

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208261Orig1s000**

**CHEMISTRY REVIEW(S)**

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name	Profile Code	Association	Alert
Approve Facility	10/17/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							(b) (4)
Approve Facility	10/12/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
Approve Facility	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>	3002807653	212559095	69410	MERCK SHARP DOHME	CTX CONTROL TESTING LABORATOR.	PENDING	None (b) (4)
Cancelled	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
Cancelled	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>	3002807653	212559095	69410	MERCK SHARP & DOHME	CTL CONTROL TESTING LABORATOR...	PENDING	None (b) (4)
No Further Evaluation	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
Approve Facility	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>	1036761	101740835	63508	MERCK SHARP & DOHME WILSON FACILITY	TCM TABLETS, PROMPT RELEASE	PENDING	None
Cancelled	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>	1036761	101740835	63508	MERCK SHARP & DOHME WILSON FACILITY	CTL CONTROL TESTING LABORATOR...	PENDING	None (b) (4)
No Further Evaluation	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
No Further Evaluation	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
No Further Evaluation	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
No Further Evaluation	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
Approve Facility	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
No Further Evaluation	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
Approve Facility	6/09/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							
Cancelled	6/04/2015	<u>NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)</u>							

<table cellpadding=0 width=1100> <tr><td style="text-align:left;font-family:Times New Roman;font-size:25px;font-style:normal;font-weight:bold;color:#000080;white-space:nowrap" class="TitleCell"> Facility Alerts</td></tr> <tr><td style="text-align:left;font-

## Facility Status View for NDA

Displays information for the facilities that are associated to NDA 208261 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

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### Overall Manufacturing Inspection Recommendations for NDA

Project Name	Sponsor Name	Overall Manufacturing Inspection	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	MERCK SHARP & DOHME	Approve	Complete	10/18/2015

### OPF Facility Recommendations for Facilities on NDA 208261 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	Facility Recommendation
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	3002807653	212559065	MERCK SHARP & DOHME	CTL CONTROL TESTING LABORATORY	
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	3002807653	212559065	MERCK SHARP & DOHME	CTX CONTROL TESTING LABORATORIES "ALBO" (DRUGS)	Approve Facility
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	1036761	101740635	MERCK SHARP & DOHME WILSON FACILITY	CTL CONTROL TESTING LABORATORY	
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	1036761	101740635	MERCK SHARP & DOHME WILSON FACILITY	TCM TABLETS, PROMPT RELEASE	Approve Facility
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)
NDA 208261-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					(b) (4)

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PHARMACEUTICAL DEVELOPMENT



**Breakthrough Application**

**Recommendation: Approval**

**NDA 208261  
Review 1  
Oct 23, 2015**

<b>Drug Name/Dosage Form</b>	Zepatier (elbasvir and grazoprevir) Tablets
<b>Strength</b>	50mg Elbasvir / 100mg Grazoprevir
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Merck Sharp & Dohme Corp.
<b>US agent, if applicable</b>	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	28-May-2015
Amendment	31-July-2015
Amendment	02-Sep-2015
Amendment	03-Sep-2015
Amendment	16-Sep-2015
Amendment	09-Oct-2015
Amendment	15-Oct-2015

**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Elbasvir Drug Substance	Sharon Kelly, Ph.D.	I/New Drug API
Grazoprevir Drug Substance	Monica Cooper, Ph.D.	I/New Drug API
Drug Product	George Lunn, Ph.D.	III/New Drug Product
Process	Ying Wang, Ph.D.	III/Process Assessment
Microbiology	Ying Wang, Ph.D.	/Microbiology Assessment
Facility	Denise DiGiulio, Ph.D.	II/Inspectional Assessment
Biopharmaceutics	Jing Li, Ph.D.	I/Biopharmaceutics
Project/Business Process Manager	Florence Aisida, Pharm.D	I/OPRO
Application Technical Lead	Stephen Miller, Ph.D.	III/New Drug Product
Laboratory (OTR)	Jason Rodriguez, Ph.D.	II/Pharmaceutical analysis
ORA Lead	Paul Perdue, Jr., Ph.D.	OGROP/ORA
Environmental Analysis (EA)	James Laurenson, MS	IO/ONDP

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Chemistry Assessment Section

## Quality Review Data Sheet

**1. LEGAL BASIS FOR SUBMISSION:**

**2. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				Adequate		
				Adequate		

Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND for Elbasvir (MK-8742)	IND 114298	
IND for Elbasvir (MK-8742) and Grazoprevir (MK-5172)	IND 110261	

**3. CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Methods Validation	In progress; no major issues identified		Oct 21, 2015	OTR (through Jason Rodriguez)
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

## Chemistry Assessment Section

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 208261 is recommended for approval from the Product Quality perspective. CMC-related labeling recommendations have been provided to the OND PM, for consideration during final labeling.

1. Summary of Complete Response issues: None
2. Action letter language, related to critical issues such as expiration date: None
3. Benefit/Risk Considerations

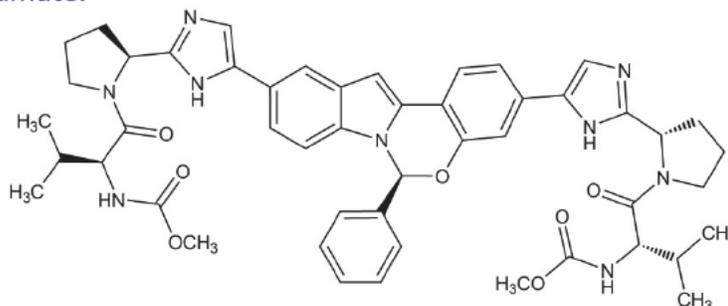
Evaluation of the quality aspects of Zepatier tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

### II. Summary of Quality Assessments

#### A. Drug Substance Elbasvir Quality Summary

1. Chemical Name or IUPAC Name/Structure USAN: Elbasvir  
Dimethyl *N,N'*-([(6*S*)-6-phenylindolo[1,2-*c*][1,3]benzoxazine-3,10-diyl]bis{1*H*-imidazole-5,2-diyl-(2*S*)-pyrrolidine-2,1-diyl}[(2*S*)-3-methyl-1-oxobutane-1,2-diyl])dicarbamate.



