CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209394Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209394
Review 2

Drug Name/Dosage Form	Glecaprevir and Pibrentasvir Tablets
Strength	100mg/40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	Dec 14, 2016	All
Amendment	Jan 24, 2017	Quality
Amendment	Feb 9, 2017	Quality
Amendment	Mar 7, 2017	Quality
Amendment	Mar 7, 2017	Quality
Amendment	Mar 28, 2017	Quality
Amendment	Mar 31, 2017	Quality
Amendment	Apr 13, 2017	Labeling
Amendment	Apr 21, 2017	Quality
Amendment	May 16, 2017	Quality
Amendment	May 17, 2017	Quality
Amendment	May 22, 2017	Quality
Amendment	June 30, 2017	Container Labels

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substances	Raymond Frankewich	Ben Stevens
Drug Product & Labeling	Danuta Gromek-Woods	George Lunn
Process & Microbiology	Ying Wang	Upinder Atwal
Environmental Analysis	James Laurenson	M. Scott Furness
Facility	Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
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				
	Type III	See Drug Product Review				
	Type IV	See Drug Product Review				
	Other	None				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127416	glecaprevir/pibrentasvir
IND	116169	glecaprevir (ABT-493)
IND	116170	pibrentasvir (ABT-530)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
OTR (St. Louis Labs)	Complete	Observations from the FDA verification of several DS and DP methods were conveyed to AbbVie on May 12. Responses were submitted in the amendments dated May 17 and May 22, 2017.		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the Product Quality perspective. This document (Review #2) contains the final evaluation of all manufacturing facilities, an example of final container labeling, the Final Risk Assessment, and the summary of all product quality aspects of the NDA. See Review #1 (June 6, 2017) for details of other product quality evaluations.

II. Summary of Quality Assessments

A. Product Overview

This product is a bi-layer tablet containing 100 mg of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and 40 mg of pibrentasvir, an HCV NS5A inhibitor. It is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection.

Proposed Indication(s) including Intended Patient Population	Treatment (b) (4) of Chronic infection with theHepatitis C Virus
Duration of Treatment	8-16 weeks
Maximum Daily Dose	Three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) with food
Alternative Methods of Administration	None

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. The manufacturing facilities for NDA 209394 are found to be acceptable. For details, see the Facility evaluation within this review (Product Quality Review #2).

Glecaprevir drug substance has low solubility by BCS criteria. The drug substance (b) (4)

Pibrentasvir has low solubility by BCS criteria. (b) (4)

(b) (4)

A significant aspect of the review of both drug substances was the evaluation of the control strategy for impurities. Appropriate controls have been established for all impurities. In addition to some known mutagens that are used or generated in the manufacturing process (Class 1 or 2 as defined in ICH M7), there were a total of 27 compounds in the Glecaprevir process which the applicant determined were Class 3 (mutagenicity predicted by (Q)SAR), and 66 Class 3 compounds identified in the Pibrentasvir process. All control strategies resulted in an estimated amount of the Class 3 compounds < (b) (4) ppm in Glecaprevir drug substance, and < (b) (4) ppm in Pibrentasvir drug substance. These levels represent the M7 TTC levels at which exposure to an impurity delivered in a drug substance will be 20 µg/day (duration of treatment >1 – 12 months), from maximum daily dosages of 300 mg for Glecaprevir and 120 mg for Pibrentasvir. The control strategies for all Class 1, 2 and 3 compounds were appropriately supported by estimated purge factors, supplemented where appropriate by analytical data and results from spike/purge studies.

The proposed retest date for both drug substances is (b) (4) months when stored at the proposed storage condition (b) (4) (b) (4). For details, see the Drug Substance evaluation within Product Quality Review#1 (June 6, 2017).

Final container labels and labeling, incorporating recommendations from product quality and other review disciplines have been submitted. An example (1-day wallet label) is included in this review. The applicant clarified on July 17 that there is no printing on the back of the blister card, which is fully enclosed by the cardboard carton of the wallet. For further details, see the Labeling evaluation within Product Quality Review#1 (June 6, 2017).

Glecaprevir and Pibrentasvir tablets are immediate release bilayer tablets containing 100 mg glecaprevir in one layer and 40 mg pibrentasvir in the other layer. They are pink-colored, film-coated, oblong biconvex shaped, and debossed with “NXT” on one side. Based on the primary stability data (including 12 months at 30°C/75%RH) a 24-month shelf-life is acceptable for product packaged in (b) (4) with aluminum foil lidding blisters when stored under the recommended conditions: "Store at or below 30°C (86°F)." The child-resistant blister cards of 3 tablets are packaged into weekly, monthly, and optionally 8-week cartons. For details, see the Drug Product evaluation within Product Quality Review#1 (June 6, 2017).

Glecaprevir (GLE) and Pibrentasvir (PIB) drug substances are (b) (4) Critical process parameters and proper ranges have been determined to ensure drug product quality.

The process is well described and controlled. For details, see the Process evaluation within Product Quality Review#1 (June 6, 2017).

The control strategy for (b) (4) and was determined to be acceptable. This control strategy includes the following elements:

(b) (4)

(b) (4)

The dissolution method [USP Apparatus 2 (paddle); 75 ± 4% rpm; 1000 mL of 0.1M acetate buffer (pH 4 ± 0.05) with 1% polysorbate 80; 37 °C; (b) (4) sinker; HPLC-UV detection at 247 nm)] was determined to be appropriate, using these acceptance criteria:

- GLE: NLT (b) (4) % at 45 min; NLT (b) (4) % at 120 min
- PIB: NLT (b) (4) % at 45 min; NLT (b) (4) % at 120 min

The to-be-marketed drug product has the same formulation and manufacturing process/equipment/site as the Phase 3 clinical/primary stability batches, however; the to-be-marketed drug product and the Phase 3 clinical drug product contain a drug substance from different manufacturers and differ in the debossing. The data provided by the Applicant in response to the FDA Information Request confirmed that the proposed changes in the debossing letters of the tablet and the manufacturing site of the drug substances do not impact the in vitro drug dissolution profiles of the final to-be-marketed drug product in the QC dissolution medium. The Applicant did not formally request a BCS designation, but stated that both glecaprevir and pibrentasvir are BCS-4 (low solubility/low permeability) drug substances. For details, see the Biopharmaceutics evaluation within Product Quality Review#1 (June 6, 2017).

