

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208624Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # NDA 208624

SUPPL # N/A

HFD # 530

Trade Name VIEKIRA XR

Generic Name (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release, fixed-dose tablets

Applicant Name AbbVie Inc.

Approval Date, If Known TBD, estimate of July 25, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

This original NDA208624 is a new co-formulated, extended release, fixed dose combination (FDC) containing the drugs dasabuvir, ombitasvir, paritaprevir and ritonavir in a single tablet (Viekira XR), and is intended to replace the drug under the approved NDA 206619 from the same applicant, for Viekira Pak, which contains the same drugs, however these are administered as a FDC of ombitasvir, paritaprevir and ritonavir administered, but with separate dasabuvir. The review of this original NDA for Viekira XR was dependent on clinical data and exposure/response analyses from two relative bioavailability studies with cross-reference to the safety, efficacy and CMC

information within NDA 206619 for the approved Viekira Pak.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Not Applicable – not a supplement

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product. – **Not Applicable. FDC Product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires

metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

**NDA# 20659, 20680, 20945, NORVIR (ritonavir) capsules, tablets, oral solution
22417**

**NDA# 21226,21251,21906 KALETRA (lopinavir/ritonavir) capsules, oral solution,
tablets**

**NDA# 206619 VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir
FDC tablet and dasabuvir tablets)**

NDA# 207931 TECHNIVIE (ombitasvir, paritaprevir, ritonavir) tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

Note: Data submitted to support the review of this original NDA for Viekira XR included primarily BA/BE studies conducted in healthy volunteers and exposure / response simulations and analyses. The efficacy and safety for Viekira XR are supported by cross-reference to the approved NDA 206619 for Viekira PAK.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

Note: Per directions in Q1 above, skipped Q2 and went directly to Q3a

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation

been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Note: This application is supported by BA/BE studies only (new studies). The clinical Investigations and data submitted to the previously approved NDA 206619 for Viekira PAK provided the safety and efficacy information to support this new NDA 208624 for Viekira XR, which is a reformulation of the same drug components Viekira PAK into a single fixed dose combination tablet.

BA/BE investigational data and exposure/response assessments were submitted to the new NDA for Viekira XR to demonstrate equivalence.

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA 206619

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Suzanne Strayhorn
Title: Regulatory Project Manager, DAVP
Date: *Refer to electronic signature date*

Name of Office/Division Director signing form: Jeffrey Murray
Title: Deputy Division Director, DAVP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE K STRAYHORN
07/06/2016

JEFFREY S MURRAY
07/06/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208624	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A – original NDA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Viekira XR Established/Proper Name: dasabuvir, ombitasvir, paritaprevir, and ritonavir extended-release tablets Dosage Form: Extended Release Tablets (216 mg / 8.33 mg /50 mg /33.33 mg)		Applicant: AbbVie, Inc. Agent for Applicant (if applicable): N/A
RPM: Suzanne Strayhorn		Division: DAVP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action: Not Applicable</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is July 28, 2016 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<p style="text-align: center;">Not Applicable</p> <input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): **Type 3**
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: **Original NDA under standard review, No REMS**

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No N/A
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	N/A
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: 07/22/2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	Included Submitted 07/21/2016
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included Submitted 09/28/2015
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	Included Submitted 07/21/2016
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included Submitted 09/28/2015
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Included Submitted 07/11/2016
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	Letter: 01/19/2016 Review: 01/14/2016
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 12/01/2015 DMEPA: 07/15/2016; 06/13/2016 DMPP/PLT (DRISK): 06/17/2016 OPDP: 06/20/2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: <i>refer to OPQ integrated assessment for review</i> Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM Review: 12/01/2016
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	07/06/2016
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 06/06/2016 & 07/06/2016 If PeRC review not necessary, explain: N/A 	
❖ Breakthrough Therapy Designation	N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	N/A
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	N/A
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	07/22/2016: Inf. Req._Label 07/21/2016: Inf. Req._Label 07/20/2016: Inf. Req._Label 07/20/2016:General Adv. PMR 07/15/2016: Inf Req._Label 07/01/2016: Inf. Req._Carton 07/01/2016: Inf. Req._Label 06/21/2016: Inf. Req._Weight 06/08/2016: Inf. Req._Label 03/17/2016: Inf. Req._OPQ (p) 02/25/2016: Inf. Req._OPQ (p) 01/21/2016: Inf. Req._OPQ (p) 11/27/2015: File. Letter 10/15/2015: Ack. Letter
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	06/28/2016: To PeRC. Assessment 05/24/2016: To PeRC. Assessment 11/24/2015:Memo in Vivo Bioeq.
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>): Prelim. Comments Accepted in lieu of mtg 	07/13/2015: Prelim. Comments
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>): Prelim. Comments Accepted in lieu of mtg 	04/14/2015: Prelim. Comments
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>): WRO 	04/24/2015: OPQ Mtg

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	None
Division Director Summary Review (<i>indicate date for each review</i>)	7/22/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	07/07/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	07/21/2016 (1)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	07/15/2015 (Peds.) 07/08/2016 (fin. discl.) 06/22/2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Addressed in clinical review of 07/08/2016 (see above) N/A
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	06/21/2016
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	N/A
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
Statistical Review(s) (<i>indicate date for each review</i>)	None

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	Refer to CDTL Review under decisional memo's
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	06/23/2016
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	03/24/2016_AbbVie 01/08/2016 Celerion
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	06/23/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ ECAC/CAC report/memo of meeting	None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	June 23, 2016 (panorama)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	June 23, 2016 (panorama – included within the Integrated Quality Assessment document)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	Acceptable (refer to Integrated Quality Assessment document) Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	N/A
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	07/22/16 Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	7/22/2016 Done
❖ Ensure Pediatric Record is accurate	
❖ Send approval email within one business day to CDER-APPROVALS	7/22/2016, Done