2. Properties/CQAs Relevant to Drug Product Quality: (b) (4) (b) (4) (b) (4) which is practically insoluble in water. Identity and chemical purity are the CQAs (u) (4)
3. Information Relevant to Impurity Control: Maximum Daily Dose of elbasvir is 50 mg/day. Acceptable Intake of Mutagenic Impurities is (b) (4) ug/day (b) (4)
4. List of starting materials: (b) (4)

## Chemistry Assessment Section

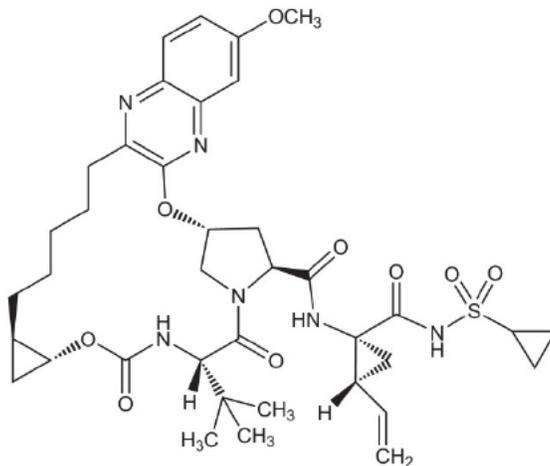
5. Suppliers of starting materials (site): Starting materials and their specifications were selected so that additional vendors and their methods of manufacturing the starting materials could be adopted under the applicant's pharmaceutical quality system.
6. Summary of Synthesis: (b) (4)
7. Process (b) (4)

b. Critical equipment: None.

8. Container Closure: (b) (4)
9. Retest Period & Storage Conditions: Retest period of (b) (4) months (b) (4)

**A. Drug Substance Grazoprevir Quality Summary**

1. Chemical Name or IUPAC Name/Structure USAN: Grazoprevir  
(1*aR*, 5*S*, 8*S*, 10*R*, 22*aR*)-*N*-[(1*R*, 2*S*)-1-[(Cyclopropylsulfonamido)carbonyl]-2-ethenylcyclopropyl]-14-methoxy-5-(2-methylpropan-2-yl)-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21,22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide



2. Properties/CQAs Relevant to Drug Product Quality

The drug substance is grazoprevir

(b) (4)  
(b) (4)  
(b) (4)  
(w) (4) It is essentially insoluble in water,  
(w) (4) Identity and chemical purity are the CQAs (b) (4)

Chemistry Assessment Section

3. Information Relevant to Impurity Control: Maximum Daily Dose of grazoprevir is 100 mg/day. Acceptable Intake of Mutagenic Impurities is (b) (4) ug/day (b) (4)
4. List of starting materials: (b) (4)
5. Suppliers of starting materials (site) Starting materials and their specifications were selected so that additional vendors and their methods of manufacturing the starting materials could be adopted under the applicant's pharmaceutical quality system.
6. Summary of Synthesis: (b) (4)
7. Process (b) (4)
  - b. Critical equipment: None
8. Container Closure: (b) (4)
9. Retest Period & Storage Conditions: (b) (4)-month retest (b) (4)

**B. Drug Product [Elbasvir and Grazoprevir Tablets] Quality Summary**

1. Strength: Elbasvir 50mg and Grazoprevir 100 mg
2. Description/Commercial Image: Beige film-coated oval tablets debossed with "770" on one side and plain on the other.
3. Summary of Product Design: (b) (4)

The specification includes tests for appearance, identity (by HPLC retention time and UV), assay (95.0-105.0% for both actives), degradants (b) (4), content uniformity (USP <905>), dissolution, (b) (4) is acceptable. The analytical methods are described in reasonable detail and have been validated. Satisfactory

## Chemistry Assessment Section

batch analyses are provided for 11 batches. [REDACTED] (b) (4)

Twelve months of data obtained at 30°C/75% RH and 6 months of data obtained at 40°C/75% RH are provided for 3 full size batches. There are no out of specification results and no trends whatsoever are observed. These batches are also tested for [REDACTED] (b) (4) and microbial limits.

Photostability testing was carried out using an open dish. No changes were observed. A further six batches will be placed on stability and tested for [REDACTED] (b) (4) microbial limits in addition to appearance, assay, degradants and dissolution. Thereafter routine stability batches will be tested for appearance, assay, degradants and dissolution.

4. List of Excipients: [REDACTED] (b) (4) carnauba wax, colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose [REDACTED] (b) (4) lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, [REDACTED] (b) (4) sodium chloride, sodium lauryl sulfate, and vitamin E TPGS. The film coat contains ferrousferic oxide, hypromellose [REDACTED] (b) (4) iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

5. Process Selection (Unit Operations Summary)

[REDACTED] (b) (4)

b. Critical equipment: None

6. Container Closure: [REDACTED] (b) (4) blisters

7. Expiration Date & Storage Conditions: The expiration dating period is 24 months with the storage statement "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). [REDACTED] (b) (4) in the original blister package until use to protect from moisture". [REDACTED] (b) (4)

8. List of co-packaged components: None

Chemistry Assessment Section

**C. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	Zepatier Tablets
<b>Non Proprietary Name of the Drug Product</b>	Elbasvir and Grazoprevir Tablets
<b>Non Proprietary Name of the Drug Substance</b>	Elbasvir and Grazoprevir
<b>Proposed Indication(s) including Intended Patient Population</b>	Treatment of chronic hepatitis C (CHC) genotypes 1 or 4 infection in adults
<b>Duration of Treatment</b>	12-16 weeks depending on genotype
<b>Maximum Daily Dose</b>	1 Tablet / day
<b>Alternative Methods of Administration</b>	None

**D. Biopharmaceutics Considerations**

1. BCS Designation:

- Drug Substance: The Applicant noted that Grazoprevir is a BCS class <sup>(b)</sup><sub>(4)</sub> drug substance and Elbasvir is a BCS class <sup>(b)</sup><sub>(4)</sub> drug substance.
- Drug Product: Not established.

2. Biowaivers/Biostudies

- Biowaiver Requests: N/A.
- PK studies: The PK studies are reviewed by the Clinical Pharmacology review team.
- IVIVC: N/A.

**E. Novel Approaches NA**

**F. Any Special Product Quality Labeling Recommendations**

At the appropriate time, please request that the applicant submit container labels with the name Zepatier replacing “Trademark”.

**G. Process/Facility Quality Summary (see Attachment A)**

**H. Life Cycle Knowledge Information (see Attachment B)**

**Overall Assessment and Signature: Executive Summary**

**Application Technical Lead Signature:**

This NDA is recommended for approval from the Product Quality perspective.