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for glecaprevir and pibrentasvir in accordance with 21 CFR Part 25.31(b). The claims for categorical exclusion from an EA for both actives were found to be acceptable, once supported by additional information for pibrentasvir. For details, see the Environmental Analysis evaluation within Product Quality Review#1 (June 6, 2017).

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendations were addressed during labeling negotiations, and incorporated into final labeling:

1. According to 21 CRF 201.57(c)(12)(i), Section 11 must also contain the route of administration, and pharmacological class of the drug.

2. Please list therapeutically inactive ingredients in alphabetical order by name and distinguish from the identification statement of the active ingredient(s).

3. Please provide drafts of immediate container (blisters) labels for your drug product.

D. Final Risk Assessment (see Attachment I at end of this Review)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209394

Date: Aug 3, 2017

Stephen Miller

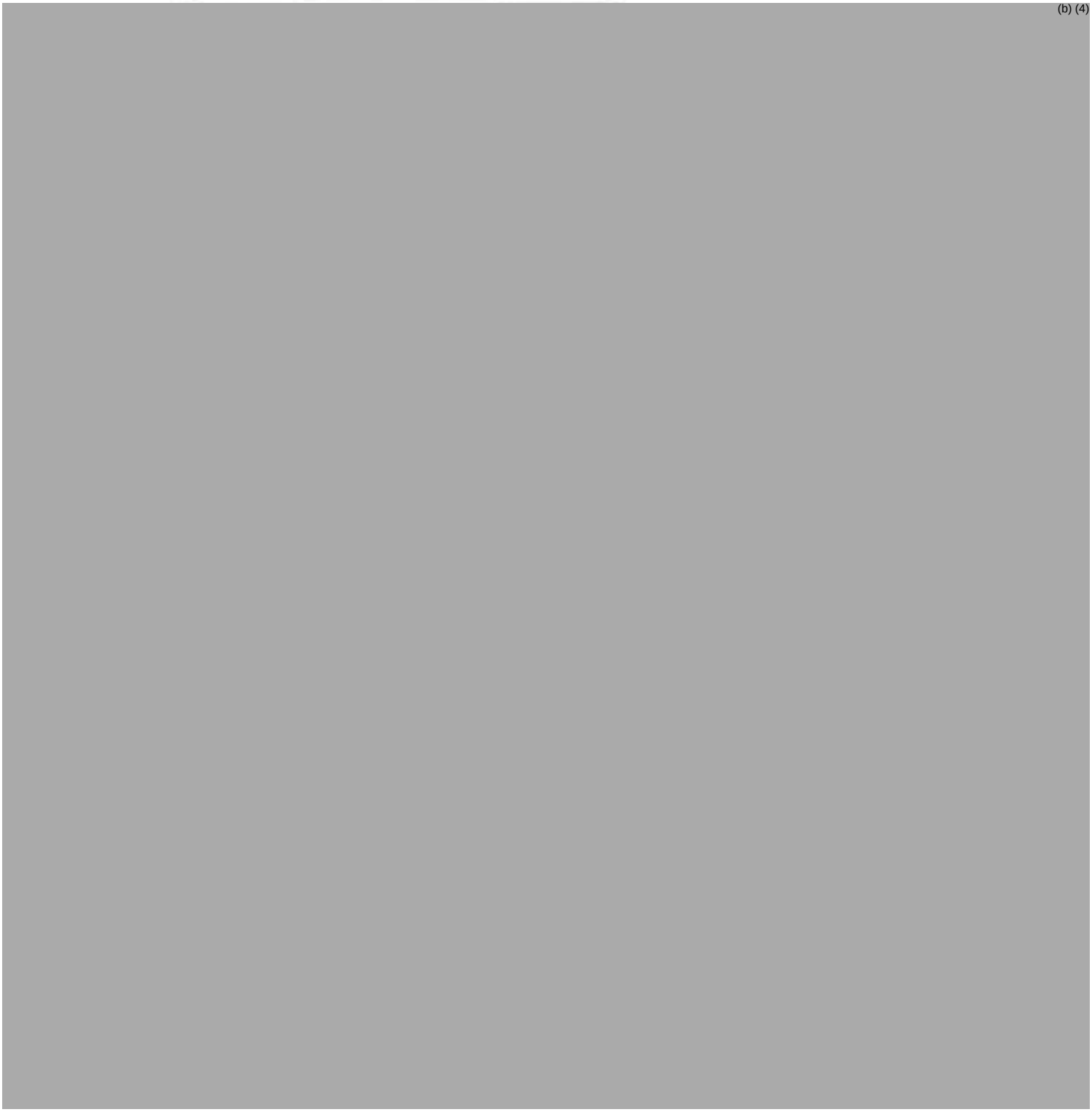
Digitally signed by Stephen Miller
Date: 8/03/2017 12:43:10PM
GUID: 508da7210002a000609476bbecd040f0

Final Container Label for NDA 209394 as submitted in Amendment 044

Final container labels were submitted on June 30, 2017, which incorporated recommendations made by the FDA review team. These final container labels are acceptable from the Product Quality perspective.