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/s/

SUZANNE K STRAYHORN
07/26/2016

**PeRC Meeting Minutes
July 6, 2016**

PeRC Members Attending:

Lynne Yao

Meshaun Payne

Gettie Audain

Robert "Skip" Nelson

Barbara Buch

Rosemary Addy

Wiley Chambers

Jackie Yancy

Thomas Smith

George Greeley NON-RESPONSIVE

Yeruk Mulugeta

Freda Cooner

Maura O'Leary NON-RESPONSIVE

[REDACTED]

Gilbert Burkhart

Gerri Baer

John Alexander

Peter Starke

Julia Pinto NON-RESPONSIVE

Hari Sachs

Daiva Shetty

Agenda

NON-RESPONSIVE

9:20	NDA 208624	Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir Fixed-dose combination tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP	DAVP	Suzanne Strayhorn	Treatment of Hepatitis C Virus Infection (GT1)
------	---------------	--	------	-------------------	--

NON-RESPONSIVE

NON-RESPONSIVE

Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir FDC Tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP

- Approved Indication: Treatment of Hepatitis C Virus Infection (GT1)
- This product triggers PREA as a new active ingredient (new combination), new dosing regimen and has a PDUFA goal date of July 28, 2016.
- The division stated Viekira Pak™ (NDA 206619, approved on December 19, 2014) which consists of a fixed-dose tablet containing ombitasvir/paritaprevir/ritonavir tablets (12.5 mg/75 mg/50 mg, 2tablets QD) co-packaged with dasabuvir tablets (250 mg, 1 tablet BID).
- The current product has been reformulated to include the four active substances in Viekira Pak™ into a single tablet dosage form, containing dasabuvir 200 mg/ ombitasvir 8.33mg/ paritaprevir 50 mg/ ritonavir 33.33 mg, to enable a once daily (QD) dosing regimen (3 tablets).
- The division stated that the plan has now changed (to include weight based dosing) from what was previously discussed at the June 8, 2016 PeRC meeting.

- The division clarified that the sponsor is unable to formulate all the components of the product into a single formulation for younger children. Also, it is unlikely that pediatric patients who weigh less than 42 kg will be able to swallow the currently available adult formulation.
- The division also stated that a waiver for patients under 3 years of age is consistent with other HCV products because HCV may spontaneously remit before the age of 3, making studies impossible or highly impracticable.
- The PeRC and division discussed that a waiver in patients weighing less than 42kg and unable to swallow the tablet could be based on the criterion that the product fails to represent a meaningful and therapeutic benefit over existing therapies, but another more appropriate grounds for waiver would be that formulation development is impossible because of a liquid would not be possible (due to formulation with dasabuvir) and the multiple number of dosage strengths that would be required for patients < 42 kg.
- *PeRC Recommendations:*
 - The PeRC agreed with the division's plan for a partial waiver in patients less than 3 years of age.
 - The PeRC also agreed to waiver in patients less than 42kg and unable to swallow the tablet due to the inability to develop an appropriate formulation
 - The PeRC also requested that the division follow up with PeRC regarding other products that have been indicated by weight without regard to age.

Post meeting follow up:

- The division followed up with PeRC on July 13, 2016 and stated the following products have been indicated by weight without regard to age: NON-RESPONSIVE

NON-RESPONSIVE

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
07/26/2016

Strayhorn, Suzanne

From: Masse, Sherie V <Sherie.Masse@abbvie.com>
Sent: Friday, July 22, 2016 11:42 AM
To: Strayhorn, Suzanne
Subject: RE: Timeline Sensitive NDA 208624 _Label FDA Review

Suzanne;
I confirm that is the correct number for the medication guide.
Thank you!

Regards,
Sherie

SHERIE VL MASSE, M.S., RAC
Director, Regulatory Affairs
Global Regulatory Strategy - Antiviral



AbbVie, Inc.
Regulatory Affairs
Bldg. AP30-1 Dept. PA72
One North Waukegan Road
North Chicago, IL 60064
OFFICE +1 847-938-9250
CELL (b) (6)
EMAIL sherie.masse@abbvie.com

abbvie.com

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From: Strayhorn, Suzanne [mailto:Suzanne.Strayhorn@fda.hhs.gov]
Sent: Friday, July 22, 2016 10:39 AM
To: Masse, Sherie V
Subject: RE: Timeline Sensitive NDA 208624 _Label FDA Review
Importance: High

Dear Sherie,

We can make this change on our end. Please confirm that this would occur on the medication guide and that number would be listed as 844-843-5472.

Thank you.

Suzanne

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Friday, July 22, 2016 11:00 AM
To: Strayhorn, Suzanne
Subject: RE: Timeline Sensitive NDA 208624 _Label FDA Review

Suzanne;

On review of our final materials in preparation for product launch activities, the team has noted a very minor inconsistency in the USPI that we would like to correct. While the customer service phone number on our cartons and containers is 844-VIEKIRA (844-843-5472), the customer service number listed in the USPI is listed as (b) (4). The difference has no impact to the patients/customers as both numbers successfully direct the caller to the combined Viekira Pak/Technivie Customer service center. (b) (4).

However, we would like to align the USPI to the 844-VIEKIRA phone number found on the cartons/containers. Would it be acceptable to make this change on submission of the final labeling within 14 days of approval?

Thanks for your continued support on this application!

Regards,

Sherie

SHERIE VL MASSE, M.S., RAC
Director, Regulatory Affairs
Global Regulatory Strategy - Antiviral



AbbVie, Inc.
Regulatory Affairs
Bldg. AP30-1 Dept. PA72
One North Waukegan Road
North Chicago, IL 60064
OFFICE +1 847-938-9250
CELL (b) (6)
EMAIL sherie.masse@abbvie.com

abbvie.com

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From: Strayhorn, Suzanne [<mailto:Suzanne.Strayhorn@fda.hhs.gov>]
Sent: Thursday, July 21, 2016 11:54 AM
To: Masse, Sherie V
Subject: RE: Timeline Sensitive NDA 208624 _Label FDA Review

Sherie,

Many thanks for this timely notification and rapid review by you and your team.