Stephen Miller  
-S

Digitally signed by Stephen Miller -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Stephen Miller -S,  
0.9.2342.19200300.100.1.1=1300087013  
Date: 2015.10.30 10:52:06 -0400

**Stephen Miller, Ph.D.; CMC-Lead; Branch 3; Division of New Drug Products I**

## Primary Quality Review

### ASSESSMENT OF THE DRUG SUBSTANCE (Elbasvir)

#### 2.3.S DRUG SUBSTANCE (Elbasvir)

##### 2.3.S.1 General Information (Elbasvir)

Recommended INN: Elbasvir

National Name (USAN): Elbasvir

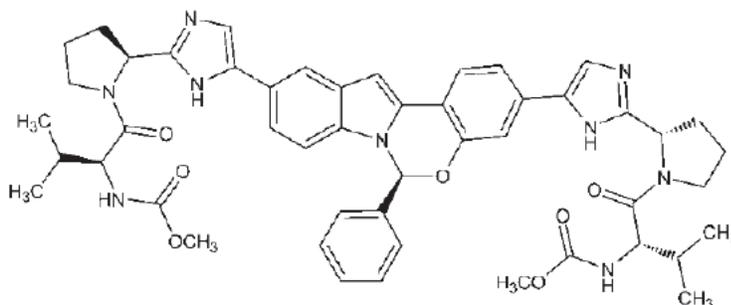
Chemical Name:

CAS Style Name: N,N'-[[[(6S)-6-Phenyl-6H-indolo[1,2-c][1,3]benzoxazine-3,10 diyl] bis[1H-imidazole-5,2-diyl-(2S)-2,1-pyrrolidinediyl][(1S)-1-(1-methylethyl) -2-oxo-2,1-ethanediyl]]]bis[carbamic acid] C,C'-dimethyl ester

Laboratory Codes: L-002469825-000G; MK-8742

Chemical Abstracts Services (CAS) Registry Number: 1370468-36-2

Structural Formula:



Molecular Formula: C<sub>49</sub>H<sub>55</sub>N<sub>9</sub>O<sub>7</sub>

Molecular Mass: 882.02

#### **Reviewer's Assessment:** *Acceptable*

The Sponsor has supplied the nomenclature and the correct molecular formula and molecular mass corresponding to the structure.

#### **Physical and Chemical Properties**

Elbasvir is a (b) (4)

(b) (4)

Chemistry Assessment Section

(b) (4)

The solubility of elbasvir was determined in water, ethyl acetate, (b) (4) acetone, (b) (4)

The solubility results are listed in Table 1.

**Table 1** Solubility Data of Elbasvir

Solvent	Solubility (mg/mL)	USP Solubility Description
Water	(b) (4)	Practically insoluble
Ethyl acetate	(b) (4)	Very soluble
Acetone	(b) (4)	Very soluble
(b) (4)	(b) (4)	(b) (4)
Ethanol	0.15	Very slightly soluble
(b) (4)	(b) (4)	(b) (4)

Elbasvir has **5 chiral centers**. (b) (4)

Elbasvir was characterized by (b) (4) The pattern indicates that the material is (b) (4)

(b) (4)

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## Chemistry Assessment Section

(b) (4)

(b) (4)

**Reviewer's Assessment: : *Acceptable***

The potential impurities (e.g. related substances, degradants, inorganic impurities, residual solvents, reagents) are identified and in-process controls provide acceptable limits. Potential genotoxic impurities are identified and assessed using the TTC level of  $\frac{(b)}{(4)} \mu\text{g/day}$  for treatment  $\frac{(b)}{(4)}$  months  $\frac{(b)}{(4)}$  which is equivalent to  $\frac{(b)}{(4)}$  ppm based on a 50 mg elbasvir drug substance daily dose. The observed limits are well below the TCC level.

Chemistry Assessment Section

**2.3.S.4 Control of Drug Substance (Elbasvir)**

Tests	Acceptance Criteria	Method
Description:	(b) (4)	Visual
Assay:*	(b) (4) wt%	HPLC (Sec. 3.2.S.4.2.1)
Impurities:	(b) (4)	HPLC (Sec. 3.2.S.4.2.1)
Specific Rotation*:	(b) (4)	(b) (4)
Residual Solvents:	(b) (4)	(b) (4)
Identity by (b) (4)	Conforms †	(b) (4)
Heavy Metals:	(b) (4)	(b) (4)

**Elbasvir Drug Substance Specification, Justification**

Controls are in place for description, assay, impurities, residual solvents, (b) (4) specific rotation, heavy metals, residual (b) (4) and identity.

**- Impurities**

Specified Related Compounds

The acceptance criteria for individual specified related compounds are established based on their corresponding specifications for starting materials and/or intermediates, their (b) (4) through the process, and the clinical as well as commercial drug substance manufacturing data. The qualification of each specified impurity that is supported by preclinical safety and clinical studies is shown below.

## Chemistry Assessment Section

(b) (4)

**Reviewer's Assessment:** *Acceptable*

Analytical Characterization of the Primary Reference Standard, (b) (4) with result (b) (4) (wt%) is in agreement with the Sponsor's justification for not including this test in the release specification.

**2.3.S.6 Container Closure System (Elbasvir)**

The container/closure system used for the packaging of elbasvir drug substance for (b) (4)

(b) (4)

**Reviewer's Assessment:** *Acceptable*

Reference also 2.3.S.7 Stability data to demonstrate suitability of the container/closure system and storage conditions.

**2.3.S.7 Stability (Elbasvir)****Stability Specification (acceptance criteria)**

The following tests will be monitored in the stability program: Description, Assay by HPLC, Impurities by HPLC. (b) (4). The chromatographic methods used in the stability studies of the commercial scale batches are the same methods as those used for the release of the drug substance.

**Stability Protocol**

Three commitment batches will be studied (b) (4)

(b) (4)

## Chemistry Assessment Section

(b) (4)

(b) (4)

**Reviewer's Assessment: Batch Analysis Adequate**

Batches manufactured at commercial scale have similar quality profiles (b) (4)

(b) (4) Total impurities (b) (4).

## Chemistry Assessment Section

**OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE  
(Elbasvir)****Reviewer's Assessment and Signature: Recommended for Approval.**

Sharon Kelly, Ph.D.  
Office of New Drug API, Branch I  
October 07, 2015

**Supervisor Comments and Concurrence: I concur.**

Kasturi Srinivasachar, Ph.D.  
Acting Branch Chief, New Drug API Division, ONDP  
10-07-2015

**ASSESSMENT OF THE DRUG SUBSTANCE (Grazoprevir)****2.3.S DRUG SUBSTANCE (Grazoprevir)****2.3.S.1 General Information (Grazoprevir)**

USAN/INN: Grazoprevir  
Chemical Name (CAS): *N*-[[[(1*R*, 2*R*)-2-[5-(3-hydroxy-6-methoxy-2-quinoxaliny)pentyl]cyclopropyl]oxy]carbonyl]-3-methyl-L-valyl-(4*R*)-4-hydroxy-L-prolyl-(1*R*, 2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-ethenylcyclopropaocarboxamide cyclic (1→2)-ether  
Chemical Name (IUPAC): (1*aR*, 5*S*, 8*S*, 10*R*, 22*aR*)-*N*-[(1*R*, 2*S*)-1-[(Cyclopropylsulfonamido)carbonyl]-2-ethenylcyclopropyl]-14-methoxy-5-(2-methylpropan-2-yl)-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21,22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[1,1,12-*b*]quinoxaline-8-carboxamide  
Laboratory Code: L-002214070 and MK-5172  
CAS Number: 1350514-68-9  
Structural Formula:



## Chemistry Assessment Section

(b) (4)

**Reviewer's Assessment:** ACCEPTABLE. The applicant provided an adequate description of the names, structure, and general properties of the drug substance.

