CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215110Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 10, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 215110 and NDA 209394/S-13
Product Name and Strength:	Mavyret (glecaprevir/pibrentasvir) Oral Pellets 50 mg/20 mg
Applicant/Sponsor Name:	AbbVie
OSE RCM #:	2020-2603-1
DMEPA Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU), container label, and carton labeling received on May 19, 2021 for NDA 215110 and NDA 209394/S-13 for Mavyret (glecaprevir/pibrentasvir) oral pellets. The Division of Antivirals (DAV) requested that we review the revised IFU, container label, and carton labeling for Mavyret (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additionally, the Applicant revised the Patient Information in response to a recommendation we made in conjunction with our Division of Medical Policy Programs (DMPP) colleagues during labeling negotiations.

[a] Bhalodia A. Human Factors Study Report and Label and Labeling Review for Mavyret (NDA 215110 and NDA 209394/S-13). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 10. RCM No.: 2020-2602, 2020-2603, 2020-2604.

2 DISCUSSION AND ASSESSMENT

The Applicant did not implement all of the recommendations to the IFU and the Patient Information as we recommended however, they have provided a justification and response for our consideration.

Regarding the IFU, we note the Applicant did not implement our recommendation to consider relocating the information regarding mixing the product with food and the amount of food to use from IFU Step 1 to IFU Steps 3 or 4. The Applicant clarified that the intention of including this instruction in IFU Step 1 is to provide initial information upfront to patients and caregivers that the packets need to be mixed with food, with further details on the types of food to be used provided in subsequent steps. The Applicant also stated that providing this information in IFU Step 1 helps to set expectations regarding the dosing regimen and encourages users to read the IFU to find the correct dosing vehicles instead of relying on past medication experience. We find the Applicant's proposal to retain the information in IFU Step 1 acceptable.

Regarding the Patient Information, we note the Applicant agreed to remove the bulleted information that provided abbreviated instructions for use, with exception of the following bullet, "Mix the pellets with a small amount of recommended food and swallow (see Instructions for Use for list of recommended food)." The Applicant proposes to retain this bulleted information because it is a useful reminder to patients that the pellets must be mixed with a small amount of recommended food and it ties in with the next bullet which instructs the patient not to store any leftover mixture. The Applicant also stated that this bullet also helps to reinforce cross-reference to the IFU for the recommended food. We find this proposal acceptable.

3 CONCLUSION

We find the revised carton labeling and container label acceptable and we have no additional recommendations at this time.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AVANI BHALODIA
06/10/2021 10:53:58 AM

EBONY A WHALEY
06/10/2021 11:00:23 AM

EBONY A WHALEY on behalf of LOLITA G WHITE
06/10/2021 11:01:25 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 9, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 215110 and NDA 209394/S-13
Product Type:	Multi-Ingredient Product
Drug Constituent Name and Strength	Mavyret (glecaprevir/pibrentasvir) Oral Pellets 50 mg/20 mg
Rx or OTC:	Rx
Applicant/Sponsor Name:	AbbVie
Submission Date:	December 10, 2020, February 16, 2021, February 26, 2021
OSE RCM #:	2020-2602, 2020-2603, 2020-2604
DMEPA Human Factors Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1. REASON FOR REVIEW

AbbVie submitted a new NDA 215110, in order to introduce a new formulation for Mavyret oral pellets. This product is already approved and marketed as oral tablets under NDA 209394. The two formulations will share a single package insert.

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 215110 and NDA 209394/S-13 for Mavyret (glecaprevir/pibrentasvir) Oral Pellets 50 mg/20 mg. The proposed product is not a combination product but has administration instructions that warrant the evaluation of HF data.

