CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215110Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 215110
Assessment # 1

Drug Product Name	Mavyret (glecaprevir/pibrentasvir oral pellets)
Dosage Form	oral pellets
Strength	Glecaprevir 50 mg and Pibrentasvir 20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Abbvie
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 001	12/10/2020	Original NDA
eCTD 005	1/21/2021	Multiple
eCTD 006	2/23/2021	Quality
eCTD 011	3/23/2021	Quality
eCTD 015	4/16/2021	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Karina Zuck	Ali Al Hakim
Drug Product	George Lunn	Erika Englund
Manufacturing	Chunsheng Cai	Bo Jiang
Microbiology	NA	
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	NA	

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)		III	(b) (4)	Adequate	4/23/2021	Reviewed by G.Lunn

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	209394	Mavyret Tablets
IND	127416	Glecaprevir and pibrentasvir tablets
IND	116170	pibrentasvir
IND	116169	Glecaprevir

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology		Refer to pharm/tox review		
CDRH	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ). The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 5/11/2021.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This NDA describes the proposed pediatric formulation for Mavyret, which will contain pink film coated glecaprevir pellets and yellow pibrentasvir pellets. The film coated tablet formulation of Mavyret was approved under NDA 209394 on 08/03/2017. NDA 209394 Supplement 13 is concurrently under review by OLDP. The proposed product in NDA 215110 will be supplied as fixed dose coated oral pellets in a sachet. The NDA describes a single strength of the product (glecaprevir/pibrentasvir 50 mg/20 mg).

Proposed Indication(s) including Intended Patient Population	Treatment of Hepatitis C Virus (HCV)
Duration of Treatment	16 weeks
Maximum Daily Dose	250 mg/100 mg per day for oral pellets
Alternative Methods of Administration	The oral pellets are administered with soft food with a low water content

B. Quality Assessment Overview

Drug Substance: Adequate

The majority of the supporting CMC information for both drug substances is referenced to the previously approved NDA 209394 (Mavyret, glecaprevir and pibrentasvir tablets). The only new information in this NDA included the COAs for batches of both drug substances used to manufacture the registration drug product batches.

The polymorphic form for Glecaprevir (b) (4) and Pibrentasvir (b) (4) is controlled in the respective drug substance specifications. The retest period for both drug substances is (b) (4) months when stored (b) (4)

This NDA is recommended for approval from a Drug Substance perspective. For additional details, refer to the review by Karina Zuck, Ph.D.

Drug Product: Adequate

The drug product consists of a child-resistant sachet containing pink film-coated pellets of glecaprevir and yellow film-coated pellets of pibrentasvir providing a total of 50 mg and 20 mg, respectively. The pellets are approximately 2 mm in diameter. This product is dosed by sprinkling the pellets onto soft foods immediately before consumption. The pellets are reasonably stable in the specified foods (peanut butter, chocolate-hazelnut spread, cream cheese, Greek yogurt, and thick jam) as shown by data in the NDA. The in-use stability studies evaluated the product at 15 min and 60 min, and all foods had acceptable stability over 15 min.

The applicant proposes an expiration dating period of 24 months with a storage statement of "Store at or below 30°C" which is reasonable.

The applicant submitted claims for both substances for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b). The claims for exclusion were found acceptable.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by George Lunn, Ph.D.

Labeling: Adequate

The labeling recommendations have been communicated to the OND PM.

Manufacturing: Adequate

(b) (4)

(b) (4)

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama on 5/11/2021.

This NDA is recommended for approval from a Manufacturing perspective. For additional details, refer to the review by Chunsheng Cai, Ph.D.

Biopharmaceutics: Adequate

The Applicant considers glecaprevir and pibrentasvir as BCS-IV (low solubility/low permeability) crystalline drug substances. (b) (4) The oral pellets exhibited pH dependent dissolution in various pH buffer media. The proposed dissolution method and acceptance criterion (Q = (b) (4)% at 45 min for both APIs) were found adequate in this NDA.

The final proposed to-be-marketed GLE/PIB oral pellets in a unit-dose sachet was evaluated in primary stability studies and in clinical studies for PK, efficacy and safety.