Regards,
Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247
Fax: (301) 796-9883
Email: Suzanne.Strayhorn@FDA.HHS.GOV

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Thursday, July 21, 2016 12:23 PM
To: Strayhorn, Suzanne
Subject: RE: Timeline Sensitive NDA 208624 _Label FDA Review

Dear Suzanne:

AbbVie confirms agreement with the draft label. Enclosed is the final clean version. Please note that due to the deletion of the [REDACTED] (b)(4) row in Table 6, the footnotes and the references to them needed to be adjusted for accuracy. The labels will be submitted to the NDA by 3:30 today.

Regards,
Sherie

SHERIE VL MASSE, M.S., RAC
Director, Regulatory Affairs
Global Regulatory Strategy - Antiviral



AbbVie, Inc.
Regulatory Affairs
Bldg. AP30-1 Dept. PA72
One North Waukegan Road
North Chicago, IL 60064
OFFICE +1 847-938-9250
CELL [REDACTED] (b) (6)
EMAIL sherie.masse@abbvie.com

abbvie.com

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From: Strayhorn, Suzanne [<mailto:Suzanne.Strayhorn@fda.hhs.gov>]
Sent: Thursday, July 21, 2016 8:43 AM

To: Masse, Sherie V

Subject: Timeline Sensitive NDA 208624 _Label FDA Review

Importance: High

Dear Sherie,

Please find attached FDA review comments to the draft label received by email last evening for Viekira XR (NDA 208624). The Division is firm regarding the language we are proposing in the above referenced draft label. Any further delay can jeopardize an action by the PDUFA date.

Please review, confirm agreement by noon and please provide a formal response to the NDA as soon as possible but no later than 3:30 pm today, to include labeling.

Kindly acknowledge receipt of this email.

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247

Fax: (301) 796-9883

Email: Suzanne.Strayhorn@FDA.HHS.GOV

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/s/

SUZANNE K STRAYHORN
07/22/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Thursday, July 21, 2016 9:43 AM
To: Masse, Sherie V (Sherie.Masse@abbvie.com)
Subject: Timeline Sensitive NDA 208624 _Label FDA Review
Attachments: NDA 208624 Sponsor Label_MU_rec 20Jul2016_FDA_21Jul2016.docx

Importance: High

Dear Sherie,

Please find attached FDA review comments to the draft label received by email last evening for Viekira XR (NDA 208624). The Division is firm regarding the language we are proposing in the above referenced draft label. Any further delay can jeopardize an action by the PDUFA date.

Please review, confirm agreement by noon and please provide a formal response to the NDA as soon as possible but no later than 3:30 pm today, to include labeling.

Kindly acknowledge receipt of this email.

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247

Fax: (301) 796-9883

Email: Suzanne.Strayhorn@FDA.HHS.GOV

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/s/

SUZANNE K STRAYHORN
07/21/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, July 20, 2016 9:32 AM
To: 'Sherie.Masse@abbvie.com'
Subject: RE: NDA 208624 _PREA PMR

Importance: High

Sherie,

We have editorial revision (underlined) to the PREA PMR for Viekira XR (NDA 208624) as follows:

Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir (VIEKIRA XR™) in pediatric patients greater than 3 years of age with chronic hepatitis C virus infection, who weigh at least 42 kg and are able to swallow tablets.

Final Protocol Submission: July 31, 2015 (submitted)
Study Completion: April 30, 2022
Final Report Submission: August 31, 2022

I wanted to make you and your team aware of this.

Kindly acknowledge receipt of this email.

Kind Regards,
Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, July 06, 2016 3:37 PM
To: 'Sherie.Masse@abbvie.com'
Subject: NDA 208624 _PREA PMR
Importance: High

**RE: NDA 208624 / Viekira XR / 3QD
Post Marketing Requirement (PREA)**

Dear Sherie,

We refer to the above referenced pending NDA for Viekira XR. We further refer to the Agreed iPSP, under IND 122839, dated August 2015, for this product.

Based on the information you have provided to date, the Division would like to propose the below PREA PMR language. Please review with your team. We would also ask that you provide the planned dates for each of the milestones listed below for our review.

PMR XXXX-X (number to be assigned later)

Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira XR™) in pediatric patients with chronic hepatitis C virus infection, who weigh at least 42 kg and are able to swallow tablets.

Final Protocol Submission: please provide dates for each of these milestones

Trial Completion:

Final Report Submission:

Please respond by July 8th, 2016 with the above requested information. We ask that you respond by email first so that we have a chance to review the dates you propose. Once we have reached agreement we will ask for an official submission to the NDA.

Kindly acknowledge receipt of this email.

Thanks in advance
Suzanne

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/s/

SUZANNE K STRAYHORN
07/20/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, July 20, 2016 12:39 PM
To: 'Masse, Sherie V'
Subject: NDA 208624_FDA Label Review Comments
Attachments: NDA 208624_Sponsor Label_MU_rec 19Jul2016 FDA comments_20Jul2016.docx

Importance: High

Dear Sherie,

Please find attached the Division's review comments, in response to the draft label you submitted yesterday for Viekira XR (NDA 208624).

We would respectfully request your response by EOB today. You can do so by email today and follow with formal submission to the NDA tomorrow before noon.

Thanking you in advance for the timeline consideration. Kindly confirm receipt of this communication.

Regards,
Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247
Fax: (301) 796-9883
Email: Suzanne.Strayhorn@FDA.HHS.GOV

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Tuesday, July 19, 2016 4:39 PM
To: Strayhorn, Suzanne
Subject: RE: NDA 208624_FDA Label Review Comments
Importance: High

Suzanne;
We have submitted our response to the July 15th labelling comments. Please let me know if you have any questions. Thanks!