1.1 PRODUCT DESCRIPTION

Mavyret oral pellets are intended to treat children from ages 3 to less than 12 years old with chronic hepatitis C virus genotypes 1, 2, 3, 4, 5, or 6 infections without cirrhosis or with compensated cirrhosis (Child-Pugh A). The Applicant intends for Mavyret oral pellets to be dispensed in unit-dose packets in cartons. Each carton contains 60 packets, and each packet contains 50 mg glecaprevir/20 mg pibrentasvir pink and yellow pellets. Depending on the weight of the child, 3 to 5 packets are used for each daily dose. See Appendix A for additional details.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

Mavyret was approved on August 3, 2017 under NDA 209394 as a tablet for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A). Mavyret is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

On April 9, 2019, the Applicant submitted a HF validation study protocol for Mavyret oral pellets under IND 127416. We recommended that the Applicant address the identified areas of concern prior to commencing the HF validation study[1]. On August 9, 2019, the Applicant submitted responses to our Human Factors Validation Study Protocol Advice. We provided responses in an HF protocol memorandum[2].

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

[1] Flint, J., Wilson, V. Human Factors Validation Study Protocol Review for Mavyret pellets IND 127416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 31. RCM No.: 2019-794.

[2] Flint, J., Vaughan, V. Review of Sponsor's Response to Human Factors Protocol Recommendations Memo for Mavyret pellets IND 127416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 16. RCM No.: 2019-794-1.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface is designed to support the safe and effective use of the proposed product.

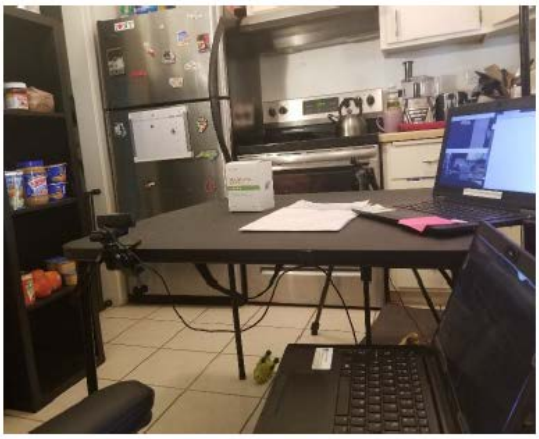
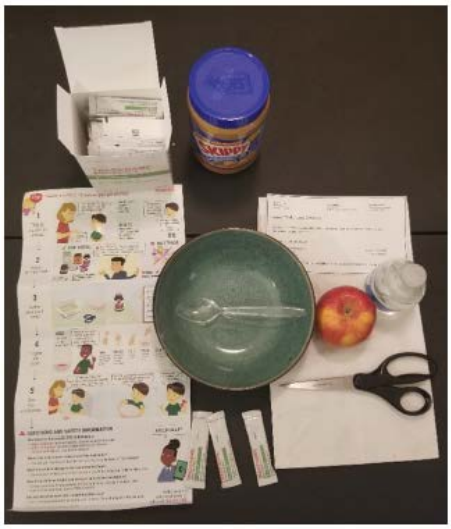
3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix D for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	• 15 untrained caregiver participants (In-person sessions), • 16 untrained pediatric patient participants aged 10-12 (In-person sessions), and • 15 trained pediatric patient participants aged 10-12 (Virtual video sessions)
Training	Based on earlier HF testing, untrained pediatric patient participants indicated that there would be some level of adult supervision and instruction in this instance. As such, the Applicant included an arm of trained pediatric patient participants in HF validation testing. The 30-minute training session consisted of a virtual simulation from a researcher, who provided the pediatric patient participant with steps necessary for use of the medication, simulating instruction like that of a caregiver. This training utilized the IFU and was based on the steps taken by the caregivers who participated in the previous summative testing sessions. The researcher provided moments throughout the training for the pediatric patient participant to ask questions during the training. This training consisted of how to use the materials from the pharmacy to identify, prepare, and administer a correct dose of medication. Pediatric patient participants returned for a second virtual remote session within 24-48 hours of their training, and a different member of the research team moderated the test session. A live video broadcast of "virtual hands" was shown to the pediatric patient participant, and the virtual hands followed the steps to prepare a dose based only on the direction of the pediatric patient participant.
Test Environment	For the in-person sessions, reasonable measures were taken to simulate a kitchen environment (refrigerator and pantry stocked with food, and countertop workstation). Common household materials were also supplied (e.g., pens, trash can, scissors, bowls, spoons, paper towels) and reasonable indoor lighting levels were ensured. However, no specific efforts were made