Since there is only one proposed strength, a biowaiver request was not applicable.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to the review by Gerlie Gieser, Ph.D.

Microbiology (if applicable): N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**

Assay		Low		Acceptable	
Physical State		medium		Acceptable	
Microbial Limits		Low		Acceptable	
Dissolution		Low	Dissolution acceptance criterion consistent with pivotal clinical lot data	Acceptable	
Dosing Accuracy		Low		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies *(Specify discipline, such as Environmental)*

Application Technical Lead Name and Date:

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(b) (4)

R REGIONAL INFORMATION

Environmental

The applicant submitted claims for both substances for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included use amounts that were consistent with the claim. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15. The applicant previously had submitted EA data to support the exclusion claim for the same substances under NDA 209394. The FDA EA Team reviewed the previous EA data and conclude that the previous data and subsequent review are still relevant, and that approval of this current application would not result in a significant environmental impact. Therefore, the claims for exclusion from an EA is acceptable (e-mail from Jim Laurenson, 1/5/21).

Assessment: *{Adequate}* The claims should be accepted.

Methods Validation or Verification Package

A Methods Validation Package, consisting of links to the analytical procedures and a promise to provide samples if required, is provided.

Assessment: *{Adequate}*

Comparability Protocols

None

Assessment: *{Adequate}*

Post-Approval Commitments

None

Assessment: *{Adequate}*

Lifecycle Management Considerations

No particular considerations. The drug product consists of film-coated pellets filled in child-resistant sachets. On stability there are no out of specification results and no obvious trends.

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: George Lunn, 4/23/21

Secondary Assessor Name and Date (and Secondary Summary, as needed): Erika Englund, 4/23/21

George Lunn

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Erika Englund

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Note: Review of oral pellets sections only. Additionally, the term "oral pellets" (not "pellets") should be used throughout.

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Mavyret oral pellets	Adequate
Established name(s)	glecaprevir and pibrentasvir oral pellets	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral Pellets: 50 mg glecaprevir and 20 mg pibrentasvir	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No score	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	The pellets should be taken together, with food, once daily. In addition, the pellets for the total daily dose should be sprinkled on a small amount of soft food with a low water content that will stick to a spoon (b) (4) be swallowed without chewing (e.g., peanut butter, chocolate hazelnut spread, cream cheese, thick jam, or Greek yogurt). Liquids or foods that would drip or slide off the spoon (b) (4) as the drug may dissolve quickly and become less effective. The mixture of food and pellets should be swallowed within 15 minutes of preparation; the pellets should not be crushed or chewed.	Data in the NDA Section 3.2.P.2.6 showed that the pellets are reasonably stable in the specified foods (peanut butter, chocolate-hazelnut spread, cream cheese, Greek yogurt, and thick jam) for 15 minutes.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Pellets	Adequate
Strength(s) in metric system	50 mg and 20 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not a salt	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	pink and yellow coated pellets in unit-dose packets. Each packet contains 50 mg glecaprevir and 20 mg pibrentasvir	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No score	Adequate
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	

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Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Mavyret (glecaprevir and pibrentasvir) oral pellets	Adequate
Dosage form(s) and route(s) of administration	Oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not a salt	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	colloidal silicon dioxide, copovidone (type K 28), croscarmellose sodium, hypromellose 2910, iron oxide red, lactose monohydrate, polyethylene glycol 3350, propylene glycol monocaprylate (type II), sodium stearyl fumarate, titanium dioxide, and vitamin E (tocopherol) polyethylene glycol succinate	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Glecaprevir is a HCV NS3/4A PI and pibrentasvir is a HCV NS5A inhibitor	Adequate

Chemical name, structural formula, molecular weight	Present in each case	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	Solubilities are provided	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Present	Adequate
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Each packet contains 50 mg glecaprevir/20 mg pibrentasvir pink and yellow pellets	Adequate
Strength(s) in metric system	50 mg and 20 mg	Adequate
Available units (e.g., bottles of 100 tablets)	60 packets in a carton	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	pink and yellow pellets NDC 0074-2600-60	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No score	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	NA	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	NA	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at or below 30°C (86°F).	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	NA	
Include information about child-resistant packaging	oral pellets are dispensed in child-resistant unit-dose packets	Adequate