Regards,
Sherie

SHERIE VL MASSE, M.S., RAC
Director, Regulatory Affairs
Global Regulatory Strategy - Antiviral



AbbVie, Inc.

Regulatory Affairs
Bldg. AP30-1 Dept. PA72
One North Waukegan Road
North Chicago, IL 60064
OFFICE +1 847-938-9250
CELL [REDACTED] (b) (6)
EMAIL sherie.masse@abbvie.com

abbvie.com

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From: Strayhorn, Suzanne [<mailto:Suzanne.Strayhorn@fda.hhs.gov>]
Sent: Friday, July 15, 2016 9:53 AM
To: Masse, Sherie V
Cc: Strayhorn, Suzanne
Subject: NDA 208624_FDA Label Review Comments
Importance: High

**RE: NDA 208624
FDA Label Review**

Dear Sherie,

The Division has reviewed the draft label for VIEKIRA XR Which you submitted on July 11, 2016. At this time we do have additional comments.

Following review, please submit your proposed draft label to the NDA, please submit track change and clean word documents. We request that you return no later than Tuesday, July 19th.

Kindly acknowledge receipt of this email.

Many thanks in advance.

Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
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/s/

SUZANNE K STRAYHORN
07/20/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Friday, July 15, 2016 10:53 AM
To: 'Masse, Sherie V'
Cc: Strayhorn, Suzanne (Suzanne.Strayhorn@fda.hhs.gov)
Subject: NDA 208624_FDA Label Review Comments
Attachments: NDA 208624_Sponsor Label_MU_rec_11Jul2016_FDA_15Jul2016.docx

Importance: High

**RE: NDA 208624
FDA Label Review**

Dear Sherie,

The Division has reviewed the draft label for VIEKIRA XR Which you submitted on July 11, 2016. At this time we do have additional comments.

Following review, please submit your proposed draft label to the NDA, please submit track change and clean word documents. We request that you return no later than Tuesday, July 19th.

Kindly acknowledge receipt of this email.

Many thanks in advance.

Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247
Fax: (301) 796-9883
Email: Suzanne.Strayhorn@FDA.HHS.GOV

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/s/

SUZANNE K STRAYHORN
07/15/2016



IND 122839

MEETING PRELIMINARY COMMENTS

AbbVie Inc.
Attention: Jamie Austin, MS, RAC
Manager, Regulatory Affairs
1 North Waukegan Road
Dept. PA77 / Building AP30
North Chicago, IL 60064-6194

Dear Ms. Austin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dasabuvir, ombitasvir, paritaprevir and ritonavir tablets.

We also refer to your correspondence, dated and received May 13, 2015, requesting a meeting to discuss the content and format of the NDA for dasabuvir, ombitasvir, paritaprevir, and ritonavir fixed-dose combination (3QD) tablets.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Elizabeth Thompson, M.S.
CDR, U.S. Public Health Service
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

IND 122839

Page 2

ENCLOSURE:

Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 16, 2015; 2:00- 3:30 pm Eastern Time
Meeting Location: Teleconference

Application Number: IND 122839
Product Name: dasabuvir, ombitasvir, paritaprevir and ritonavir tablets
Indication: Treatment of genotype 1 chronic hepatitis C virus (HCV) infection
Sponsor Name: AbbVie, Inc.

FDA ATTENDEES (tentative)

Division of Antiviral Products

Debra Birnkrant, Division Director
Jeffrey Murray, Deputy Director
Russell Fleischer, Acting Clinical Team Leader
Jules O'Rear, Clinical Virology Team Leader
Patrick Harrington, Clinical Virology Reviewer
Hanan Ghantous, Pharmacology/Toxicology Team Leader
Mark Seaton, Pharmacology/Toxicology Reviewer
Elizabeth Thompson, Chief, Project Management Staff

Office of Clinical Pharmacology

Islam Younis, Clinical Pharmacology Team Leader
Vikram Arya, Clinical Pharmacology Reviewer
Jeffry Florian, Pharmacometrics Team Leader

Office of Biostatistics

Greg Soon, Biostatistics Team Leader
Karen Qi, Biostatistics Reviewer

Office of New Drug Products

Steve Miller, CMC-Lead
Bamidele (Florence) Aisida, Regulatory Business Project Manager
Angelica Dorantes, Acting Biopharmaceutics Branch Chief
Elsbeth Chikhale, Acting Biopharmaceutics Lead

SPONSOR ATTENDEES

Barry M. Bernstein, Divisional Vice President, Infectious Disease Development
Daniel E. Cohen, Senior Medical Director, Clinical Project Team
Barbara Da Silva-Tillmann, Senior Medical Director, HCV Product Safety Lead
Melanie Gloria Director, Infectious Diseases Clinical Program Development
Martin King, Director, Statistics
Sherie Masse, Associate Director, CMC Regulatory Affairs
Kevin McDonald, Director, Regulatory Affairs, Global Product Strategy
Rajeev M. Menon, Senior Director, Clinical Pharmacology and Pharmacometrics
John Morris Director, CMC Project Management
Tami Pilot-Matias, Associate Director, Clinical Virology
Thomas J. Podsadecki, Project Director, Antiviral Clinical Project Team
Akshanth Polepally, Associate Principal Pharmacokineticist, Clinical Pharmacology and Pharmacometrics
Andrew Sansone, Sr. Director, Regulatory Affairs, US and Canada
Sara Siggelkow, Program Lead I, HCV Clinical Program Development
Yijie Zhou, Associate Director, Statistics
Jamie Austin, Manager, Regulatory Affairs, US and Canada

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for July 16, 2015 between AbbVie, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

AbbVie Inc. is developing the fixed-dose combination of dasabuvir, ombitasvir, paritaprevir and ritonavir (3QD tablet) for the treatment of genotype 1 chronic hepatitis C virus (HCV) infection. This fixed-dose combination tablet is an alternative formulation of the currently-approved drug

product Viekira Pak (NDA 206619), consisting of ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets. AbbVie has requested a pre-NDA meeting to gain FDA agreement on specific CMC, nonclinical, and clinical proposals for the planned NDA, as well as the overall content and format of the NDA, the proposal to fulfill PREA and the proposed filing strategy regarding cross-referencing.