Example: 1-Day Wallet Package

(b) (4)



ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Glecaprevir and Pibrentasvir Tablets (NDA 209394)

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)		M	See bulleted outline in Executive Summary	Acc	Additional testing of initial commercial lots was agreed-upon with the Applicant
Content uniformity		M	See Process Review	Acc	
Microbial limits		L		Acc	
(b) (4) **of bi-layer tablets**		L			
Dissolution – BCS Class II or IV		M	Method and AC are suitably discriminatory.	Acc	

Stephen Miller

Digitally signed by Stephen Miller
Date: 8/03/2017 12:42:30PM
GUID: 508da7210002a000609476bbecd040f0

Recommendation: Pending

NDA 209394
Review 1

Drug Name/Dosage Form	Glecaprevir and Pibrentasvir Tablets
Strength	100mg/40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	Dec 14, 2016	All
Amendment	Jan 24, 2017	Quality
Amendment	Feb 9, 2017	Quality
Amendment	Mar 7, 2017	Quality
Amendment	Mar 7, 2017	Quality
Amendment	Mar 28, 2017	Quality
Amendment	Mar 31, 2017	Quality
Amendment	Apr 13, 2017	Labeling
Amendment	Apr 21, 2017	Quality
Amendment	May 16, 2017	Quality
Amendment	May 17, 2017	Quality
Amendment	May 22, 2017	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substances	Raymond Frankewich	Ben Stevens
Drug Product & Labeling	Danuta Gromek-Woods	George Lunn
Process & Microbiology	Ying Wang	Upinder Atwal
Environmental Analysis	James Laurenson	M. Scott Furness
Facility	Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
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				
	Type III	See Drug Product Review				
	Type IV	See Drug Product Review				
	Other	None				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127416	glecaprevir/pibrentasvir
IND	116169	glecaprevir (ABT-493)
IND	116170	pibrentasvir (ABT-530)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
OTR (St. Louis Labs)	Complete	Observations from the FDA verification of several DS and DP methods were conveyed to AbbVie on May 12. Responses were submitted in the amendments dated May 17 and May 22, 2017.		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

At this time a recommendation cannot be made from the product quality perspective because the evaluation of the manufacturing facilities is on-going. Specifically, of the 15 facilities involved in the manufacturing, testing and packaging of this product, 2 foreign facilities were inspected between (b) (4). Additionally, findings from three other recent foreign inspections are under evaluation at the present time.

II. Summary of Quality Assessments

A. Product Overview

This product is a bi-layer tablet containing 100 mg of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and 40 mg of pibrentasvir, an HCV NS5A inhibitor. It is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection.

Proposed Indication(s) including Intended Patient Population	Treatment (b) (4) of Chronic infection with theHepatitis C Virus
Duration of Treatment	8-16 weeks
Maximum Daily Dose	Three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) with food
Alternative Methods of Administration	None

B. (b) (4) Assessment Overview

Glecaprevir drug substance has low solubility by BCS criteria. The drug substance (b) (4)

Pibrentasvir has low solubility by BCS criteria. (b) (4)

A significant aspect of the review of both drug substances was the evaluation of the control strategy for impurities. Appropriate controls have been established for all

impurities. In addition to some known mutagens that are used or generated in the manufacturing process (Class 1 or 2 as defined in ICH M7), there were a total of 27 compounds in the Glecaprevir process which the applicant determined were Class 3 (mutagenicity predicted by (Q)SAR), and 66 Class 3 compounds identified in the Pibrentasvir process. All control strategies resulted in an estimated amount of the Class 3 compounds < (b) (4) ppm in Glecaprevir drug substance, and < (b) (4) ppm in Pibrentasvir drug substance. These levels represent the M7 TTC levels at which exposure to an impurity delivered in a drug substance will be 20 µg/day (duration of treatment >1 – 12 months), from maximum daily dosages of 300 mg for Glecaprevir and 120 mg for Pibrentasvir. The control strategies for all Class 1, 2 and 3 compounds were appropriately supported by estimated purge factors, supplemented where appropriate by analytical data and results from spike/purge studies.

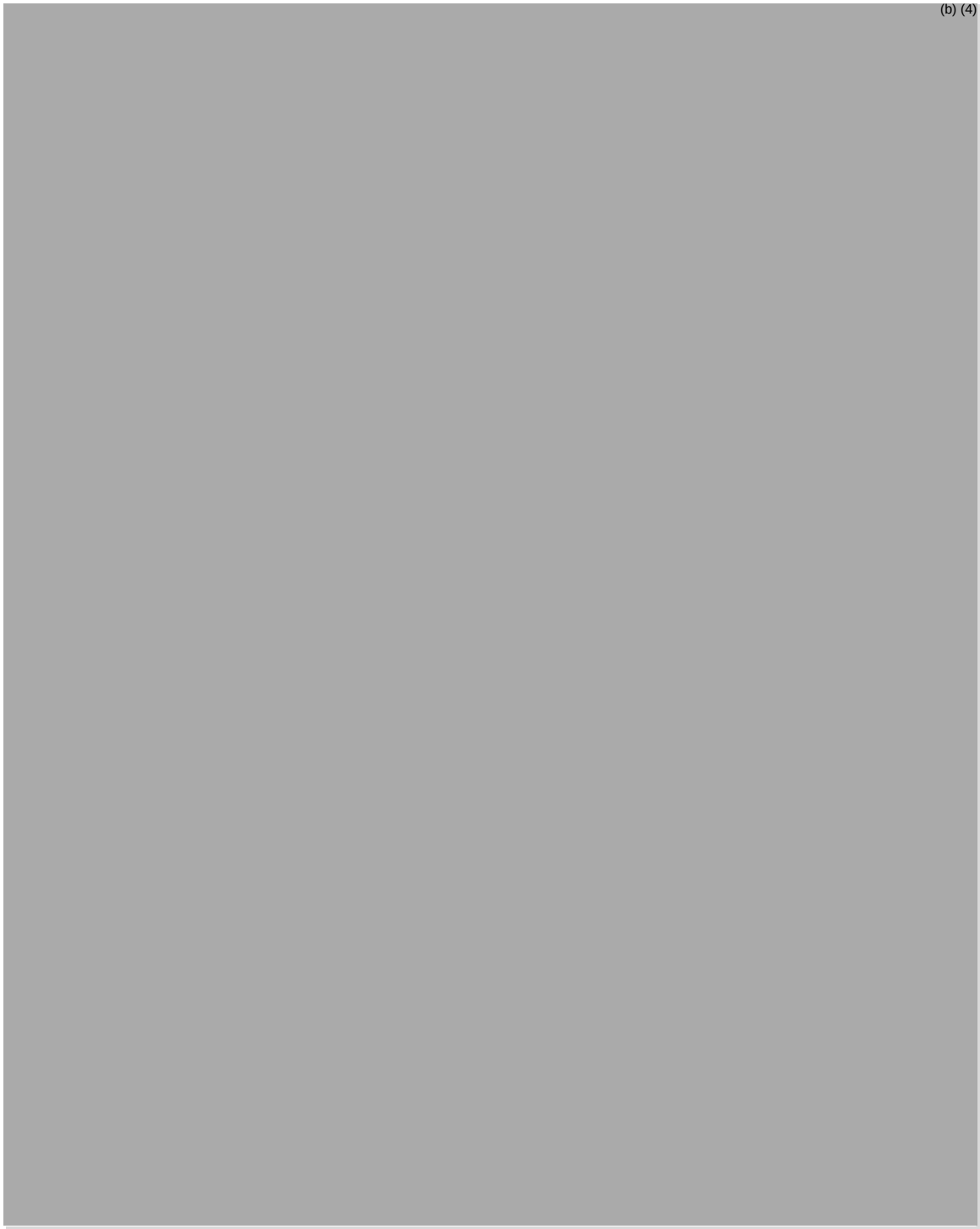
The proposed retest date for both drug substances is (b) (4) months when stored at the proposed storage condition (b) (4)