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by AbbVie Inc., North Chicago, IL 60064	Adequate

(b) (4)

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Item	Information Provided in the NDA	Assessor's Comments
Patient Information		
Patient Information	See above	DMEPA found that "86°F (30°C)" with the F value first was acceptable.
Instructions for Use	See above	Seems reasonable from the CMC perspective but would defer to DMEPA

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label


(b) (4)

	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	MAVYRET glecaprevir/pibrentasvir Each packet contains pink and yellow pellets	Generally adequate. Change "pellets" to "oral pellets".
Dosage strength	50 mg/20 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Adequate
Net contents (e.g. tablet count)	50 mg/20 mg	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	NDC 0074-2600-60	Adequate
Lot number and expiration date	Both present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at or below 30º C (86º F).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Not present	Should be added

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	AbbVie Inc. North Chicago, IL 60064	Adequate
Medication Guide (if applicable)	See above	Adequate
No text on Ferrule and Cap overseal	NA	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	NA	

3.2 Carton Labeling

	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	MAVYRET glecaprevir/pibrentasvir Each packet contains pink and yellow pellets	Generally adequate. Change "pellets" to "oral pellets".
Dosage strength	50 mg/20 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Adequate
Net contents (e.g. tablet count)	60 packets	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	NDC 0074-2600-60	Adequate
Lot number and expiration date	Both present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at or below 30º C (86º F).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Not present	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling

Name of manufacturer/distributor	AbbVie Inc. North Chicago, IL 60064	Adequate
Medication Guide (if applicable)	See above	Adequate
No text on Ferrule and Cap overseal	NA	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	See Package Insert for full Prescribing Information Area for pharmacy label See top of carton for Customs Country of Origin	Adequate

Assessment of Carton and Container Labeling: *{Adequate/Inadequate}*

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

"Oral pellets" is the correct terminology and should be changed throughout in the PI and container and carton labels. This issue has been communicated to the OND review team and DMEPA.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 5/13/21

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Erika Englund, Ph.D., 5/13/21

George Lunn

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Erika Englund

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 215110 (cross-referenced to NDA 209394/S-13)
Assessment Cycle Number	Original 505(b)(1) NDA
Drug Product Name/ Strength	MAVYRET® (glecaprevir/pibrentasvir) Pellets, 50 mg/20 mg in a sachet
Route of Administration	Oral, Immediate Release
Applicant Name	Abbvie
Therapeutic Classification/ OND Division	Hepatitis C NS3/4A protease inhibitor/Division of Antivirals
Proposed Indication/ Proposed Dosage	Based on bodyweight: 3 to 5 sachets once daily. Mix the pellets with one of the specified soft-food vehicles. Take with food.

Assessment Recommendation: **APPROVAL**

Assessment Summary:
The proposed dissolution method (as shown in the table below) was deemed adequate by FDA prior to NDA submission. Based mainly on the submitted dissolution profile data of the pivotal clinical trial lot, the proposed dissolution acceptance criterion was found acceptable.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
1 (basket)	75 rpm	14.8 mM Sodium Acetate Buffer, pH 4.0 (equivalent to 0.1 M Acetate) with 1.0% (w/v) Polysorbate 80 (37 ± 0.5°C)	500 mL	Q = (b) % at 45 minutes

As shown in the table below, the final risk assessment ranking for dissolution is low.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	BCS-IV drug substance; adequate dissolution method	Low	Dissolution acceptance criterion consistent with pivotal clinical lot data

The final proposed to-be-marketed GLE/PIB oral pellets (in unit dose sachet) was evaluated in the non-intensive PK (non-IPK) portion of the pivotal clinical efficacy/safety trial, and in primary stability studies. The Office of Clinical Pharmacology confirmed that (1) an adequate PK bridge was established between the GLE/PIB presentations used in the IPK and non-IPK portions of the clinical trial, and (2) the resulting drug exposures achieved when the oral pellets were mixed with soft-food vehicles were within the therapeutic range as observed when the approved MAVYRET® oral tablets were administered to adults. In terms of ability to protect the proposed drug product, the proposed commercial packaging configuration [i.e., unit dose sachet with secondary packaging (carton box)] is not anticipated to perform worse than the packaging configuration (i.e., unit dose sachet) that was used to contain the drug product evaluated in primary stability studies.