2.0 DISCUSSION

2.1 Chemistry, Manufacturing, and Controls Questions

Question 1: Does the FDA agree with the cross-referencing proposal for Module 3?

FDA Response to Question 1: *We understand that for the NDA sections listed in Table 1 (page 20) you are proposing to include a copy of the sections from NDA 206619 or 20659 for convenience during the review, and that these sections in the 3QD NDA will not be updated in the future. This approach does seem useful, especially if each of these sections begins with a statement such as, "This section is a copy of the information in NDA 206619 as of [date the 3QD NDA is written]. At this time, the most recent update of this section of NDA 206619 was [date of 206619 submission or date it was revised]."*

Question 2a: Does the FDA agree with the proposal for not including method validation information that was previously submitted for the drug substances in NDA 206619?

FDA Response to Question 2a: *The Division agrees. We understand that the Review Guide in Module 1.4.4 will clarify where current information can be found for sections of the 3QD NDA not shown in the Appendix A table. Regarding Analytical Procedures for the drug substances, since the cross-referenced NDAs are also AbbVie applications, the Review Guide could simply list the date(s) when the most current analytical procedures were submitted to NDA 206619 or 20659. In that case, sections 3.2.S.4.2 would not need to be included in the 3QD NDA.*

Question 2b: Does FDA agree with the proposal to include a document in 3.2.R with hyperlinking to the relevant Module 3 sections in order to meet the requirements for the Method Validation Package?

FDA Response to Question 2b: *The Division agrees.*

Question 3: Does the FDA agree with the shelf-life dating proposal for the 3QD tablet?

FDA Response to Question 3: *Your proposal is generally acceptable. We recommend that the*

(b)(4)

Question 4: Does the FDA agree with the batch record proposal?

FDA Response to Question 4: *The Division agrees. If additional batch records are requested during the review, e.g., stability batch(es), how long would it take before you could supply them?*

Question 5a: Does the FDA agree with the proposal to control the [REDACTED] components in the 3QD tablet? (b)(4)

FDA Response to Question 5a: *The Division agrees.*

Question 5b: Does the FDA agree with the proposal to include a commitment in the 3QD application to evaluate and implement a test to detect the presence [REDACTED] (b)(4)

FDA Response to Question 5b: *The Division agrees.*

2.2 Nonclinical Questions

Question 6: Does the FDA agree with the cross-referencing proposal for Module 4?

FDA Response to Question 6: *The Division agrees.*

Question 7: Does the FDA agree with the cross-referencing proposal for nonclinical summaries in Module 2?

FDA Response to Question 7: *The Division agrees.*

2.3 Clinical Questions

Question 8: Does the FDA agree with the cross-referencing proposal for clinical data summaries in Module 2?

FDA Response to Question 8: *The Division agrees.*

Question 9: Does the FDA agree with the cross-referencing proposal for Module 5?

FDA Response to Question 9: *The Division agrees.*

Question 10a: Does the FDA agree that the new Module 5 data planned for inclusion in the NDA do not warrant updates to the Summary of Clinical Efficacy?

FDA Response to Question 10a: *The Division agrees.*

Question 10b: Does the FDA agree that the new Module 5 data planned for inclusion in the NDA do not warrant updates to the Summary of Clinical Safety?

FDA Response to Question 10b: *The Division agrees.*

Question 11a: Does the FDA agree with the proposal to address the ISE requirement?

FDA Response to Question 11a: *The Division agrees.*

Question 11b: Does the FDA agree with the proposal to address the ISS requirement?

FDA Response to Question 11b: *The Division agrees.*

Question 12: Does the FDA agree that the datasets proposed for inclusion in the planned NDA are adequate and that the formats are acceptable?

FDA Response to Question 12: *The Division agrees.*

Question 13: Does the FDA agree with the proposal to [REDACTED] (b) (4)?

[REDACTED] (b) (4)

Question 14: Does the FDA agree with the cross-referencing proposal for the pharmacovigilance plan?

FDA Response to Question 14: *The Division agrees.*

2.4 Regulatory Questions

Question 15: Does the FDA agree with the proposed strategy to incorporate relevant information from NDA 206619, as originally approved and thereafter supplemented/reported, to the planned 3QD NDA via cross-reference on an ongoing basis?

FDA Response to Question 15: *We generally agree with the cross-referencing strategy, and have the following recommendation regarding the ongoing aspect.* (b) (4)

Question 16: Does the FDA agree that the proposed format and content for the NDA is adequate for the application to be considered as complete?

FDA Response to Question 16: *The proposed format and content appear to be adequate.*

Question 17: Does the FDA agree that Study M14-566 is the only study included in the proposed NDA that constitutes a "covered" study for purposes of complying with financial disclosure requirements of 21 CFR 54?

FDA Response to Question 17: *The Division agrees.*

Question 18: Does the FDA agree that the planned NDA would be assessed a user fee of \$1,167,600.00?

FDA Response to Question 18: *The Division agrees. Please note that if the NDA is submitted later than September 30, 2015, the FY 2016 user fee rates will apply.*

Question 19: Does the FDA agree that the proposed initial Pediatric Study Plan (iPSP) fulfills the PREA requirements?

FDA Response to Question 19: No, [REDACTED] (b) (4)
[REDACTED] Please see prior communications regarding the iPSP.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

We acknowledge your iPSP submitted on April 15, 2015. Your Agreed iPSP, along with any requests for waivers or deferrals, should be included in your New Drug Application.

4.0 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](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

5.0 MANUFACTURING FACILITIES

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.				