**2.3.S.2      Manufacture (Grazoprevir)***S.2.2 Description of the Manufacturing Process and Controls***Manufacturers (Section S.2.1)**

(b) (4)

**Stability Testing of Grazoprevir Drug Substance:**

Merck Sharp & Dohme Corp.  
4633 Merck Road  
Wilson, North Carolina 27893

## Chemistry Assessment Section

### Manufacturers of Grazoprevir Intermediates

(b) (4)



### Description of Manufacturing Process and Process Controls (Section S.2.2)

(b) (4)



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## Chemistry Assessment Section

(b) (4)

**Reviewer's Assessment: ACCEPTABLE.** The characterization data support the proposed structure and the potential impurities are understood and controlled appropriately.



## Chemistry Assessment Section

based on 12 months of long-term and 6 months of accelerated stability data. No statistical analyses were provided. According to ICH Q1E, the applicant should provide justification for the omission of statistical analyses. The following issue was sent to the applicant in an Information Request dated 19-Aug-2015:

(b) (4)

**Reviewer Notes:** The long-term stability data for the 3 primary batches meet the drug substance specification (b) (4). The applicant's proposed (b) (4)-month retest date for the grazoprevir drug substance is acceptable. (b) (4)

**Reviewer's Assessment:** ACCEPTABLE. A (b) (4)-month retest date is acceptable for the grazoprevir drug substance (b) (4)

**OVERALL ASSESSMENT AND SIGNATURES: GRAZOPREVIR DRUG SUBSTANCE**

Chemistry Assessment Section

**Reviewer's Assessment and Signature: Recommended for Approval.**  
**Monica D. Cooper, Ph.D.**  
**24-Sep-2015**

**Supervisor Comments and Concurrence: I concur.**  
  
**Kasturi Srinivasachar, Ph.D.**  
**Acting Branch Chief, New Drug API Division, ONDP**  
**25 Sep. 2015**

**ASSESSMENT OF THE DRUG PRODUCT**

**2.3.P DRUG PRODUCT**

(Include a summary of how the product design relates to the proposed patient population and the clinical indication. (e.g., rationale for the dosage selections, unique design features of the proposed drug product etc.).

**2.3.P.1 Description and Composition of the Drug Product**

The composition of the tablets is as follows

Component	Function	Amount
(b) (4)		
MK-5172 (b) (4)		(b) (4)
Sodium lauryl sulfate, NF		
Copovidone, NF (b) (4)		
(b) (4)		(b) (4)
(b) (4)		
Mannitol, USP		(b) (4)
Croscarmellose sodium, NF		
Sodium chloride, USP		
Colloidal silicon dioxide, NF		
Magnesium stearate, NF		
(b) (4)		(b) (4)

Chemistry Assessment Section

MK-8742 Active 50.00 mg  
Hypromellose (b) (4), NF (b) (4)  
Vitamin E TPGS, NF (b) (4)

(b) (4)

(b) (4)

Microcrystalline cellulose, NF (b) (4)  
Lactose monohydrate, NF (b) (4)  
Croscarmellose sodium, NF (b) (4)  
Sodium chloride, USP (b) (4)  
Colloidal silicon dioxide, NF (b) (4)  
Magnesium stearate, NF (b) (4)

(b) (4)

*Film coat* (b) (4)

Carnauba wax, NF Wax (b) (4)

(b) (4)

(b) (4)

The film coat contains lactose monohydrate, NF, hypromellose (b) (4) NF, titanium dioxide, NF, triacetin, NF, iron oxide yellow, NF, iron oxide red, NF, and ferrousferic oxide, NF. (b) (4)

The tablets are 21.22 mm x 10.34 mm.

**Reviewer's Assessment:**  
Adequate. The grade and vendor of each excipient is described in the Amendment of 7/31/15, see section P.4 for a discussion of this issue. (b) (4)  
(b) (4)

Chemistry Assessment Section

**2.3.P.2 Pharmaceutical Development**

***P.2.1 Components of the Drug Product***

The drug substances are chosen for reasons of clinical necessity. MK-5172 is an NS5A protease inhibitor and MK-8742 is an NS5A replication complex inhibitor. (b) (4)

(b) (4)

***P.2.1.1 Drug Substance***

(b) (4)

***P.2.1.2 Excipients***

Copovidone (b) (4) sodium lauryl sulfate (b) (4). Hypromellose (b) (4) and Vitamin E TPGS (b) (4). These excipients were selected after experiments comparing them with other, similar excipients.

(b) (4)  
Various excipients were evaluated in preliminary experiments and those that provided the optimum tablet properties were selected. Colloidal silicon dioxide (b) (4) magnesium stearate (b) (4)

The film coat (b) (4)  
carnauba wax (b) (4)

**Reviewer's Assessment: Adequate**

***P.2.2 Drug Product***

## Chemistry Assessment Section

*P.2.2.1**Formulation Development*

(b) (4)

The planned commercial product has the same formulation as the tablets used for the formal stability studies and for the pivotal Phase 3 studies [REDACTED] (b) (4)

**Reviewer's Assessment:**

Adequate. The planned commercial product has the same formulation as the tablets used for the formal stability studies and for the pivotal Phase 3 studies [REDACTED] (b) (4)

*P.2.2.2**Overages*

## Chemistry Assessment Section

None

**P.2.2.3**                    *Physicochemical and Biological Properties*

MK-5712 is BCS Class (b) (4) and MK-8742 is BCS Class (b) (4)

**Reviewer's Assessment: Adequate**

**P.2.4**                    *Container Closure System*

The container-closure system is an (b) (4) blister to protect against light and moisture. (b) (4)

**Reviewer's Assessment: Adequate. See also the stability section**

**P.2.5**                    *Microbiological Attributes*

Ten lots conformed to USP <61> and <62>. (b) (4)

(b) (4)

**Reviewer's Assessment: Adequate. See also Microbiology review.**

**P.2.6**                    *Compatibility*

NA

Chemistry Assessment Section

**2.3.P.4 Control of Excipients**

**P.4.1 Specifications**

(b) (4) (b) (4) the excipients are USP/NF compendial and are as follows. (b) (4)

(b) (4)

(b) (4) At the Request of FDA this information was included in the Amendment of 7/31/15.

Excipient	Function	Grade	Vendor
		(b) (4) NA	NA
Carnauba wax, NF	Wax		(b) (4)
Colloidal silicon dioxide, NF			
Copovidone, NF			
Croscarmellose sodium, NF			
Hypromellose (b) (4) NF			
Lactose monohydrate, NF			
Magnesium stearate, NF			
Mannitol, USP			
Microcrystalline cellulose, NF			
		(b) (4) NA	NA
Sodium chloride, USP			(b) (4)
Sodium lauryl sulfate, NF			
Vitamin E TPGS, NF			

## Chemistry Assessment Section

(b) (4)

The (b) (4) Beige film coat is covered by DMF (b) (4). A Letter of Authorization to refer to this DMF, dated 2/26/15, is provided. (b) (4)

(b) (4)

## Component

(b) (4)

Lactose monohydrate, NF  
Hypromellose (b) (4) NF  
Titanium dioxide, USP  
Triacetin, USP  
Iron oxide yellow, NF  
Iron oxide red, NF  
Ferrosoferric oxide, NF

(b) (4)

Incoming material is tested by Merck for appearance and identity (b) (4)

**P.4.2 Analytical Procedures**

The excipients are tested using USP/NF procedures. The film coat is tested by visual examination and by (b) (4) according to USP (b) (4).