Glecaprevir and Pibrentasvir tablets are immediate release bilayer tablets containing 100 mg glecaprevir in one layer and 40 mg pibrentasvir in the other layer. They are pink-colored, film-coated, oblong biconvex shaped, and debossed with “NXT” on one side. Based on the primary stability data (including 12 months at 30°C/75%RH) a 24-month shelf-life is acceptable for product packaged in (b) (4) (b) (4) with aluminum foil lidding blisters when stored under the recommended conditions: "Store at or below 30°C (86°F)." The child-resistant blister cards of 3 tablets are packaged into weekly, monthly, and optionally 8-week cartons.

(b) (4) Critical process parameters and proper ranges have been determined to ensure drug product quality. The process is well described and controlled.

The control strategy (b) (4) and was determined to be acceptable. This control strategy includes the following elements:

(b) (4)



There are 15 facilities involved in the manufacturing, testing and packaging of this product. Findings from five recent foreign inspections are under evaluation at the present time. All other facilities have been found to be acceptable.

The dissolution method [USP Apparatus 2 (paddle); 75 ± 4% rpm; 1000 mL of 0.1M acetate buffer (pH 4 ± 0.05) with 1% polysorbate 80; 37 °C; (b) (4) sinker; HPLC-UV

detection at 247 nm)] was determined to be appropriate, using these acceptance criteria:

- GLE: NLT (b) (4)% at 45 min; NLT (b) (4)% at 120 min
- PIB: NLT (b) (4)% at 45 min; NLT (b) (4)% at 120 min

The to-be-marketed drug product has the same formulation and manufacturing process/equipment/site as the Phase 3 clinical/primary stability batches, however; the to-be-marketed drug product and the Phase 3 clinical drug product contain a drug substance from different manufacturers and differ in the debossing. The data provided by the Applicant in response to the FDA Information Request confirmed that the proposed changes in the debossing letters of the tablet and the manufacturing site of the drug substances do not impact the in vitro drug dissolution profiles of the final to-be-marketed drug product in the QC dissolution medium. The Applicant did not formally request a BCS designation, (b) (4)

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for glecaprevir and pibrentasvir in accordance with 21 CFR Part 25.31(b). The claims for categorical exclusion from an EA for both actives were found to be acceptable, once supported by additional information for pibrentasvir.

C. Special Product Quality Labeling Recommendations (NDA only)

The following comments should be considered during labeling negotiations:

1. According to 21 CRF 201.57(c)(12)(i), Section 11 must also contain the route of administration, and pharmacological class of the drug.

2. Please list therapeutically inactive ingredients in alphabetical order by name and distinguish from the identification statement of the active ingredient(s).

3. Please provide drafts of immediate container (blisters) labels for your drug product.

D. Final Risk Assessment (see Attachment I at end of this Review)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209394

Date: June 6, 2017

Stephen Miller

Digitally signed by Stephen Miller
Date: 6/06/2017 11:09:35PM
GUID: 508da7210002a000609476bbecd040f0

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Glecaprevir and Pibrentasvir Tablets (NDA 209394)

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)		M	See bulleted outline in Executive Summary	Acc	Additional testing of initial commercial lots was agreed-upon with the Applicant
Content uniformity		M	See Process Review	Acc	
Microbial limits		L		Acc	
(b) (4) of bi-layer tablets		L			
Dissolution – BCS Class II or IV		M	Method and AC are suitably discriminatory.	Acc	

Stephen Miller

Digitally signed by Stephen Miller
Date: 6/06/2017 11:09:41PM
GUID: 508da7210002a000609476bbecd040f0

LABELING

I. Package Insert

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	MAVYRET (glecaprevir and pibrentasvir) tablets
Dosage form, route of administration	Tablets, for oral use
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	Tablets: 100 mg glecaprevir and 40 mg pibrentasvir

2. *Section 2 Dosage and Administration*

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)	The recommended oral dosage of MAVYRET is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	100 mg glecaprevir and 40 mg pibrentasvir per tablet
Active moiety expression of strength with equivalence statement	100 mg glecaprevir (anhydrate) 40 mg pibrentasvir
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	MAVYRET tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with “NXT” on one side.

4. *Section 11 Description*

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	MAVYRET (glecaprevir and pibrentasvir)
Dosage form and route of administration	Film-Coated Immediate Release Tablets for oral use
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>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Not included – please see the comment at the end of this review.
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

Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	100 mg/40 mg glecaprevir/pibrentasvir tablets
Available units	MAVYRET is dispensed in a 4-week (monthly) or an 8-week carton. Each weekly carton contains seven daily dose wallets. Each monthly carton contains four weekly cartons. Each 8-week carton contains 2 monthly cartons.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink-colored, film-coated, oblong biconvex shaped, debossed with "NXT" on one side.
Special handling (e.g., protect from light)	No
Storage conditions	Store at or below 30°C (86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	AbbVie Inc., North Chicago, IL 60064, Illinois, USA

The following labeling issues will be addressed to the applicant:

Section 11:

- ***According to 21 CRF 201.57(c)(12)(i), Section 11 must also contain the route of administration, and pharmacological class of the drug.***
- ***Please list therapeutically inactive ingredients in alphabetical order by name and distinguish from the identification statement of the active ingredient(s).***

1. **Reviewer's Assessment of Package Insert:** Adequacy of labeling related to Package Insert is under discussion with the Review Team. Comments to the applicant (including CMC related sections) will be addressed and are coordinated by OND.

