducted on exhibit batches at 0 and 12 months. Analytical evaluations are currently ongoing.

The information provided by the applicant was adequate.

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Strength	Test	Test Method	Acceptance Criteria
240 mg/Vial	Bacterial Endotoxins	USP<85>	(b) (4) EU/mg
	Sterility	USP<71>	Sterile
480 mg/Vial	Bacterial Endotoxins	USP<85>	(b) (4) EU/mg
	Sterility	USP<71>	Sterile

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25°C/60%RH

Test	Time (Months)								
	0	3	6	9	12	15	18	24***	36
Bacterial Endotoxins	X*	-**	-	-	X	-	-	X	X
Sterility	X	-	-	-	X	-	-	X	X

*, X = Test will be performed
**, - = Test will not be performed
***, A 30-month time point will be added if needed to support a 30-day month shelf life.

Stability Commitment - The applicant commits to placing at least one batch per production year (unless none is produced) will be placed on long term stability.

The information provided by the applicant was adequate.

Acceptable

P.8.3 Stability Data

Strength	Batch Number	Stability Conditions and Orientation	Sterility (USP<71>)	Endotoxin (USP<85>)
240 mg/Vial	WL00061067	Long Term Storage: 25°C / 60%RH (Upright and Inverted) and Accelerated Storage:	No Growth at the Tested Timepoints	(b) (4) at the Tested Timepoints
	WL00061068			
	WL00061109			
480 mg/Vial	WL00062184			
	WL00062185			
	WL00062186			

		40°C/75 RH (Upright and Inverted)		

A Appendices

N/A

A.2 Adventitious Agents Safety Evaluation

N/A

A.2.1 Materials of Biological Origin

N/A

A.2.2 Testing at Appropriate Stages of Production

N/A

A.2.3. Viral Testing of Unprocessed Bulk

N/A

A. 2.4 Viral Clearance Studies

N/A

R Regional Information

Executed lot #(s): Executed batch record summaries were available for the 240 mg/Vial and 480 mg/Vial exhibit batches. The batches generated were: 240 mg/Vial - L00061109, WL00061067, and WL00061068; 480 mg/Vial - WL00062184, WL00062185, and WL00062186. Although the batches were (b) (4) (b) (4) according to the proposed parameters, they were not generated at the Carlow facility.

Note to Reviewer: The Chemistry reviewer has been informed the exhibit batches with corresponding batch records belong to batches which have not been generated at the proposed manufacturing facility. A batch record was not provided for the two batches (0000560203 and 0000562099) manufactured at the proposed Carlow facility.

The information provided by the applicant was adequate.

Acceptable

Comparability Protocols

N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2. A. Package Insert

Note to Reviewer: The recommended drug product dose was provided in Module 1 of the accompanying NDA, NDA number 209939.

Letermovir Injection is supplied as a 20 mg/mL formulaiton in two different configurations, 240 mg/Vial and 480 mg/Vial. Both drug product configurations are single dose sterile solutions to be stored at 20-25°C (with excursions between 15-30°C) in the carton with protection from light. The drug product should be administered intravenously at the recommended dose of 480 mg. Admixtures can be prepared with 0.9% saline and 5% dextrose for up to 24 hours at room temperature conditions and up to 48 hours storage at 2-8°C. In-use microbiological proliferation studies were performed to evaluate the post-reconstitution hold times. Two drug product dilutions, 0.96 mg/mL and 1.92 mg/mL, were prepared with 0.9% saline and 5% dextrose and subsequently inoculated with approximately 50 CFU/mL of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, *Aspergillus brasiliensis*, and *Bacillus subtilis*. The dilutions used in the study are identical to those prepared prior to patient administration, when the contents of both drug products are transferred to the 250 mL pre-filled 0.9% saline or 5% dextrose IV bags. All of the challenge organisms failed to grow when inoculations were stored at 2-8°C for up to 72 hours and by 48 hours at room temperature.

The information provided by the applicant was adequate.

Acceptable

Post-Approval Commitments:

N/A

Lifecycle Management Considerations

N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Jonathan Burgos, Ph.D.
03 August, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Erika Pfeiler, Ph.D.
03 August, 2017

Jonathan Burgos

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Date: 8/04/2017 10:36:30AM
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Erika Pfeiler

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Date: 8/04/2017 11:04:49AM
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Letermovir Injection (NDA 209940)

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**
Sterility		H	See Microbiology review	Acc	
Endotoxin Pyrogen		M	See Microbiology review		
Assay, Stability		L		Acc	
Assay (Preservative)	(b) (4)	NA		NA	
Assay (anti-oxidant)		NA		NA	
Uniformity of Dose (fill Vol / deliverable vol)		L		Acc	
Osmolality		L		Acc	
Ph (low)		L		Acc	
Particulate Matter		M	See DP Review and Process Review	Acc	
Leachables Extractables		L		Acc	
Appearance (color, turbidity)		L	(b) (4)	Acc	
Patient Use Considerations		L		Acc	

Stephen Miller

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Comments: ATL for NDA 209940