## Chemistry Assessment Section

**P.4.3      *Validation of Analytical Procedures***

Not required for USP/NF procedures.

**P.4.4      *Justification of Specifications***

Not required for USP/NF specifications. The (b) (4) specification is reasonable.

**P.4.5      *Excipients of Human or Animal Origin***

The lactose monohydrate is sourced from (b) (4)  
The magnesium stearate is of (b) (4) origin

**P.4.6      *Novel Excipients***

None

**Reviewer's Assessment:** Adequate. (b) (4)  
The grade of each excipient is specified. The film coat is composed of compendial components.

(b) (4)

**2.3.P.5      *Control of Drug Product*****P.5.1      *Specification(s)***

Chemistry Assessment Section

The drug product specification is as follows.

Test	Method	Acceptance criterion
Appearance	Visual	Beige film-coated oval tablet debossed with "770" on one side and plain on the other
Assay	HPLC	95.0-105.0% (each active)
Degradants	HPLC	
From MK-5172		(b) (4)
Any single		
Total		
From MK-8742		
Any single		(b) (4)
Total		
Identity	HPLC	Retention times conform (b) (4) % (each active)
Identity	UV spectrum	Conforms to reference standard (each active)
Content uniformity	USP <905>	Conforms
Dissolution	USP <711>	
MK-5172		Q= (b) (4) % in (b) (4) min
MK-8742		O= (b) (4) % in (b) (4) min

(b) (4)

Note that identity tests are only performed at release.

**Reviewer's Assessment: Adequate**

**P.5.2 Analytical Procedures and P.5.3 Validation of Analytical Procedures**

(b) (4)

(b) (4)



**Reviewer's Assessment:** Adequate.

(b) (4)

(b) (4)

See also the Biopharmaceutics and Quality Micro reviews.

#### **P.6 Reference Standards or Materials [Elbasvir and Grazoprevir Tablets]**

See the drug substance sections, 3.2.S.5.

**Reviewer's Assessment:** Adequate

**2.3.P.7 Container Closure System**

The container-closure system is an (b) (4) blister. (b) (4)

(b) (4)

Incoming material is tested for identity (b) (4), appropriate documentation, appearance, and thickness.

Test blisters were tested (b) (4)

**Reviewer's Assessment: Adequate.**

**2.3.P.8 Stability**

**P.8.1 Stability Summary and Conclusion and P.8.3 Stability Data**

*Registrational Stability Data*

The following stability data are provided. All batches were manufactured (b) (4)

Batch	Color	Size	30°C/75% RH	40°C/75% RH
WL00056639	(b) (4)	(b) (4)	12 months	6 months
WL00056641			12 months	6 months
WL00056643			12 months	6 months

The following ranges of data are reported.

Test	Specification	30°C/75%	40°C/75%
------	---------------	----------	----------

Appearance	Conforms	Conforms	Conforms
Assay	 (b) (4)		
MK-5172			
MK-8742			
Degradants			
From MK-5172			
Any single			
Total			
From MK-8742			
Any single			
Total			
Dissolution*			
MK-5172	Q= (b) (4)	in 45 min	(b) (4)
MK-8742	O= (b) (4)	in 30 min	(b) (4)
 (b) (4)			
Microbial limits	Conforms	Conforms	Conforms

All impurities are below the reporting threshold  (b) (4) (Amendment of 7/31/15).

\*Individual values (profiles are also provided)

There are no out of specification results and no trends whatsoever are observed. This includes  (b) (4) microbial limits.

Photostability testing was carried out  (b) (4) No changes were observed.

 (b) (4)

(b) (4)

The applicant proposes an expiration dating period of 24 months with the storage statement “Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). (b) (4) in the original blister package until use to protect from moisture.”

**Reviewer’s Assessment:** Adequate. There are no out of specification results and no trends whatsoever are observed. Photostability testing showed no changes. An expiration dating period of 24 months with the storage statement “Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). (b) (4) in the original blister package until use to protect from moisture” is reasonable. (b) (4)

(b) (4)

#### *P.8.2 Postapproval Stability Protocol and Stability Commitment*

(b) (4)



**Comments:** Adequate. The annual stability batch protocol is acceptable. The registration, commitment, and three additional batches will be monitored on stability

(b) (4)

(b) (4)



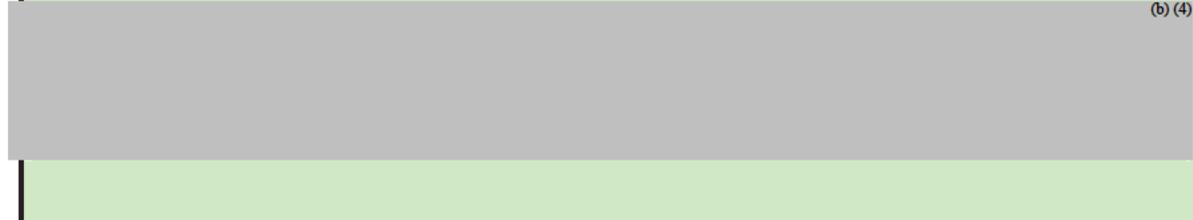
**Reviewer's Assessment:** Adequate as amended. The annual stability batch protocol is acceptable. The registration, commitment, and three additional batches will be monitored

(b) (4)

three additional batches will be monitored for microbial limits.

(b) (4)

(b) (4)



### Environmental Analysis

The applicant requests a categorical exclusion from the requirement to prepare an Environmental Analysis under 21 CFR 25.31 (b) on the grounds that the concentration of active ingredient in the aquatic environment is expected to be less than 1 ppb. The applicant had not provided an explicit statement regarding their knowledge of any extraordinary circumstances. Upon request by FDA, the applicant has now provided an adequate statement. James Laurenson, Environmental Officer, ONDP concurs (e-mail of 9/1/15).

**Reviewer's Assessment:** Adequate. The claim is reasonable and should be accepted.

### R.2 Comparability Protocols

A comparability protocol is provided

(b) (4)

(b) (4)

Data will be reported in the Annual Report.

**Reviewer's Assessment:** Adequate. This proposal is in accordance with current guidances and practice but it is not clear that it requires a comparability protocol.

**OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT****Reviewer's Assessment and Signature:**

**From the drug product point of view this application is recommended for approval.**

**George Lunn, Ph.D. Oct 23, 2015  
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ**

**Supervisor Comments and Concurrence:**

**I concur with Dr. Lunn's recommendation.**

**Stephen Miller, Ph.D. Oct 23, 2015  
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ**

**ASSESSMENT OF THE PROCESS**

All questions in this section have not been provided to the applicant and therefore there is no applicant's response in the submission. All information immediately follows the questions is relevant information gathered from the submission.

**2.3.P DRUG PRODUCT****2.3.P.2.3 Manufacturing Process Development**

1. Does the information described in the pharmaceutical development section support the proposed drug product manufacturing process?

Grazoprevir/Elbasvir Tablet is a fixed dose combination (b) (4) that has been developed through a systematic risk-based development program to achieve a robust manufacturing process. The manufacturing process has been demonstrated at multiple scales including the intended commercial launch scale for all unit operations. Both the developed manufacturing process and the associated control strategy have been described in detail in the manufacturing process development section. (b) (4)

8. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

**Reviewer's Assessment:**

The drug product is a solid oral dosage form and does not require sterile manufacturing process or environment.

**R.2 Comparability Protocols**

9. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change? How will the changes be reported?

**Reviewer's Assessment:**

There is no Comparability Protocol in the application for manufacturing process or manufacturing site post approval changes.

**OVERALL ASSESSMENT AND SIGNATURES: PROCESS**

**Reviewer's Assessment and Signature: Recommend for Approval from Process Perspective****Ying Wang 09/21/2015**

The manufacturing process is adequately developed based on the characteristics of the drug product and risk assessment. The main focus of the manufacturing process development and risk mitigation is on maintenance of the physical stability of the (b) (4) and the final drug product. The processing and storage temperature and (b) (4) are the major factors (b) (4). The manufacturing process is adequately controlled to ensure the quality of the drug product.

**Secondary Review Comments and Concurrence:**

Concur Upinder Atwal 09/21/2015

Note: additional reviewers can be added, as appropriate

**ASSESSMENT OF THE FACILITIES****2.3.S DRUG SUBSTANCE****2.3.S.2 Manufacture***Manufacturer(s)*

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**OVERALL ASSESSMENT AND SIGNATURES: FACILITIES****Reviewer's Assessment and Signature: Acceptable/Denise DiGiulio 10/20/2015**

Based on this inspection information, there is confidence in (b) (4) (b) (4) and MERCK SHARP & DOHME WILSON FACILITY's commercial manufacturing capability for this specific NDA being reviewed. There are no relevant product, facility, or process risks

Based on this inspection information, there is confidence in (b) (4) (b) (4) MERCK SHARP & DOHME WILSON FACILITY, and MERCK SHARP & DOHME UK's commercial manufacturing capability for this specific NDA being reviewed. There are no relevant product, facility, or process risks.

Pre-Approval Inspections were requested as part of the facility assessment of this NDA (b) (4)

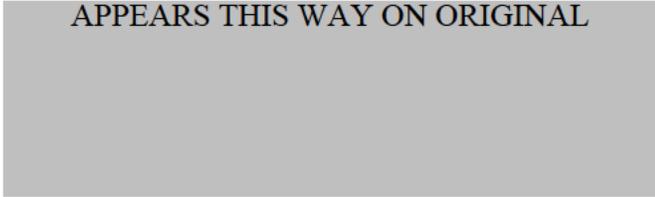
(b) (4)

(b) (4)

**Supervisor Comments and Concurrence:****Concur, 10/23/15****Mahesh Ramanadham  
Branch Chief, DIA/IAB2**

Note: additional reviewers can be added, as appropriate

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## ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

### 10. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Yes. The proposed in vitro dissolution test is adequate for quality control. The selection of the dissolution conditions (e.g., medium, surfactant, apparatus, rotation speed, etc.) was adequately justified. The discriminating ability of the dissolution method was demonstrated. The method was validated. The proposed acceptance criteria are supported by the dissolution data for the clinical batches.

The review is focused on the following aspects pertaining to in vitro dissolution test:

- Drug substance solubility
- Formulation
- Dissolution method and development
- Discriminating power of the dissolution method
- Proposed dissolution acceptance criteria
- Stability dissolution data

#### ➤ Drug Substance Solubility:

The Applicant noted that Grazoprevir (GZR) is classified as a Biopharmaceutics Classification System (BCS) (b) (4) compound and elbasvir (EBR) is classified as a BCS (b) (4) compound. Both (b) (4)

Table 33-1 Solubility of GZR in various solvents

Solvent	Solubility (mg/mL)	Solubility Description (per USP)
Water	(b) (4)	Practically insoluble
(b) (4)	(b) (4)	(b) (4)
Acetone	(b) (4)	Freely soluble
(b) (4) EtOH	(b) (4)	Freely soluble
(b) (4)	(b) (4)	(b) (4)
DMF	(b) (4)	Freely soluble
THF	(b) (4)	Freely soluble

Table 33-2 Solubility of EBR in various solvents

(b) (4)	Solvent	Solubility (mg/mL)	USP Solubility Description
	Water	(b) (4)	Practically insoluble
	Ethyl acetate	(b) (4)	Very soluble
	Acetone		Very soluble
			(b) (4)
	Ethanol	0.15	Very slightly soluble
			(b) (4)



(b) (4) The composition of the proposed fixed dose combination (FDC) drug product is shown in Table 33-4.

Table 33-4 Grazoprevir/ Elbasvir Tablet (100 mg/ 50 mg) - Composition

Components	Reference	Function	mg/tablet
(b) (4)			(b) (4)
Grazoprevir	In-house	Active	100.0 <sup>1</sup>
Sodium Lauryl Sulfate	USP-NF	(b) (4)	(b) (4)
Copovidone	USP-NF		(b) (4)

Mannitol	USP-NF			(b) (4)
Croscarmellose Sodium	USP-NF			
Sodium Chloride	USP-NF			
Colloidal Silicon Dioxide	USP-NF			
Magnesium Stearate	USP-NF			
Elbasvir	In-house	Active	50.00	
Hypromellose (b) (4)	USP-NF			(b) (4)
Vitamin E Polyethylene Glycol Succinate	USP-NF			(b) (4)
Cellulose, Microcrystalline	USP-NF			(b) (4)
Lactose Monohydrate	USP-NF			
Croscarmellose Sodium	USP-NF			
Sodium Chloride	USP-NF			
Colloidal Silicon Dioxide	USP-NF			
Magnesium Stearate	USP-NF			(b) (4)
<b>Film Coat</b>	(b) (4)			
(b) (4) Beige	(b) (4)	In-house	Film coat	(b) (4)
Carnauba Wax	USP-NF		Wax	

➤ **Dissolution Method:**

The proposed dissolution method is as follows:



Figure 34-1 Formulations used in development and clinical trials

There are 4 relative BA studies conducted to compare the formulations used in the clinical trials.