	to control distractions that may occur naturally during testing (e.g., ambient noise, participant's cell phone ringing). For the remote sessions, a kitchen environment (including refrigerator and pantry stocked with food, tabletop workstation) was broadcasted for the pediatric patient participant to view via a virtual video platform. Common household materials were supplied (e.g., pens, trash can, scissors, bowls, spoons, paper towels) and reasonable indoor lighting levels were ensured. However, no specific efforts were made to control distractions that may have occurred naturally during testing (e.g., ambient noise, participant's cell phone ringing). **Figure 1.** Pantry and refrigerator set up with acceptable and unacceptable foods for remote testing  **Figure 2.** Lab environment for remote testing

	 
Sequence of Study	Simulated use Knowledge task questions Root Cause Analysis

3.2 RESULTS AND ANALYSES

Table 3 describes the study results, AbbVie's analyses of the results, and DMEPA's analyses and recommendations.

Our review of the study methodology identified concerns with acceptability of the results from the trained pediatric participant user group. Specifically, the remote testing environment was not reflective of real world use due to the use of "virtual hands", which did not allow for participants to have any hands-on interaction with the product. This raises concerns regarding whether such data can be extrapolated or relied upon in our evaluation of the user interface. We determined that due to flaws in the methodology of the remote testing, such results cannot be considered in our overall evaluation of acceptability of the user interface. Furthermore, we also note that the user group was trained. While training may occur for some users of this product, it does not represent a higher risk use scenario of no training that may occur in real world use. We note that this is a product intended for home use where it cannot be guaranteed that training will consistently or routinely occur, nor did the sponsor develop a specific training program as part of their user interface that they validated as part of this study. As such, we focused our evaluation on the data collected for the untrained pediatric participants' that the Applicant provided.

Table 3: Summary and Analyses of Study Results				
Tasks	**Number and Description of Failures/Use Errors, Close Calls and Use Difficulties**	**Applicant's Root Cause Analysis (RCA)**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Administer the medication (Users simulated administration of 3 packets)	N = 15 Failures • 2 caregiver participants and 12 untrained pediatric participants only administered the contents of one packet. • 1 untrained pediatric participant administered the contents of five packets. Subjective feedback of note included: • "I would do just one…it [IFU] says 'packet' not 'packets', so I would think just one." • "…[points to IFU -Step 4] it only showed them using one packet." • "…I saw one, so I just thought to use one [packet]" and pointed to Step 4. • "I thought I was taking 1 dose of it" • "…I picked one like I was doing it like ones I do at home".	The Applicant's RCA for the caregivers user group mainly attributed the failures to the wording in IFU Step 4 which stated 'packet' and not 'packets' and negative transfer from how they prepare their child's current medicine. The Applicant's RCA for untrained pediatric participants mainly attributed the failures to users relying on previous experience, not reading the IFU or pharmacy label, unfamiliarity with word sachet, confused due to graphic and wording in the instructions 'packet' vs 'packets' in Step 4 or typically having parental assistance.	The Applicant stated that no mitigation strategies are needed.	Based on the Applicant's use-related risk analysis (URRA), if the wrong number of packets are selected, there is risk of overdose or underdose resulting in increased or decreased exposure. Our review of the study results and subjective feedback finds that improvements can be made to the IFU to increase understanding of how many packets to select for each patient specific dose. Our review notes that some participants got confused due to wording in the instructions 'packet' vs 'packets' in IFU Step 4. Failure to complete this step or to complete this