II. Labels:

1. ***Blister Labels***

Immediate container (blisters) labels are not provided.

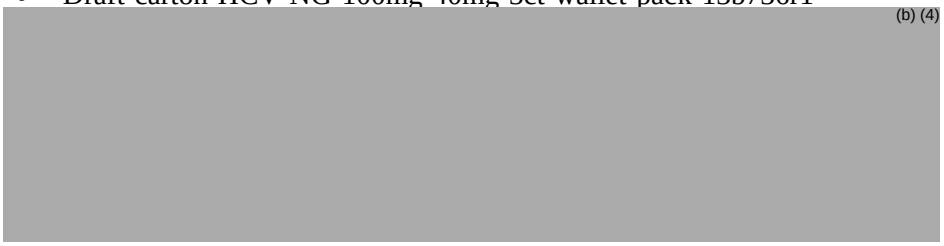
The following comment will be sent to the applicant:

- ***Please provide drafts of immediate container (blisters) labels for your drug product.***

2. *Carton Label*

There are 6 immediate container labels provided:

- Draft-carton-HCV-NG-100mg-40mg-3ct-wallet-pack-13b736r1



As an example of a carton label, a label of Draft-carton-HCV-NG-100mg-40mg-3ct-wallet-pack is provided below:

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Not provided	Adequate
Dosage strength	Not provided	Adequate
Net contents	Not provided	Adequate
"Rx only" displayed prominently on the main panel	Not provided	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Not provided	Yes
Lot number and expiration date (21 CFR 201.17)	Not provided	No – The comment will be sent to the applicant
Storage conditions	Not provided	Yes
Bar code (21CFR 201.25)	Not provided	Yes
Name of manufacturer/distributor	Not provided	Yes
And others, if space is available	NA	NA

Adequacy of the carton labeling is under review. The following labeling issues will be addressed to the applicant:

- ***Please provide drafts of immediate container (blisters) labels for your drug product.***

Reviewer's Assessment of Labels: CMC related comments in the PI are coordinated by OND. Any CMC issues will be addressed to the applicant, along with comments issued from all other disciplines of the Review Team. Adequacy of labels and labeling will continue to be discussed with the Review Team.

Overall Assessment and Recommendation:

Adequacy of drug product labeling is under discussion with the Review Team.

Primary Labeling Reviewer Name and Date: Danuta Gromek-Woods, Ph.D., 22-Mar-2017

Secondary Reviewer Name and Date: George Lunn, Ph.D., 23-May-2017

George Lunn

Digitally signed by George Lunn
Date: 5/25/2017 04:24:35PM
GUID: 508da72000029f40833369b0a181e8b3

Danuta Gromek-Woods

Digitally signed by Danuta Gromek-Woods
Date: 5/26/2017 11:25:35AM
GUID: 505c6aed000011bcf869666d0c4c8a78

ENVIRONMENTAL ANALYSIS

R Regional Information

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for glecaprevir and pibrentasvir 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 for pibrentasvir. The provided information, as well as other information obtained by FDA, was reviewed. The claim for a categorical exclusion from an EA for glecaprevir and pibrentasvir was found to be acceptable. (b) (4)

Environmental Analysis

The applicant submitted a claim for a categorical exclusion from an EA for glecaprevir and pibrentasvir in accordance with 21 CFR Part 25.31(b). FDA subsequently requested that, to assist the review of these "next generation" new molecular entities (NMEs), the applicant provide estimated use in kg/year and expected introduction concentration (EIC) in µg/L. The applicant responded with estimates of each active ingredient across five years, with the highest estimates for the year 2020: (b) (4) kg and (b) (4) µg/L for glecaprevir, and (b) (4) kg and (b) (4) µg/L for pibrentasvir.

While the EICs submitted by the applicant were below the categorical exclusion level of 1 µg/L (1 ppb), they were above the approximately 0.0023 µg/L EIC (100 kg) currently being used by FDA to screen which NME exclusions to examine in more detail. In addition, data from the Toxicology Written Summary, module 2.6.6, indicated the possibility of reproductive/developmental toxicity, albeit at high levels (sections 2.6.6.6.2.3 and 2.6.6.6.2.4 for glecaprevir and sections 2.6.6.7.2.3 and 2.6.6.7.2.4—incorrectly labeled as 2.6.6.6.2.3 and 2.6.6.6.2.4—for pibrentasvir). Therefore, FDA utilized a fish plasma model (FPM) to screen for aquatic risk, per Huggett et al. (2003), as described below.

- For glecaprevir, based on an EIC of (b) (4) µg/L, a therapeutic concentration of (b) (4) µg/mL (Cmax from section 2.5.3.3 of module 2.5, Clinical Overiew), and a log D of (b) (4) (pH 7.4; from www.chemspider.com), the effect ratio (b) (4) which is (b) (4) orders of magnitude greater than the threshold of 1,000 from Huggett et al. (2003) that below which would indicate the need for additional information.
- For pibrentasvir, based on an EIC of (b) (4) µg/L, a therapeutic concentration of (b) (4) µg/mL (Cmax from section 2.5.3.3 of module 2.5, Clinical Overiew), and a log D of (b) (4) (pH 7.4; from www.chemspider.com), the (b) (4) which is more than (b) (4) orders of magnitude less than the threshold of 1,000 from Huggett et al. (2003).