(b) (4)

(u) (4)

(b) (4)

**Reviewer's Assessment:**

Grazoprevir/elbasvir (GZR/EBR; MK-5172A) is a fixed dose combination tablet of two components: grazoprevir (GZR, MK-5172) and elbasvir (EBR, MK-8742). The drug product is an immediate release product. The proposed indication of the GZR/EBR fixed dose combination tablet (GZR/EBR FDC) is the treatment of chronic HCV infection in adult patients with or without cirrhosis, including those with chronic kidney disease, and those with HCV/HIV-1 co-infection. In specific populations, the addition of ribavirin (RBV) or sofosbuvir may be recommended. The proposed dosing regimen is 100 mg GZR/50 mg EBR provided in a single tablet once daily (QD) with or without food.

(b) (4)

- The proposed dissolution method and the acceptance criteria are as follows:

(b) (4)

Acceptance Criteria	Elbasvir	Q= (b) (4) % in 30 min
	Grazoprevir	Q= (b) (4) % in 45 min

- The development report for the dissolution method was provided. Adequate justifications for the selection of the medium, (b) (4) concentration, apparatus, rotational speed, basket mesh size are provided. The method was adequately validated.
- The proposed dissolution methodology developed has been shown to be discriminating (b) (4) and appears to be suitable to control the quality of Grazoprevir/Elbasvir Tablet.
- The proposed dissolution acceptance criteria are acceptable.
- The dissolution data on (b) (4) market batches and the stability batches conform to the proposed dissolution acceptance criteria. No trend of change in the dissolution data is observed (b) (4)
- No formulation bridging is needed for the drug product, (b) (4)

**OVERALL ASSESSMENT AND SIGNATURES:  
BIOPHARMACEUTICS**

**Reviewer's Assessment and Signature:**

From a Biopharmaceutics perspective, NDA 208261 for elbasvir and grazoprevir tablets (50 mg/100 mg) is recommended for **APPROVAL**.

**Jing Li, Ph.D., 9/11/2015**

Biopharmaceutics Reviewer  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality

**Supervisor Comments and Concurrence:**

I concur with Dr. Li's assessment and recommendation.

**Elsbeth Chikhale, Ph.D., 9/14/2015**

Biopharmaceutics Lead  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality

## ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

The microbiological attributes of the excipients were characterized during the development program. All excipients meet USP <1111> *Microbial Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* and Ph. Eur. 5.1.4 *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*, when tested in accordance with USP <61> and <62>, and Ph. Eur. 2.6.12 and 2.6.13, where applicable.

Current Good Manufacturing Practices are used which minimize the possibility for microbial contamination for the finished product. (b) (4)

(b) (4) All lots met the USP <1111> criteria for nonaqueous preparations for oral use (Total Aerobic Microbial Count NMT (b) (4) CFU/gram, Total Combined Yeast and Mold Count NMT (b) (4) CFU/gram and (b) (4) (b) (4) in (b) (4) gram).

(b) (4)

Based on the guidance from ICH Q6A, Decision Tree 8 (Microbiological Attributes of Non-sterile Drug Products), it is concluded that microbial quality is not necessary for routine testing.

### **Reviewer's Assessment: Adequate**

The applicant provides adequate justification for not conducting routine microbial test for this solid oral dosage form of the drug product.

### 2.3.P.6 Reference Standards or Materials

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

**Reviewer's Assessment:** N/A

## A APPENDICES

### A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

**Reviewer's Assessment:** Adequate

The excipient lactose monohydrate is a common excipient and is derived from milk certified to originate from healthy animals (b) (4)

The information provided above is adequate to ensure low risk of potential TSE per discussion with DP reviewer who reviews excipients for the DP.

Also see DP review section.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Reviewer's Assessment:** N/A

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY****Reviewer's Assessment and Signature: Recommend for Approval from Microbiology Perspective****Ying Wang 9/21/2015**

The drug product is a solid oral dosage form with commonly used excipients and common tablet manufacturing processes. There is adequate data and justification for not performing routine microbial test for the drug product.

**Secondary Review Comments and Concurrence:****Concur, Upinder Atwal 09/24/2015**

Note: additional reviewers can be added, as appropriate

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1****Labeling & Package Insert****1. Package Insert**

**(a) “Highlights” Section (21CFR 201.57(a))**

TITLE:  
TRADEMARK™ (elbasvir and grazoprevir) tablets, for oral use

**DOSAGE FORMS AND STRENGTHS**

- Tablets: 50 mg elbasvir and 100 mg grazoprevir (3)

Item	Information Provided in NDA	Reviewer’s Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	Proprietary: TRADEMARK is currently listed in the PI. This will be changed to the agreed Trade Name of Zepatier. Established Name: elbasvir and grazoprevir tablets	Adequate
Dosage form, route of administration	Dosage: 50 mg and 100 mg Route: oral	Adequate
Controlled drug substance symbol (if applicable)		NA
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths	Tablets: 50 mg elbasvir and 100 mg grazoprevir	Adequate

**Conclusion: Adequate**

**(b) “Full Prescribing Information” Section**

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

**3 DOSAGE FORMS AND STRENGTHS**

TRADEMARK is available as a beige-colored, oval-shaped, film-coated tablet debossed with “770” on one side and plain on the other. Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Tablet	Adequate
Strengths: in metric system	50 mg of elbasvir and 100 mg of grazoprevir	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	TRADEMARK is available as a beige-colored, oval-shaped, film-coated tablet debossed with “770” on one side and plain on the other. Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.	Adequate

**Conclusion: Adequate**

**#11: Description (21CFR 201.57(c)(12))**

**11 DESCRIPTION**

TRADEMARK is a fixed-dose combination tablet containing elbasvir and grazoprevir for oral administration.

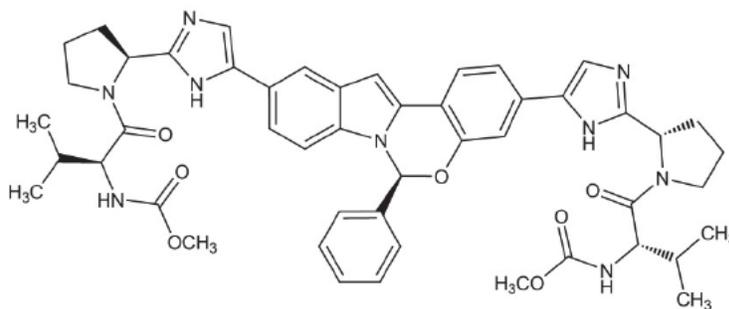
Elbasvir is an HCV NS5A inhibitor, and grazoprevir is an HCV NS3/4A protease inhibitor.

Each tablet contains 50 mg elbasvir and 100 mg grazoprevir. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium chloride, sodium lauryl sulfate, and vitamin E polyethylene glycol succinate. The tablets are film-coated with a coating material containing the following inactive ingredients: carnauba wax, ferrousferic oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

#### Elbasvir:

The IUPAC name for elbasvir is Dimethyl *N,N'*-([(6*S*)-6-phenylindolo[1,2-*c*][1,3]benzoxazine-3,10-diyl]bis{1*H*-imidazole-5,2-diyl-(2*S*)-pyrrolidine-2,1-diyl}[(2*S*)-3-methyl-1-oxobutane-1,2-diyl])dicarbamate.