	• Usually they [parents] just leave me out one dosage/one pill, so I'm used to taking one..." • "…did not really read the instruction before… I thought I knew what to do but then it was in a packet shape instead of pills….packet shape told me there were little pieces instead of the pill form which I was expecting. I would take it the same way as my pill because it's basically just smaller pills." • "I didn't want to risk overdosing, I did not know how much would be enough for this". • Did not use pharmacy label • "If you take out a bunch you could lose them, but if you take out 1, you won't." • "My mom would set out my medicine on the table". • "I just assumed because if it was meant to pick two it would just come in one packet if you were meant to have two doses… It makes the most sense to me to choose 1 [packet] since that's what I'm used to doing...also when I read the instructions it said to only take one".			step correctly may lead to patient harm (e.g. overdose or underdose). We disagree with the Applicant that no further mitigation is needed. **As such, we provide IFU recommendation #2 in Table 5 to revise the IFU to refer to plural "packets" instead of "packet" or add the phrase "all of the packets"**. In this particular instance, we find this revision can be implemented without submission of additional HF validation data.

	• "It [IFU] said don't give yourself a double dose of it" • Focused on speech bubbles • Participant felt like it's not too much medicine, so she decided to take 4 or 5.			
Knowledge task question 11: What should you not do while taking the medicine? Correct answer: not chew the granules located in Step 2 or Step 5. (corresponds to critical task of 'Administer the medication')	N = 3 incorrect responses/did not locate • 3 untrained pediatric participants had incorrect responses Subjective feedback of note included: • Shouldn't drink water and located it in Questions and Safety Information. • Mentioned not to mix it and indicated the answer was in Step 4. • Stated 'don't give yourself a double dose of medicine and don't mix it with other foods' in Question and Safety Information.	The Applicant's RCA attributed failures to one untrained pediatric participant looking for the keyword 'medicine' in the IFU to indicate what he should not do, not reading the full speech bubble in Step 5 and fatigue. One of the pediatric patient participants stated that he did not read the full speech bubble in Step 5 stating "do not chew the granules". He stated he only read half of the statement.	The Applicant did not provide any mitigation strategies.	Based on the Applicant's use-related risk analysis (URRA), if the user chews the granules, there is risk of decrease exposure- lack of effect, and potential of virological resistance due to incomplete dose. Our review of the study results and subjective feedback indicated there is a lack of prominence of this important information in IFU Step 5. Failure to complete this step or to complete this step correctly may lead to patient harm (e.g. lack of effect, and potential of virological resistance due to incomplete dose). The Applicant did not provide

				any mitigation strategies. **As such, we provide IFU recommendation #3 in Table 5 to revise the IFU to separate the two statements in the speech bubble on the left panel of Step 5 such that both statements stand out and are distinct.** In this particular instance, we find this revision can be implemented without submission of additional HF validation data.

3.3 ANALYSIS OF OTHER TASK ERRORS

The HF validation study showed use errors, (e.g. failures, difficulties, and close calls) with the following three critical tasks and two non-critical tasks. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis and Applicant's proposed risk mitigation strategy to determine acceptability. The following list of critical and non-critical tasks represent those where we determined that the residual risk is acceptable without further need for risk mitigation strategies:

- Choose an appropriate food
- Open Packet(s) (assessed via knowledge task)
- Mix Medication (no crushing)
- Patient takes medication within 15 minutes (assessed via knowledge task)
- Patient eats meal or snack with/after medication (assessed via knowledge task)

3.4 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the submitted packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. These recommendations can be implemented without submission of additional HF validation data.

Table 4: Identified Issues and Recommendations for Division of Antivirals (DAV)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Full Prescribing Information			
1.	Each numerical value in Table 3: Recommended Dosage in Pediatric Patients 3 Years of Age and Older is not followed by units of measure. value.	Lack of units of measure may contribute to confusion and wrong dose errors.	Revise Table 3 to ensure that each instance of weight is followed by the unit of measure to mitigate the risk of wrong dose errors. For example, revise "20 to less than 30 kg" to "20 kg to less than 30 kg".