List of Submissions Assessed:

Document(s)	Date Received
SDN-1 Original NDA	12/10/2020
SDN-6 (Response to Cumulative Quality IR – including cream cheese stability, and Early Biopharm IR)	2/23/2021

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

The Applicant considers glecaprevir and pibrentasvir as BCS-IV (low solubility/low permeability) crystalline drug substances. Like the approved MAVYRET® glecaprevir/pibrentasvir oral tablets, the oral pellets use (b) (4) Note that majority of the CMC information for the drug substances (b) (4) in the current NDA for the pellets were cross-referenced from the NDA of the approved MAVYRET® oral tablets (NDA 209394).

Assessment: Adequate

Solubility: *Low*
The Biopharmaceutics Review of NDA 209394 for the approved MAVYRET® oral tablets states: “At least 8.3 x 10^{-4} mg/mL GLE and at least < 9.1 x 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.”

Thus, the quantities of GLE and PIB (50 mg and 20 mg, respectively) in the sachet would not be expected to completely dissolve in 250 mL media across the physiologic pH range. Note that the proposed labeling of the GLE/PIB oral pellets states that the recommended bodyweight-based dosage in younger children is three to five 50 mg/20 mg packets of the pellets once daily.

Permeability: *Low*
The Biopharmaceutics Review of NDA 209394 for the approved MAVYRET® oral tablets states: "As reported by the Applicant, using the MDCK cell line, GLE drug substance exhibits *low/moderate permeability* (P_{app} 1.4 x 10^{-6} cm/sec). PIB drug substance exhibits *low permeability* (P_{app} <1 x 10^{-6} cm/sec).

Dissolution: *Not Rapid to Very Rapid*
The film-coated GLE/PIB (50mg/20 mg) pellets exhibit 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 (500 mL of pH 4.0 buffer with 1% polysorbate 80), (b) (4)% of the label amounts of GLE and PIB dissolves within (b) (4) minutes, suggesting *slow dissolution* of the proposed immediate-release drug product.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD – Adequate

Note that the proposed dissolution method [USP Apparatus 1 (basket) at 75 rpm; 500 mL of 14.8 mM Sodium Acetate Buffer, pH 4.0 (equivalent to 0.1 M Acetate) with 1.0% (w/v) Polysorbate 80; 37°C ± 0.5°C] had previously been determined to be acceptable for the routine QC of the glecaprevir/pibrentasvir 50 mg/20 mg oral pellets in a sachet at batch release and stability testing. For details, refer to the Biopharmaceutics Review of IND 127416 (SDN-183) by Drs. Gerlie Gieser and Elsbeth Chikhale finalized in DARRTS on 10/27//2020. The approved dissolution method parameters are excerpted below.

Parameter	Condition
Apparatus	USP/Ph. Eur. Dissolution Apparatus 1 (Basket, (b) (4)
Basket Mesh Size	(b) (4)
Medium	500 mL of 14.8 mM Sodium Acetate Buffer adjusted to pH 4.0 (b) (4) (equivalent to 0.1 M Acetate) with 1.0% (w/v) Polysorbate 80
Medium deaeration	No
Temperature	37°C ± 0.5°C
Rotation Speed	75 RPM ± 4%
Filter	(b) (4)
Sampling time points	Multiple (10, 15, 20, 30, 40, 45, 50, 60 and 90 minutes)
Volume Replacement	Not Applicable

Test Sample: entire contents of one sachet. Protect from Light.