It has a molecular formula of  $C_{49}H_{55}N_9O_7$  and a molecular weight of 882.02. It has the following structural formula:

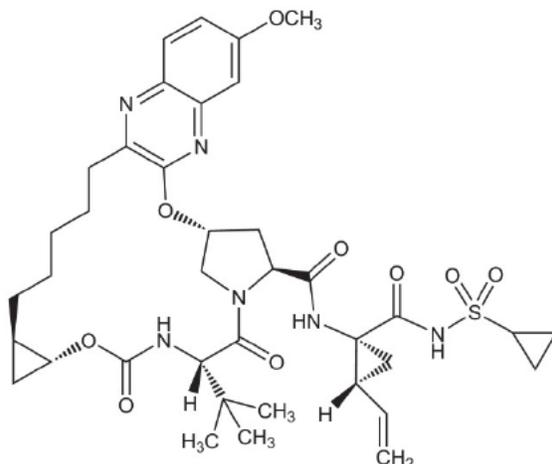


Elbasvir is practically insoluble in water (<0.1 mg/mL) and very slightly soluble in ethanol (0.2 mg/mL), but is very soluble in ethyl acetate and acetone.

#### Grazoprevir:

The IUPAC name for grazoprevir is (1*aR*,5*S*,8*S*,10*R*,22*aR*)-*N*-[(1*R*,2*S*)-1-[(Cyclopropylsulfonamido)carbonyl]-2-ethenylcyclopropyl]-14-methoxy-5-(2-methylpropan-2-yl)-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21,22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide.

It has a molecular formula of  $C_{38}H_{50}N_6O_9S$  and a molecular weight of 766.90. It has the following structural formula:



Grazoprevir is practically insoluble in water (<0.1 mg/mL) but is freely soluble in ethanol and some organic solvents (e.g., acetone, tetrahydrofuran and N,N-dimethylformamide).

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADEMARK is a fixed-dose combination tablet containing elbasvir and grazoprevir for oral administration.	Adequate
Dosage form and route of administration	Fixed-dose combination tablet, oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Present and in alphabetical order	Adequate
Statement of being sterile (if applicable)		NA
Pharmacological/ therapeutic class	Elbasvir is an HCV NS5A inhibitor, and grazoprevir is an HCV NS3/4A protease inhibitor.	Adequate
Chemical name, structural formula, molecular weight	Present for both actives	Adequate
If radioactive, statement of important nuclear characteristics.		NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	Present for both actives	Adequate

**Conclusion:**

**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

TRADEMARK tablets are beige, oval-shaped, film-coated, debossed with “770” on one side and plain on the other. The tablets are packaged into a carton (NDC 0006-3074-02) containing two (2) 14-count child-resistant dose packs for a total of 28 tablets.

Store TRADEMARK in the original blister package until use to protect from moisture.

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

Item	Information Provided in NDA	Reviewer’s Assessment
Strength of dosage form	From Section 11: Each tablet contains 50 mg elbasvir and 100 mg grazoprevir	Adequate
Available units (e.g., bottles of 100 tablets)	Carton containing two (2) 14-count child-resistant dose packs for a total of 28 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Beige, oval-shaped, film-coated, debossed with “770” on one side and plain on the other	Adequate
Special handling (e.g., protect from light, do not freeze)	Store TRADEMARK in the original blister package until use to protect from moisture.	Adequate
Storage conditions	Store TRADEMARK at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F) [see USP Controlled Room Temperature].	Adequate

**Manufacturer/distributor name listed at the end of PI, following Section #17**

Item	Information Provided in NDA	Reviewer’s Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA. Manufactured by: MSD International GmbH, Ballydine, Clonmel, Ireland	Adequate

**Conclusion:** Adequate

**2. Labels**

The container closure system consists of an outer carton that holds two Dosepaks. Each Dosepak holds a blister card containing 14 tablets in individual blisters.

The outer carton which holds two Dosepaks is as follows.

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Present on outer carton, Dosepak, outer blister, inner blister	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Present on outer carton, Dosepak, outer blister, inner blister	Adequate
Net contents (21 CFR 201.51(a))	Present on outer carton, Dosepak	Adequate
Lot number per 21 CFR 201.18	Present on outer carton, not present on Dosepak or blisters. DMEPA has requested that lot number be placed on the Dosepak.	Adequate
Expiration date per 21 CFR 201.17	Present on outer carton, not present on Dosepak or blisters. DMEPA has requested that expiration date be placed on the Dosepak.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present on outer carton, Dosepak	Adequate
Storage	Present on outer carton, Dosepak	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present on outer carton, Dosepak, outer blister	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present on outer carton, Dosepak, outer blister	Adequate
Name of manufacturer/distributor	Present on outer carton, Dosepak, outer blister	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][ 201.10(a), 21CFR201.100(b)(5)(iii)]	Present in Package Insert and Patient Package Insert only	Adequate
Sterility Information (if applicable)	NA	
"See package insert for dosage information" (21 CFR 201.55)	Present on outer carton, Dosepak. Dosepak and inner surface of blister pack also state "Take 1 pill every day" (which is the usual dose).	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Present in Patient Package Insert only	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	NA	

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

\*\*Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

**Conclusion:** Adequate as amended.

## II. List of Deficiencies To Be Communicated

- A. Drug Substance
- B. Drug Product
- C. Process/Facility
- D. Biopharmaceutics
- E. Microbiology
- F. Label/Labeling

### III. Attachments

#### A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)			Low facility risk, medium product and process risk	acceptable
			Low facility , product and process risk	acceptable
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)			Low facility risk, medium product and process risk	acceptable
			Drug product packager	MERCK SHARP & DOHME WILSON FACILITY
(b) (4)			Medium facility and process risk, low product risk...R&D facility in past...PAI inspection needed	acceptable
			Medium facility product and product risk... R&D facility in past...PAI inspection needed	acceptable
FINISHED DOSAGE STABILITY TESTER	MERCK SHARP & DOHME	3002807653	Low facility and process risk, medium product risk	acceptable

#### B. Lifecycle Knowledge Management

##### a) Drug Substance



(b) (4)

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability		L		L	
Physical stability (b) (4)	(b) (4)	M	(b) (4)	M Acceptable	(b) (4)
Content uniformity	(b) (4)	L		L	
Microbial limits		L	(b) (4)	L	
Dissolution –	(b) (4)	M		L	The dissolution method is discriminating (b) (4)
Tablet content (b) (4)	(b) (4)	M		L	
Drug Product Impurity Control		L		L	
Container Closure		L	(b) (4)	L	(b) (4)

			blister		(b) (4)
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\*Risk ranking applies to product attribute/CQA

\*\*For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.