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/s/

ELIZABETH G THOMPSON
07/13/2015

NDA 208624

Medical reviewer: Tanvir Bell, MD

Subject: Financial Disclosure

Date submitted: July 8, 2016

Sponsor: Abbvie

Product: Viekira XR

There are no investigators who participated in Study M14-566 holding financial interests that require disclosure.

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/s/

TANVIR K BELL
07/08/2016

ISLAM R YOUNIS
07/08/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Friday, July 01, 2016 10:42 AM
To: Sherie.Masse@abbvie.com
Cc: Strayhorn, Suzanne
Subject: NDA 208624_Viekira XR_Labeling Review
Attachments: NDA 208624_Sponsor Label rec 14Jun2016_MU_1Jul2016 FDA edit.docx; NDA 208624_Med Guide rec 14Jun2016_1Jul2016 FDA edit.docx

Importance: High

**RE: NDA 208624/Viekira XR
FOR REVIEW: FDA Proposed Labeling Edits**

Dear Sherie,

Please find attached our review comments to the PI and Medication Guide following review of your submission dated June 14, 2016.

- Please note that the Medication Guide review comments are now in a separate document so as not to compromise any further revised format changes. Therefore, it is important that you use the version of the medication guide that we have attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

If you are in agreement with the proposed changes to the medication guide, please do combine back with the PI, ensuring that formatting is correct. If you are recommending additional changes, we ask that you keep these documents separate until such a time as we have reached final agreement.

- We also ask that you incorporate all changes to the proposed Viekira XR label that were approved under the recent supplement for Viekira XR (Supplement 11).
- I will also be sending you today as a separate email, our proposed changes to the carton and container labeling.

Please review and provide clean and redlined labeling on or before July 8, 2016. Additionally, please confirm receipt of this email.

Thanking you in advance,
Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247

Fax: (301) 796-9883

Email: Suzanne.Strayhorn@FDA.HHS.GOV

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

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/s/

SUZANNE K STRAYHORN
07/01/2016

**PeRC Meeting Minutes
June 8, 2016**

PeRC Members Attending:

John Alexander
Meshاون Payne
Gettie Audain
Dianne Murphy
Raquel Tapia
Gregory Reaman
Robert “Skip” Nelson
Barbara Buch
Rosemary Addy
Shrikant Pagay
Adrienne Hornatko-Munoz
Wiley Chambers
Jackie Yancy
Thomas Smith
George Greeley
Yeruk Mulugeta
Ikram Elayan
Freda Cooner
Maura O’Leary
Michelle Roth Kline

Agenda

NON-RESPONSIVE

10:50	NDA 208624	Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir FDC Tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP	DAVP	Suzanne Strayhorn	Indicated for the treatment of adult patients with chronic hepatitis C virus (HCV): (1) genotype 1b without cirrhosis or with compensated cirrhosis (2) genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin
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NON-RESPONSIVE

NON-RESPONSIVE

**Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir FDC Tablets (Partial Waiver/Deferral/Plan)
with Agreed iPSP**

- Approved Indication: Indicated for the treatment of adult patients with chronic hepatitis C virus (HCV): (1) genotype 1b without cirrhosis or with compensated cirrhosis (2)

genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

- This product triggers PREA as a new active ingredient (new combination) and new dosage form and has a PDUFA goal date of July 28, 2016.
- The division stated this is a fixed-dose combination tablet. Dasabuvir was a separate tablet taken twice a day and Ombitasvir, Paritaprevir and Ritonavir were in one tablet taken twice a day.
- PeRC Recommendations:
 - The PeRC recommended the division follow up with PeRC regarding whether the protocols for the “Safety/Efficacy Study” and “Long Term Follow-up Study” were submitted by the sponsor for each of the products included within this fixed dose combination.
 - The PeRC agreed with the sponsor’s plan for a partial waiver in patients 0 to less than 3 years of age because the drug does not represent a meaningful therapeutic over existing therapies and to a deferral in pediatric patients 3 years to 17 years of age.
- **Post PeRC Comment:** The division followed up with PeRC on June 9, 2016 indicating the Safety/Efficacy Study and Long Term Follow-up Study were submitted to the following INDs:
 - Paritaprevir IND 103526
 - Dasabuvir IND 101636
 - Ombitasvir IND 108434
 - Paritaprevir/Ritonavir/Ombitasvir 75 mg/ 50 mg/ 12.5 mg Tablets (“2DAA”) IND 120467

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
06/30/2016

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

AbbVie, Inc. has submitted an original New Drug Application (NDA) for FDA review for Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (3QD) Film-Coated Tablets with or without ribavirin (RBV) for the treatment of patients with genotype (GT1) chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. This new NDA submission represents a reformulation of an already approved product, Viekira Pak™ (NDA 206619, approved on December 19, 2014) which consists of a fixed-dose tablet containing ombitasvir/paritaprevir/ritonavir tablets (12.5 mg/75 mg/50 mg, 2tablets QD) co-packaged with dasabuvir tablets (250 mg, 1 tablet BID).

Under the New NDA, AbbVie has reformulated the four active substances in Viekira Pak™ into a single tablet dosage form, containing dasabuvir 200 mg/ ombitasvir 8.33mg/ paritaprevir 50 mg/ ritonavir 33.33 mg, to enable a once daily (QD) dosing regimen (3 tablets).

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

NDA#: 208624

PRODUCT PROPRIETARY NAME: Viekira XR (tentative approval or proprietary name)

ESTABLISHED/GENERIC NAME: dasabuvir, ombitasvir, paritaprevir, ritonavir (fixed-dose combination tablets)

APPLICANT/SPONSOR: AbbVie, Inc.

PREVIOUSLY APPROVED INDICATION/S: The components of Viekira XR are currently approved; this new NDA will not change the previously approved indications.