Given the above results for pibrentasvir, FDA decided to collect additional data and conduct addition analysis to determine whether a categorical exclusion is appropriate for pibrentasvir. In particular, FDA asked the applicant to provide a more realistic predicted environmental concentration (PEC), more

relevant toxicity data (including from similar molecules), and any other relevant and available information or environmental risk assessments. The applicant responded by noting that they are

(b) (4)

[redacted]

Reference: 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.

Reviewer's Assessment:

The claim for a categorical exclusion from EAs per 21 CFR Part 25.31(b) is appropriate for the anticipated amounts of each drug to be used (< 1 µg/L EICs). The calculations appear accurate, and adequate statements of no extraordinary circumstances per 21 CFR 25.15 are present.

The clinical and nonclinical toxicity data for glecaprevir indicating possible reproductive/developmental toxicity provide little or no indication of hormonal effects or other extraordinary circumstances at the expected exposure levels in the environment. The effects seen were at the highest doses only, above clinical exposures. The studies also were range finding, and the vehicle was implicated. The FPM ER for glecaprevir is (b) (4) orders of magnitude above the threshold of 1,000. Finally, the mechanisms of action does not appear to include hormonal involvement. 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 no additional information was requested from the applicant following the initial request for the EIC. FDA finds that the claim for a categorical exclusion for glecaprevir is acceptable. (b) (4)

For pibrentasvir, the clinical and nonclinical toxicity data provided by the applicant also provided little or no indication of hormonal effects. As with glecaprevir, the effects seen were above clinical exposures, the studies were range finding, and the vehicle was implicated. The ER from the FPM is less than 1, however, and thus additional information had been requested. The additional data included an (b) (4)

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 pibrentasvir is acceptable. (b) (4)

Primary EA Reviewer Name and Date: James P. Laurenson, May 24, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): M. Scott Furness, May 26, 2017

James Laurenson

Digitally signed by James Laurenson
Date: 5/25/2017 07:41:04AM
GUID: 51dc6bdb0000c62de59b85452e59746f

Michael Furness

Digitally signed by Michael Furness
Date: 5/25/2017 09:40:56AM
GUID: 502e8c7600003dd8331cf6eebf43697a

BIOPHARMACEUTICS

Product Background:

NDA: 209394
Submission Type: 505(b)(1) NDA; Double NME (Priority)
Drug Product Name / Strength: MAVIRET® (glecaprevir/pibrentasvir) Film-Coated Tablets, 100 mg/40 mg
Route of Administration: oral
Dosage form: Immediate release, fixed-dose combination [FDC] bilayer Tablet
Applicant Name: AbbVie, Inc.
Associated INDs: IND #127416 (glecaprevir/pibrentasvir); IND #116170 (pibrentasvir or ABT-530); IND #116169 (glecaprevir or ABT-493)

Review Summary:

For the routine QC testing of the Glecaprevir/Pibrentasvir Fixed Dose Combination (100mg/40mg) Bilayer Tablets at batch release and during shelf-life, the following proposed dissolution method and acceptance criteria as shown in the table below, are found acceptable.

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddles), with sinker	75 ± 4 rpm	0.1 M Acetate Buffer (pH 4 ± 0.05) with 1% polysorbate 80 (37 ± 0.5°C)	1000 mL	Glecaprevir: NLT (b)(4)% at 45 min; NLT % at 120 min Pibrentasvir: NLT (b)(4)% at 45 min; NLT % at 120 min

The to-be-marketed drug product has the same formulation and manufacturing process/equipment/site as the Phase 3 clinical/primary stability batches, however; the to-be-marketed drug product and the Phase 3 clinical drug product contain a drug substance from different manufacturers and differ in the debossing. The data provided by the Applicant in response to the FDA Information Request confirmed that the proposed changes in the debossing letters of the tablet and the manufacturing site of the drug substances do not impact the *in vitro* drug dissolution profiles of the final to-be-marketed drug product in the QC dissolution medium.

From the Biopharmaceutics perspective, NDA 209394 for Glecaprevir/Pibrentasvir Fixed-Dose Combination Tablet, 100 mg/40 mg is recommended for **APPROVAL**.

List Submissions reviewed:
SDN-1, 12/14/2016 - (Original)
SDN-8, 02/09/2017- (Applicant's Response to Quality Information Request)
SDN-14, 03/7/2017 – (Applicant's Response to Quality Information Request)
SDN-24, 3/28/2017 – (Applicant's Response to Quality Information Request)

Highlight Key Outstanding Issues from Last Cycle:
Not Applicable

Concise Description Outstanding Issues:
None

BCS Designation

The Applicant did not formally request a BCS designation, but stated that both glecaprevir (GLE) and pibrentasvir (PIB) are BCS-4 (low solubility/low permeability) drug substances.

Reviewer's Assessment:
Solubility: Per BCS criteria, both crystalline GLE and PIB exhibit *low solubility* because the amounts (100 mg and 40 mg, respectively) contained in the bilayer tablet will not be solubilized completely in 250 mL media with pH across the entire physiologic range. At least 8.3×10^{-4} mg/mL GLE and at least $< 9.1 \times 10^{-5}$ mg/mL PIB dissolve in various pH media; see the respective pH-solubility profiles at 37°C in Section 3.2.S.1.3 of the NDA. The solubility of GLE increases with increasing pH whereas PIB's solubility decreases with increasing pH, but the solubilities are both very low at pH range 3.5 to 4.5. Note that per the proposed labeling, the recommended oral dosage for the treatment of Hepatitis B Virus (HBV) infection is three (3) GLE/PIB (100 mg/40 mg) tablets once daily with food.

Permeability: As reported by the Applicant, using the MDCK cell line, GLE drug substance exhibits *low/moderate permeability* (P_{app} 1.4×10^{-6} cm/sec). PIB drug substance exhibits *low permeability* (P_{app} $<1 \times 10^{-6}$ cm/sec).