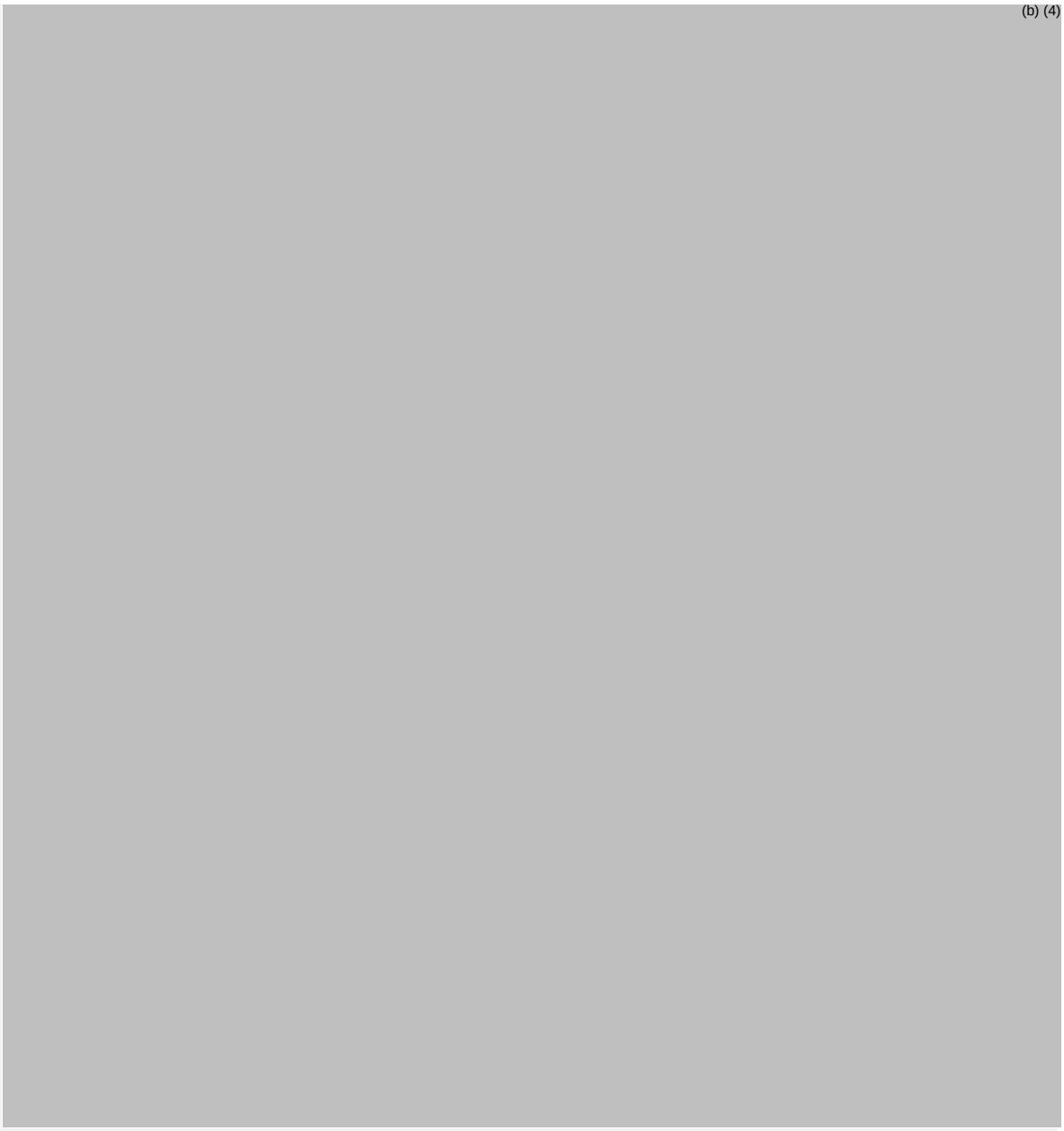
The sampling time points in the table above are used to obtain dissolution profile data. Quantification of drugs in the dissolution samples is accomplished using HPLC with UV detection at 247 nm.

Note also that based on the Applicant's IR response in SDN-6, the Drug Product Reviewer (George Lunn) confirmed the adequacy of the analytical method validation for dissolution.