(1) _____

PROPOSED INDICATIONS:

VIEKIRA XR is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV):

(1) genotype 1b without cirrhosis or with compensated cirrhosis

(2) genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin

NDA STAMP DATE: September 28, 2015

PDUFA GOAL DATE: July 28, 2016

SUPPLEMENT TYPE: Not Applicable (N/A) - New NDA

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW *active ingredient(s) (includes new combination);* *indication(s);* *dosage form;* *dosing regimen;* or *route of administration?*

Did the sponsor submit an Agreed iPSP? Yes *No*

(Agreed iPSP previously approved on April 15, 2015 under IND (b)(4) and included with this original NDA submission)

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes *No* *previously agreed*

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes *No*

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes *No*

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes *No*

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived.

Pediatric patients younger than 3 years of age.

Pediatric patients weighing ≤ 42 kg and unable to swallow tablet.

2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to

support this claim for review by the Division, and this data will be publicly posted. (*This reason is for Partial Waivers Only*)

3. Provide justification for Waiver:

Patients <3 years of age: The applicant has requested a waiver in pediatric patients younger than 3 years of age on the basis that the product would not provide meaningful therapeutic benefit and is unlikely to be used in a substantial number of patients in this age group. The Review Team agrees with this request. A diagnosis of chronic HCV is difficult to establish definitively in young pediatric patients. Spontaneous resolution of HCV, depending upon mode of transmission and genotype, occurs in pediatric patients generally up to age 4, and the risk of progression of liver disease in HCV-infected patients prior to age 3 is very low. Among perinatally infected children, an estimated 20-30% will have spontaneous clearance of HCV and clearance is most likely in the first 2-3 years of life. Therefore, we anticipate very few pediatric patients younger than 3 years of age will require treatment for chronic HCV infection.

Patients weighing less than 42 kg and unable to swallow tablets whole: The sponsor is unable to formulate all the components of Viekira XR into a single formulation for younger children. Further, it is unlikely that pediatric subjects who weigh less than 42 kg will be able to swallow the currently available adult Viekira XR formulation. The sponsor is developing the components of Viekira XR under the Viekira Pak PMR.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

The Division agrees with the applicant's current proposed language in Section 8.4 of the label, which reads as follows:

8.4 Pediatric Use

Safety and effectiveness of VIEKIRA XR in pediatric patients less than 18 years of age have not been established.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

 basal cell and squamous cell skin cancer

 bladder

 breast

 cervical

 colorectal

 endometrial

 esophageal

cancer (continued):

 follicular lymphoma

 gastric

 hairy cell leukemia

 hepatocellular

 indolent non-Hodgkin lymphoma

 lung (small & non-small cell)

 multiple myeloma

 oropharynx (squamous cell)

 ovarian (non-germ cell)

 pancreatic

 prostate

 refractory advanced melanoma

 renal cell

 uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request: [Pediatric patients weighing at least 42 kg and able to swallow tablets](#)

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**
A partial waiver planned for pediatric patients who weigh < 42 kg and unable to swallow tablet due to lack of significant therapeutic benefit over existing therapies. In addition, pediatric patients younger than 3 years of age are waived from studies investigating HCV therapeutics because of lack of significant therapeutic benefit.
3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
- a. Other (specify): All components of this product are already approved. There is an Agreed iPSP and pediatric studies are ongoing.
4. **Provide projected date for the submission of the pediatric assessment (deferral date):** April 30, 2022
5. **Did applicant provide certification of grounds for deferring assessments?** Yes No
6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** Yes No
2. **Does the division agree with the sponsor's plan?** Yes No
3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** Yes No

At present the applicant has provided the following milestone dates:

PK (≥42 kg):

- a. Protocol Submission: 7/31/2015 submitted

b. Study Completion: 01/31/2017

Safety/Efficacy Study (> 42 kg)

- a. Protocol Submission: 10/30/2015 submitted
- b. Study Completion: 4/30/2022
- c. Final Report: 8/31/2022

- 4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
- 5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

The components for treatment for Hepatitis C in these studies are paratapravir, ritonavir, ombtasvir and dasabuvir. Paratapravir, ritonavir and ombitasvir are co-formulated as parts of a single pill in the 3DAA (Viekira Pak) and 3QD (Viekira XR) formulations, and dasabuvir is formulated as a stand-alone tablet. The dasabuvir component is now included in the 3QD (Viekira XR) formulation.

(b)(4)

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Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments:

Division comments on product efficacy:

The efficacy (SVR₁₂) of the 3 DAA regimen of parataprevir, ritonavir, ombitasvir with dasabuvir + ribavirin ranges from 90-100%, depending on treatment history and presence or absence of cirrhosis.

Division comments on sponsor proposal to satisfy PREA:

The proposal is acceptable.

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/s/

SUZANNE K STRAYHORN
06/28/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Tuesday, June 21, 2016 12:32 PM
To: 'Sherie.Masse@abbvie.com'
Cc: Strayhorn, Suzanne (Suzanne.Strayhorn@fda.hhs.gov)
Subject: Information Request - NDA 208624_PREA PMR

Importance: High

Dear Sherie,

The purpose of this Information Request (IR) is to finalize the PREA Post-Marketing Requirements (PMRs) for Viekira XR.

- Please provide the lowest weight of pediatric subjects who should be able to swallow the adult formulation of Viekira XR.
- Please provide your response by COB June 24, 2016 or sooner if possible.

Kindly acknowledge receipt of this email.

Many thanks in advance,
Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247

Fax: (301) 796-9883

Email: Suzanne.Strayhorn@FDA.HHS.GOV

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/s/

SUZANNE K STRAYHORN
06/21/2016

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, June 08, 2016 4:14 PM
To: 'Sherie.Masse@abbvie.com'
Cc: Strayhorn, Suzanne (Suzanne.Strayhorn@fda.hhs.gov)
Subject: NDA 208624_Division Review of Proposed Labeling
Attachments: NDA 208624 Sponsor Label_MU_v rec 2May2016_To Abbvie_08Jun2016.docx

**RE: NDA 208624/ dasabuvir, ombitasvir, paritaprevir, ritonavir (fixed-dose combination tablets)
DAVP Label - Review Comments**

Dear Sherie,

The Division has reviewed your proposed labeling for the above referenced NDA. At this time we do have comments and proposed edits, please refer to the attached.