Table 5: Identified Issues and Recommendations for AbbVie (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	The content in Step 1 can be better presented to align with the step title. For example, Step 1 is titled, "Find the number of packets" however, there is also information in that step regarding mixing the product with food. Specifically, , we note the middle panel states, "Mix the day's packets together with food." and "About 1-2 teaspoons of an acceptable food like the ones below".	Instructions for use should follow a naturalistic flow and sequence of events.	Consider relocating information regarding mixing the product with food and the amount of food to use from Step 1 to in Step 3 or in Step 4.
2.	Step 4 Prepare the dose does not indicate that mixing and administration of more than one packet is required to complete the dose.	In the human factors validation study, four participants noted confusion regarding the number of packets to use based on the wording 'packet' vs 'packets' and/or imagery of one packet being opened and poured out. Confusion regarding the correct number of packets to mix and administer might result in wrong dose errors.	Revise Step 4 to refer to plural "packets" instead of "packet" or add the phrase "all of the packets".

3.	The presentation of the information in Step 5 Give the medication lacks prominence. For example, the left panel has two statements in one speech bubble "It's important that we take this right away. Be careful not to chew the pellets".	In the human factors validation study (knowledge task questions), there was subjective feedback from one participant which indicated that they did not read the full speech bubble. Based on URRA, if the user does not read the second statement in the speech bubble and chews the pellets, there is risk of decreased exposure- lack of effect, and/or potential of virological resistance due to incomplete dose	We recommend you separate the two statements such that both statements stand out and are distinct. For example, you may revise into two separate speech bubbles or two separate statements.
Container Labels			
1.	A linear barcode is missing from the immediate container label.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual container as required per 21CFR 201.25(c)(2).
2.	As currently presented, the manufacturer name competes in prominence with the established name and strength.	The prominence of the manufacturer's name may take the readers' attention away from important information such as established names and strength.	We recommend decreasing the font size of the manufacturer name as it competes in size and prominence with the other important information like drug name and strength.
3.	As currently presented, the (b) (4) statement is not included.	The container label is not in concurrence with 21 CFR 201.55, "...labels for prescription drugs	Add the statement "Recommended Dosage: See Prescribing Information."

		bear a statement of the recommended or usual dosage."	
4.	The display of the finished dosage form can be improved.	To increase readability of important product characteristics, the finished dosage form should appear either in the same line as the established name or directly below the established name.[3]	Revise the container label display to display the dosage form to show Mavyret (glecaprevir/pibrentasvir) Oral Pellets or Mavyret (glecaprevir/pibrentasvir) Oral Pellets Additionally, other instances of the dosage form should refer to product according to the correct dosage form term, 'oral pellets'.
Carton Labeling			
1.	As currently presented, the (b) (4) statement is not in the correct format.	Per 21 CFR 201.55, "…labels for prescription drugs bear a statement of the recommended or usual dosage."	To ensure consistency with the Prescribing Information, revise the statement (b) (4) to read "Recommended Dosage: See Prescribing Information."
2.	The location of the finished dosage form can be improved.	To increase readability of important product characteristics, the finished dosage form should	Consider relocating dosage form "Oral Pellets" so that it appears either in the same

[3] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

		appear either in the same line as the established name or directly below the established name.[4]	line as the established name or directly below the established name.

[4] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

4. CONCLUSION AND RECOMMENDATIONS

Based on the results of the HF validation study, we have determined that certain changes should be implemented in the design of the user interface to further support safe and effective use of the product. These changes can be implemented without additional HF validation testing. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for the Division and Table 5 for AbbVie. We ask that the Division convey Table 5 in its entirety to AbbVie so that recommendations are implemented prior to approval of this NDA 215110 and NDA 209394/S-13.