DISSOLUTION ACCEPTANCE CRITERIA – Adequate

Based on the dissolution data of clinical, primary stability and (b) (4) batches of the proposed drug product, the Applicant proposed a dissolution acceptance criterion of "Q = (b) (4)% at 45 minutes" for both APIs. (b) (4)

Based mainly on the dissolution profile data of the pivotal clinical lot (1109257, as shown in Reviewer Figure 1) which is also one of three primary registration lots of the proposed commercial drug product, as well as the capability to reject lots with unacceptable quality (b) (4) the proposed dissolution acceptance criterion (Q = (b) (4)% at 45 min for both APIs) is acceptable.



Dissolution on Stability

Based on 12 months of long-term (30°C/75% RH) and 6 months of accelerated (40°C/75% RH) stability data for three primary stability lots, the proposed expiration dating period for the fixed-dose combination of GLE/PIB oral pellets in sachets is 24 months when stored at or below 30 ℃. The Applicant reported that there was no meaningful change in GLE and PIB dissolution of the primary stability lots during the study period. Note that one of these three primary stability lots was used in the non-IPK portion of the pivotal clinical trial (see Reviewer Figure 1).

Long-term stability data are also available for one early clinical batch of each active ingredient coated pellets (Lots 1000207309 and 1000207308) packaged in HDPE bottles with desiccant. Per the Applicant, there was no significant change in dissolution and other quality attributes of the clinical pellets lots during the 24-month long-term storage and the 6-month accelerated stability study periods.

The Drug Product Reviewer will determine the acceptability of the proposed expiration dating/shelf life of the drug product based on the totality of the provided stability information.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Not Applicable*

Reviewer Note:
The drug substances (b) (4) . Thus, the quality control strategy for the active ingredients, intermediates and the finished product of the proposed oral pellets (b) (4) were made consistent with that in place for the approved oral tablets.

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: *Adequate*

For ease of dosage form administration to younger children and for taste-masking purposes, in the pivotal Phase 2/3 clinical PK/efficacy/safety study (Study M16-123/Part 2) and in the proposed labeling, the proposed GLE/PIB oral pellets are recommended to be incorporated into soft food vehicles (b) (4) and low water content such as 1 – 2 tsp of peanut butter, chocolate hazelnut spread, cream cheese, thick jam or Greek yoghurt) prior to oral administration. Note that MAVYRET™ oral tablets are approved to be co-administered with a meal, so incorporation into edible soft-food vehicles (as recommended for the proposed to-be-marketed oral pellets) is not anticipated to significantly alter GLE/PIB clinical PK as compared to when the whole tablets are taken by adults and older children with food. Additionally, the Clinical Pharmacology Reviewer (Dr. Xiaoxia Yang) concluded that when administered with label-recommended soft-food vehicles in patients <45 kg, the proposed MAVYRET® oral pellets dosage produced GLE and PIB PK parameters falling within the ranges observed in patients ≥ 45 kg given the approved dosage of MAVYRET® oral tablets with food.

The Applicant stated [redacted] (b) (4) [redacted] the labeling also states: "the oral pellets should not be crushed or chewed."

Furthermore, the Applicant indicated that low moisture soft-food vehicles were recommended based on acceptable product chemical stability found after food contact at ambient temperature for the recommended in-use dosing period, not to exceed 15 minutes; per the Drug Product Reviewer (Dr. George Lunn), the provided in-use stability data of the oral pellets in the label-recommended soft-food vehicles are adequate to support the proposed labeling statement: "The entire mixture of food and oral pellets should be swallowed within 15 minutes of preparation.

REVIEWER NOTE:
The proposed MAVYRET® oral pellets and the approved MAVYRET® bilayer tablets will share a common labeling/package insert. In the Response to the Clinical Pharmacology Information Request (SN-11), the Applicant submitted Relative BA data showing that grinding or crushing the oral tablets clinically significantly reduces glecaprevir/pibrentasvir exposures, and produces unacceptable organoleptic properties and palatability profile as compared to the whole or intact MAVYRET® tablets. Thus, FDA will add the following labeling statement: "The tablets should not be ground or crushed." [redacted] (b) (4) [redacted] Furthermore, in the labeling meeting, the FDA review team decided that the use of half-split tablets will not be recommended as an alternative to the oral pellets for patients who cannot swallow the whole tablets.