Dissolution: The film-coated GLE/PIB (100mg/40 mg) bilayer tablet exhibits pH-dependent GLE and PIB dissolution in various pH buffer media (without surfactant) consistent with the respective pH-solubility trends observed for the crystalline drug substances. In the proposed QC dissolution medium (1000 mL of pH 4.0 acetate buffer with 1% polysorbate 80), (b) (4)% of the label amounts of GLE and PIB dissolves within 120 minutes, suggesting *slow dissolution* of the proposed immediate-release drug product.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

DISSOLUTION METHOD – *ACCEPTABLE*

The proposed QC dissolution method uses USP Apparatus 2 (paddle) rotating at 75 ± 4% rpm; 1000 mL of 0.1M acetate buffer (pH 4 ± 0.05) with 1% polysorbate 80; 37 °C ± 0.5°C; (b) (4) sinker. HPLC-UV (at 247 nm) is used for quantification of the two APIs in the dissolution samples.

Justification for Proposed Method Parameters

(b) (4)

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

Dissolution of Stability Samples

There were no apparent trends in the GLE and PIB dissolution data for the primary stability batches at the proposed dissolution specification time points (45 and 120 min), and the proposed dissolution acceptance criteria were met over 12 months storage at 30°C/60%RH and 40°C/75%RH. For GLE, the reported ranges of the means were 41 – 52% (45 min) and 92 – 98% (120 min). For PIB, the reported ranges of the means were 52 - 64% (45 min) and 95 - 101% (120 min). The proposed shelf-life for the GLE/PIB film-coated bilayer tablets in the proposed packaging when stored below 30°C is 24 months.

Clinical relevance of dissolution method & acceptance criteria

Reviewer's Assessment: *IVIVR (but not Level* (b) (4) *IVIVC) demonstrated*

Using a two-stage, numerical deconvolution approach, the Applicant was not successful in establishing a Level (b) (4) IVIVC for the proposed GLE/PIB fixed-dose combination drug product. Overall, the model appears to be slightly to significantly under-predicting the observed GLE and PIB plasma exposures (as shown in Figures 6 and 6A), and the Applicant was not able to derive a single correlation between *in vitro* and *in vivo* profiles for all three formulations (administered under fasted conditions). The unsuccessful Level (b) (4) VIVC was attributed to confounding factors such as the boosting effect of GLE on PIB plasma concentrations, as well as the use of PK data from three different Phase 1 bioavailability studies which was believed to have contributed to increased variability thereby making it difficult to meet the predictability criteria for establishing IVIVC.

Figure 6. Observed and Predicted Plasma Concentration-Time Profiles for Glecaprevir (ABT-493)

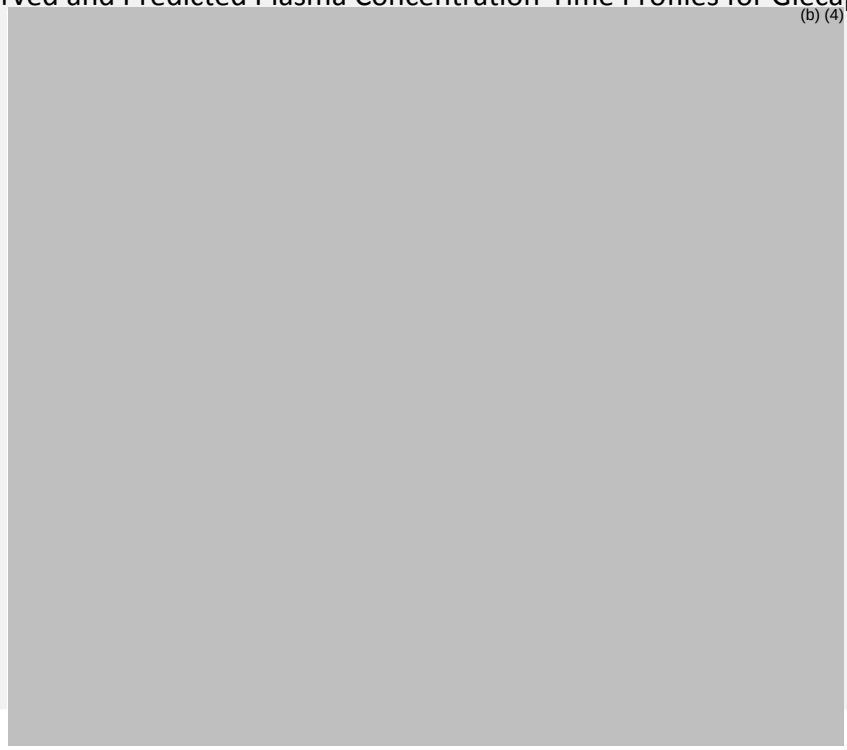
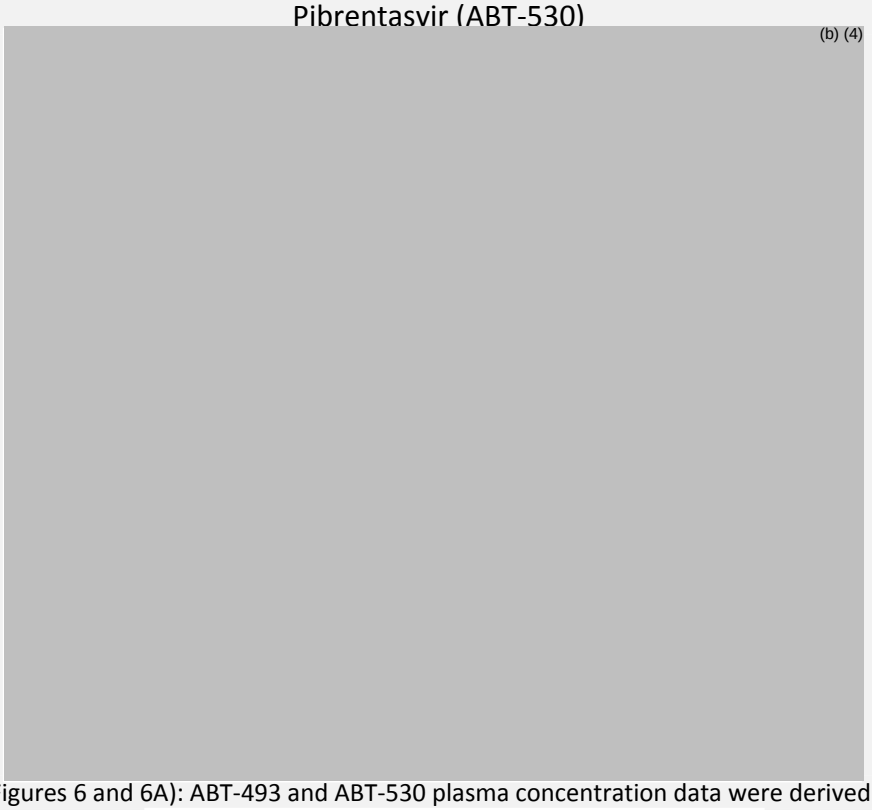