4.1 RECOMMENDATIONS FOR ABBVIE

Our evaluation of the proposed packaging, label and labeling and the results of your HF validation study identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 5 and we recommend that you implement these recommendations prior to approval of this NDA 215110 and NDA 209394/S-13.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Mavyret (glecaprevir/pibrentasvir) Oral Pellets that AbbVie submitted on 12/10/2020.

<table>
<tr><th colspan="2">Table 6. Relevant Product Information</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Therapeutic Drug Class or New Drug Class</td><td>NS3/4A protease inhibitor, NS5A inhibitor</td></tr>
<tr><td>Active Ingredient (Drug or Biologic)</td><td>glecaprevir/pibrentasvir</td></tr>
<tr><td>Indication</td><td>To treat children (b) (4) with chronic hepatitis C virus genotypes 1, 2, 3, 4, 5, or 6 infections without cirrhosis or with compensated cirrhosis.</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>Pellets for oral administration</td></tr>
<tr><td>Strength</td><td>glecaprevir 50 mg / pibrentasvir 20 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Depending on the weight of the child, 3-5 packets are used for each daily dose.
<table>
<tr><th>Body Weight (kg) or Age (yrs)</th><th>Daily Dose of glecaprevir/pibrentasvir</th><th>Dosing of MAVYRET</th></tr>
<tr><td>Less than 20 kg</td><td>150 mg/60 mg per day</td><td>Three 50 mg/20 mg packets of oral pellets once daily</td></tr>
<tr><td>20 to less than 30 kg</td><td>200 mg/80 mg per day</td><td>Four 50 mg/20 mg packets of oral pellets once daily</td></tr>
<tr><td>30 to less than 45 kg</td><td>250 mg/100 mg per day</td><td>Five 50 mg/20 mg packets of oral pellets once daily</td></tr>
<tr><td>45 kg and greater
OR
12 years of age and older</td><td>300 mg/120 mg per day</td><td>Three 100 mg/40 mg tablets once daily</td></tr>
</table></td></tr>
</table>

How Supplied Container Closure/Device Constituent	Carton containing 60 packets, IFU, and a US Package Insert (USPI)
Storage	Store at or below 30°C (86°F)
Intended Users	Caregivers for pediatric patients with HCV or by pediatric patients as young as 10 years old
Intended Use Environment	home environment

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On January 21, 2021, we searched previous DMEPA reviews relevant to this current review using the terms, 127416, 215110, and Mavyret.

B.1.2 Results

Our search identified two previous reviews[5,6], and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\nda215110\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hcv\5354-other-stud-rep\hf\hf-summative-rpt-peds-oral-med.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On February 11, 2021, we sent an Information Request to obtain Summary Use FMEA that is clear and readable. The Applicant responded on February 16, 2021. See response in link below:
  - \\CDSESUB1\evsprod\nda215110\0007\m1\us\111-information-amendment\agency-response-2021-feb-11.pdf
- On February 24, 2021, we sent an Information Request to obtain clarification on which participants participated in in-person sessions and which participants participated in remote sessions. We also asked the Applicant to provide an updated uFMEA to include

[5] Flint, J., Wilson, V. Human Factors Validation Study Protocol Review for Mavyret pellets IND 127416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 31. RCM No.: 2019-794.

[6] Flint, J., Vaughan, V. Review of Sponsor's Response to Human Factors Protocol Recommendations Memo for Mavyret pellets IND 127416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 16. RCM No.: 2019-794-1.

analysis of the risk of a caregiver and pediatric patient delivering a double dose. The Applicant responded on February 26, 2021. See response in links below:

- \\CDSESUB1\evsprod\nda215110\0009\m1\us\111-information-amendment\agency-response-2021-feb-24.pdf
- \\CDSESUB1\evsprod\nda215110\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hcv\5354-other-stud-rep\hf\hf-summative-rpt-peds-oral-med.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[7] along with postmarket medication error data, we reviewed the following Mavyret labels and labeling submitted by AbbVie.

