CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215110Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 127416

MEETING REQUEST-
WRITTEN RESPONSES

AbbVie Inc.
Attention: Aansh Jarmarwala, PharmD
Senior Manager, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72/Bldg. AP30-1
North Chicago, Illinois 60064

Dear Dr. Jarmarwala:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glecaprevir and pibrentasvir 50 mg/20 mg oral pellets.

We also refer to your submission dated June 26, 2020, containing a meeting request. The purpose of the requested meeting was to discuss the efficacy and safety results from Study M16-123 (part 2), and to gain FDA feedback on the planned original NDA for GLE/PIB which includes data to support treatment of pediatric patients (≥ 3 to < 12 years of age) with the new pediatric formulation of oral pellets.

Further reference is made to our Meeting Granted letter dated July 21, 2020, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your July 24, 2020 background package.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at 301-796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Antivirals Group
Office of Regulatory Operations
Division of Regulatory Operations for Infectious Diseases
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	pre-NDA
Application Number:	IND 127416
Product Name:	**Mavyret (**glecaprevir and pibrentasvir)
Proposed Indication:	pediatric patients aged ≥ 3 to < 12 years with chronic HCV infection
Sponsor Name:	AbbVie Inc.
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Mavyret (glecaprevir and pibrentasvir [GLE/PIB]) 100 mg/40 mg tablets is approved for the treatment of patients with chronic hepatitis C viral (HCV) infection (genotype 1, 2, 3, 4, 5, or 6 infection). In the 4th quarter of 2020, AbbVie intends to submit an original NDA to update the Mavyret USPI with pharmacokinetic (PK), efficacy, and safety results from Part 2 of Study M16-123 to expand the patient population to include pediatric patients (aged ≥ 3 to < 12 years) infected with chronic HCV infection. The original NDA will also include results from Study M17-142, which evaluated bioavailability of the new pediatric coated pellets formulation compared with the adult bilayer tablet formulation and provided data to support the proposed dosing regimen in pediatric patients.

On June 26, 2020 AbbVie submitted a Type B pre-NDA meeting request, WRO. The responses to the questions contained in the July 24, 2020 meeting background package are contained below. A separate pre-NDA CMC only meeting request will be submitted.

AbbVie was granted Orphan Designation for the treatment of pediatric patients with chronic hepatitis C virus infection on January 9, 2017.

2.0 QUESTIONS AND RESPONSES

2.1. Clinical

Question 1: Does the Agency agree that the PK, efficacy, and safety data from Part 2 of Study M16-123 are sufficient to support submission and review of the planned NDA for the proposed indication?

FDA Response to Question 1: We agree that the PK, efficacy, and safety data from Part 2 of Study M16-123 are sufficient to support submission and review of the planned NDA for the proposed indication, however a final determination is a review issue.

2.2. Statistics

***Question 2**:* Does the FDA agree with AbbVie's proposal regarding provision of clinical and resistance datasets, PK datasets, and SAS programs for Study M16-123 and clinical and PK datasets for Study M17-142?

FDA Response to Question 2: We agree with AbbVie's proposal regarding provision of clinical and resistance datasets, PK datasets and SAS programs for Study M16-123 and clinical and PK datasets for Study M17-142.

For the submission of PK datasets and population PK analysis/datasets, please refer to Guidelines for submission of model data format and content (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format), and Study Data Technical Conformance Guide which can be found in https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

2.3 Regulatory

Question 3: Does the Agency agree that the format and content of the planned NDA, as indicated in the table of contents, along with the identified cross-reference strategy to NDA 209394 is adequate to be considered a complete application?

FDA Response to Question 3: We agree that the format and content as indicated in the table of contents of the planned NDA and the cross-reference strategy to NDA 209394 are sufficient.

Question 4: AbbVie intends to market both the adult and pediatric formulations under the same package insert. Does the Agency agree?

FDA Response to Question 4: Yes, we agree with your plan to include the pediatric oral pellet formulation in the same package insert as the adult tablet formulation. Please also see the additional comments below regarding the proprietary name review.

Question 5: Would the Agency agree that the proposed data package can fulfill the requirements agreed to in the Written Request, and would be supportive of a request for determination of pediatric exclusivity at the time of NDA filing?

FDA Response to Question 5:

If you have determined that you have met all criteria outlined in the Written Request, you may submit your request for determination of pediatric exclusivity with your application. The Agency will determine whether the submitted pediatric studies were conducted in accordance with commonly accepted scientific principles and protocols and reported in accordance with the requirements of filing of an original marking application or supplement to an approved application. Pediatric exclusivity determination is made by the Pediatric Exclusivity Board. You will be notified within 120

days upon receipt of the application on the Agency's final determination for pediatric exclusivity.

Question 6: Does the Agency agree that the proposed data package is in alignment with the requirements agreed to in the iPSP?

FDA Response to Question 6: Yes, it appears that there is alignment, however a final assessment will be a review issue.

2.4 Safety

Question 7: *Does the FDA agree with AbbVie's proposal for the 4-Month Safety Update for Study M16-123?*

FDA Response to Question 7: Yes, we agree with the proposal.

Additional Comments

Regulatory:

1. Please submit a supplement to the tablet NDA (NDA 209394) simultaneously with the original NDA for the oral pellets. In addition to the 356h form, the supplemental NDA should include the following information:
    a. Cover letter should explicitly state the submission is in response to a PREA PMR and all information associated with the PMR
    b. Letter of cross reference to the applicable applications
    c. Any exclusivity and/or patent claims
    d. Proposed labeling including SPL. Do not include the carton and container labeling for the oral pellets.

OSE/DMEPA:

2. We note your intention to market the oral pellet formulation under the same proprietary name, Mavyret, and prescribing information as the fixed-dose combination tablet formulation. As such, we recommend you submit a Request for Proprietary Name Review (PNR) along with your NDA submission.

    The PNR submission must include either labels and labeling (draft) or all the product characteristics for a submission without labeling as outlined on page 12 of the "Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names" (link below).

    Once we receive your name request for review, a 90-day OSE PDUFA clock will be opened and review of your proposed name will begin.

Please follow the procedure below to ensure that the document room accurately codes for a "Proprietary Name/Request for Review" and opens an OSE PDUFA clock for the NDA name reviews.

When submitting a proprietary name request for review to the Agency, it is crucial to:

- Check "Request for Proprietary Name Review" in Box 21 of FDA form 356h.
- Include the statement **"REQUEST FOR PROPRIETARY NAME REVIEW"** in bold capital letters, at the **top** of your cover letter **and** at the **top** of the first page of the main submission document (refer to the complete submission guidance link below).
- Please clearly state in the cover letter and supporting documentation the exact name you are requesting for review and include the phonetic spelling of the name.
- If you have already submitted draft labels & labeling, please add a link to them in the cover letter.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication and this specific patient population has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for

[4] https://www.fda.gov/media/84223/download
[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[6] https://www.fda.gov/media/85061/download

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/

ALICIA MORUF
08/25/2020 12:35:56 PM