B.12 BRIDGING

Assessment: *Adequate*

In summary, the PK bridge between the final proposed commercial presentation (a fixed-dose combination of film-coated glecaprevir coated pellets and pibrentasvir coated pellets in a sachet) and the earlier clinical presentation (consisting of separately packaged film-coated glecaprevir and pibrentasvir coated pellets) was adequately established. A comparison overview of the drug

products evaluated in the pivotal clinical efficacy/safety study, BA/BE and primary stability studies is provided in the following table.

Component	Phase 1, Phase 2/3 Clinical (Bioavailability Pharmacokinetic Studies)		Phase 2/3 Clinical and Primary Stability
Clinical Protocol(s)	M17-142 and M16-123 (IPK portion)		M16-123 (non-IPK portion)
Formulation	GLE Coated Granules	PIB Coated Granules	GLE/PIB Coated Granules
Composition	GLE portion as in *Section 3.2.P.1*	PIB portion as in *Section 3.2.P.1*	As in *Section 3.2.P.1*
Presentation Type	Co-administered with PIB Coated Granules	Co-administered with GLE Coated Granules	Unit-dose sachets co-filled with GLE Coated Granules and PIB Coated Granules
Package Configuration	HDPE bottle	HDPE bottle	Sachet

IPK (intensive PK); non-IPK (non-intensive PK); GLE (glecaprevir); PIB (pibrentasvir)
Source: Table 1 of 2.7.1 Biopharmaceutics Summary

The details of the bridging assessment are provided below.
The final proposed commercial fixed-dose combination oral GLE/PIB coated pellets in sachet drug product is represented by the GLE/PIB coated pellets (Lot 1109257) that was used in the non-intensive PK **(non-IPK) portion** of the pivotal Phase 2/3 Clinical study (Study M16-123/Part 2;) and the primary stability studies. Lot 1109257 was produced by the proposed commercial drug product manufacturer (Abbvie/Italy) [redacted (b) (4)]

Clinical PK, efficacy and safety data are also available for the [redacted (b) (4)]% GLE coated pellets and the [redacted (b) (4)]% PIB coated pellets (Lots 1000207309 and 1000207308, respectively) that were mixed into soft food vehicles and administered together in the **IPK portion** of Study M16-123/Part 2. Both lots of GLE coated pellets and PIB coated pellets were manufactured by a developmental drug product manufacturer, Abbvie/Germany, and packaged separately in HDPE bottles with desiccant. These coated pellets separately packaged in HDPE bottles were also used in early clinical studies including Relative BA/Food-Effect Study M17-142 which compared the bioavailability of the oral pellets to the approved oral tablet in healthy adults.

The FDA Clinical Pharmacology Reviewer (Dr. Xiaoxia Yang) confirmed that based on Population PK analysis, GLE and PIB exposures in both the non-IPK portion and the IPK portion (at the final fixed dose combination GLE/PIB ratio of 50 mg/ 20 mg) of Part 2 of the pivotal clinical study were within therapeutic ranges as observed in adults and adolescents dosed with the MAVYRET® bilayer tablet. (b) (4)

(b) (4)

Reviewer Note:
Comparative *in vitro* dissolution bridging of the IPK and non-IPK presentations (GLE + PIB and GLE/PIB) oral pellets was not used to support the scientific bridge because dissolution testing of the earlier clinical lots used in the IPK portion of the pivotal clinical study was performed separately instead of in combination.

B. 13 BIOWAIVER REQUEST

Assessment: *Not Applicable*

There is only one proposed strength of the GLE/PIB oral pellets which was evaluated for clinical PK, efficacy, and safety.

R. REGIONAL INFORMATION

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: *Gerlie Gieser, Ph.D. 4/23/2021*

Secondary Assessor Name and Date: *Elsbeth Chikhale, Ph.D. 4/23/2021*

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 4/23/2021 11:15:41AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 4/23/2021 11:41:28AM
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