- Container label received on December 10, 2020
  - EDR link: \\CDSESUB1\evsprod\nda215110\0001\m1\us\114-labeling\draft\carton-and-container\draft-cntnr-mavyret-50mg20mg-60ct-sachet-20065805.pdf
- Carton labeling received on December 10, 2020
  - EDR link: \\CDSESUB1\evsprod\nda215110\0001\m1\us\114-labeling\draft\carton-and-container\draft-carton-mavyret-50mg20mg-60ct-20065872.pdf
- Instructions for Use received on December 10, 2020
  - EDR link: \\CDSESUB1\evsprod\nda215110\0001\m1\us\114-labeling\draft\carton-and-container\typeset-draft-ifu-mavyret-50mg20mg-60ct-20065806.pdf
- Prescribing Information (Image not shown) received on April 20, 2020
  - EDR link: \\CDSESUB1\evsprod\nda215110\0016\m1\us\114-labeling\draft\labeling\neg-lbl-6951.docx

F.2 Label and Labeling Images

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

[7] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

AVANI BHALODIA
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EBONY A WHALEY
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EBONY A WHALEY on behalf of LOLITA G WHITE
06/09/2021 10:51:43 AM

IRENE Z CHAN
06/10/2021 10:02:39 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 10, 2021
To:	Myung-Joo Patricia, MS Senior Regulatory Project Manager Division of Antivirals (DAV)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	MAVYRET (glecaprevir and pibrentasvir)
Dosage Form and Route, Application Type/Number, Supplement Number:	tablets, for oral use, NDA 209394/S-013 coated pellet, for oral use, NDA 215110
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On December 10, 2020, AbbVie, Inc. submitted for the Agency's review an original New Drug Application (NDA) for MAVYRET (glecaprevir/pibrentasvir) coated pellets and a supplement to their NDA 209394/S-013 for MAVYRET (glecaprevir/pibrentasvir) tablets. The Applicant proposes a new dosage form MAVYRET coated pellets and a new indication for the treatment of adult and pediatric patients 3 years and older (weighing at least 12 kg) with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on December 16, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for MAVYRET (glecaprevir and pibrentasvir) tablets and coated pellets.

2 MATERIAL REVIEWED

- Draft MAVYRET (glecaprevir and pibrentasvir) tablets and coated pellets PPI and IFU received on December 10, 2020, and received by DMPP and OPDP on April 26, 2021.
- Draft MAVYRET (glecaprevir and pibrentasvir) tablets and coated pellets Prescribing Information (PI) received on December 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 26, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
05/10/2021 11:45:51 AM

NIMA OSSAREH
05/10/2021 11:47:16 AM

LASHAWN M GRIFFITHS
05/10/2021 12:00:05 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 5/10/2021

To: Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations for Infectious Diseases

From: Nima Ossareh, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for Mavyret™ (glecaprevir and pibrentasvir) tablets, for oral use; MAVYRET® (glecaprevir and pibrentasvir) oral pellets

NDA: 209394/Supplement 13; 215110

In response to DAVP consult request dated December 16, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for MAVYRET (glecaprevir and pibrentasvir) tablets, for oral use and MAVYRET® (glecaprevir and pibrentasvir) oral pellets.

PI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from Division of Antiviral Products (DAVP) on April 27, 2021, and are provided below.

PPI, IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

NIMA OSSAREH
05/10/2021 09:35:00 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/16/2021

TO: Division of Antivirals (DAV)
Office of Infectious Diseases (OID)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215110
NDA 209394/S-013

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the analytical site in February 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: NDAs 209394/S-006 (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	AbbVie, Inc.	Drug Analysis Department, 1 North Waukegan Road, North Chicago, IL

James J. Lumalcuri -S

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JAMES J LUMALCURI
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