Figure 6A. Observed and Predicted Plasma Concentration-Time Profiles for Pibrentasvir (ABT-530)



Reviewer Note (Figures 6 and 6A): ABT-493 and ABT-530 plasma concentration data were derived from three Phase 1 bioavailability studies (b) (4) and M14-715(film-coated bilayer tablet)].

Bridging of Formulations

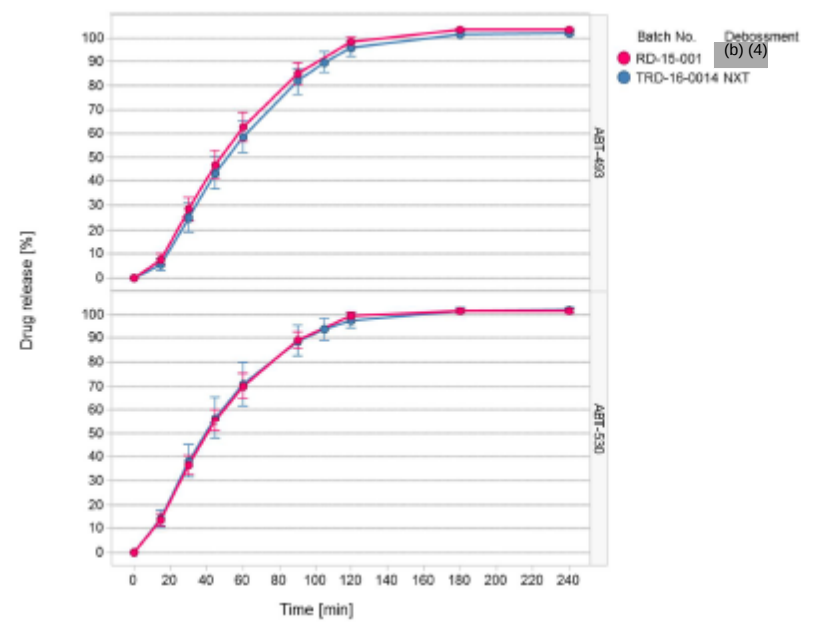
Reviewer's Assessment:

The proposed commercial FDC tablet has the same formulation and manufacturing site/equipment/process and has a similar (b) (4) manufacturing scale as the tablets evaluated in the "Registrational" (Phase 3) clinical trials and in pivotal Phase 1 Studies (M14-714 [Relative BA and Food-Effect], and M14-715[DDI]). Note that the 3 primary registration stability batches with up to 12-month stability data were also used in the "Registrational" (Phase 3 and pivotal Phase 1) clinical trials.

Additionally, in response to the Reviewer's Information Request, the Applicant provided comparative dissolution profile data to support the change in the debossing letters. That the dissolution profiles of GLE and PIB were approximately or exactly superimposable between the pivotal clinical trial/primary stability batch and a developmental batch (fully representative of the proposed commercial manufacturing process/site/scale) manufactured with the proposed commercial debossment "NXT" confirms that this particular Appearance change and the drug

substances manufacturing site change [from Abbvie Chicago (US) to Abbvie Sligo (Ireland)] have no significant impact on the performance of the proposed commercial film-coated GLE/PIB bilayer tablet (Figure 7).

Figure 7. Comparative Dissolution Profiles of the Film-Coated Bilayer Tablets used in the Pivotal (Phase 3/Phase 1) Clinical Trials versus the Final Proposed Commercial Film-Coated Bilayer Tablets



Reviewer Notes: The reference batch (RD-15-001) was used in Phase 3 Clinical trials (M15-464/ENDURANCE-2, M13-594/ENDURANCE-3) and the Phase 1 Studies M14-714 (Relative BA and Food-Effect) and M14-715 (DDI with omeprazole). The test batch (TRD-16-0014) is different only from the reference batch in terms of the debossment (b) (4) → "NXT"), the slight higher (b) (4) manufacturing scale, and the drug substances manufacturing site (AbbVie USA → Abbvie Ireland). Note that per the FDA SUPAC-IR Guidance, a change in the manufacturing site of the finished *drug product* requires documentation of comparable *in vitro* dissolution profile in the application/compendial medium between the pre-change and the post-change drug products. Based on the Division of Biopharmaceutics Internal Policy Guidance regarding changes in the site of *drug substance* manufacture, the same principle is applied here.

Additionally, the dissolution profile data at batch release of three production batches were comparable to those of the 3 primary stability/clinical trial batches; the f_2 values were all >50 for all possible pair-wise comparisons. These data provide further evidence that the change in the *drug substances* manufacturing site, i.e., from Abbvie Chicago (US) to Abbvie Sligo (Ireland) as well as the (b) (4) scale change between the primary registration/clinical batches and the production batches did not impact the dissolution profiles of GLE and PIB.

QUALITY ASSESSMENT

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

A biowaiver was not requested nor required. The proposed fixed-dose combination (FDC) product contains two New Molecular Entities (NMEs); clinical PK and clinical studies were conducted to evaluate the PK, efficacy and safety of the proposed strength of the proposed commercial (formulation of the) FDC film-coated bilayer tablet.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (5/11/2017)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur with Dr. Gieser's assessment and recommendation.

Elsbeth Chikhale, PhD (5/22/2017)

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 5/22/2017 02:21:15PM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 5/22/2017 04:02:55PM
GUID: 50743ccc000031928b54eba1769a5df9