Please review and provide revised labeling (clean and track change versions) by June 14, 2016. When you provide updated labeling for Division review, please only include any new proposed edits (accept any changes you agree with).

Kindly confirm receipt of this email.

Thanks in advance.
Suzanne

Suzanne Strayhorn, MSc
Regulatory Health Project Manager
Center for Drug Evaluation and Research (CDER)
Office of Antimicrobial Products (OAP)
Division of Antiviral Products (DAVP)
10903 New Hampshire Ave., Bldg. 22, Room 6349
Silver Spring, MD 20993-0002

Phone: (240) 402-4247
Fax: (301) 796-9883
Email: Suzanne.Strayhorn@FDA.HHS.GOV

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE K STRAYHORN
06/08/2016

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

AbbVie, Inc. has submitted an original New Drug Application (NDA) for FDA review for Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (3QD) Film-Coated Tablets with or without ribavirin (RBV) for the treatment of patients with genotype (GT1) chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. This new NDA submission represents a reformulation of an already approved product, Viekira Pak™ (NDA 206619, approved on December 19, 2014) which consists of a fixed-dose tablet containing ombitasvir/paritaprevir/ritonavir tablets (12.5 mg/75 mg/50 mg, 2tablets QD) co-packaged with dasabuvir tablets (250 mg, 1 tablet BID).

Under the New NDA, AbbVie has reformulated the four active substances in Viekira Pak™ into a single tablet dosage form, containing dasabuvir 200 mg/ ombitasvir 8.33mg/ paritaprevir 50 mg/ ritonavir 33.33 mg, to enable a once daily (QD) dosing regimen (3 tablets).

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

NDA#: 208624

PRODUCT PROPRIETARY NAME: Viekira XR (tentative approval or proprietary name)

ESTABLISHED/GENERIC NAME: dasabuvir, ombitasvir, paritaprevir, ritonavir (fixed-dose combination tablets)

APPLICANT/SPONSOR: AbbVie, Inc.

PREVIOUSLY APPROVED INDICATION/S: The components of Viekira XR are currently approved; this new NDA will not change the previously approved indications.

(1) _____

PROPOSED INDICATIONS:

VIEKIRA XR is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV):

(1) genotype 1b without cirrhosis or with compensated cirrhosis

(2) genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin

NDA STAMP DATE: September 28, 2015

PDUFA GOAL DATE: July 28, 2016

SUPPLEMENT TYPE: Not Applicable (N/A) - New NDA

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW *active ingredient(s) (includes new combination);* *indication(s);* *dosage form;* *dosing regimen;* or *route of administration?*

Did the sponsor submit an Agreed iPSP? Yes *No*

(Agreed iPSP previously approved on April 15, 2015 under IND (b)(4) and included with this original NDA submission)

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes *No* *previously agreed*

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes *No*

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes *No*

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes *No*

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived. [Pediatric patients younger than 3 years of age.](#)
2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (*This reason is for Partial Waivers Only*)

3. Provide justification for Waiver:

The applicant has requested a waiver in pediatric patients younger than 3 years of age on the basis that the product would not provide meaningful therapeutic benefit and is unlikely to be used in a substantial number of patients in this age group. The Review Team agrees with this request. A diagnosis of chronic HCV is difficult to establish definitively in young pediatric patients. Spontaneous resolution of HCV, depending upon mode of transmission and genotype, occurs in pediatric patients generally up to age 4, and the risk of progression of liver disease in HCV-infected patients prior to age 3 is very low. Among perinatally infected children, an estimated 20-30% will have spontaneous clearance of HCV and clearance is most likely in the first 2-3 years of life. Therefore, we anticipate very few pediatric patients younger than 3 years of age will require treatment for chronic HCV infection.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

The Division agrees with the applicant's current proposed language in Section 8.4 of the label, which reads as follows:

8.4 Pediatric Use

Safety and effectiveness of VIEKIRA XR in pediatric patients less than 18 years of age have not been established.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

 basal cell and squamous cell skin cancer

 bladder

 breast

 cervical

 colorectal

 endometrial

 esophageal

cancer (continued):

 follicular lymphoma

 gastric

 hairy cell leukemia

 hepatocellular

 indolent non-Hodgkin lymphoma

 lung (small & non-small cell)

 multiple myeloma

 oropharynx (squamous cell)

 ovarian (non-germ cell)

 pancreatic

 prostate

 refractory advanced melanoma

 renal cell

 uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

<p>DEFERRAL REQUEST</p> <p><i>Please attach:</i> <input checked="" type="checkbox"/> <i>Pediatric Record</i></p> <p>1. Age groups included in the deferral request: (b)(4)</p>
--

2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request: Partial waiver requested for pediatric patients < 3 years of age due to lack of significant therapeutic benefit to children in this age group.
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
- a. Other (specify): All components of this product are already approved. There is an Agreed iPSP and pediatric studies are ongoing.
4. Provide projected date for the submission of the pediatric assessment (deferral date): April 30, 2022
5. Did applicant provide certification of grounds for deferring assessments? Yes No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No

Applicant has provided 'Protocol Submission' and 'Study Completion' dates, but has not provided dates for Study Submission. The missing information will be requested. The missing information will be requested.

At present the applicant has provided the following milestone dates:

PK Study (b)(4)

- a. Protocol Submission: Submitted (b)(4)
- b. Study Completion: January 31, 2107

Safety/Efficacy Study

- a. Protocol Submission: October 31, 2015
- b. Study Completion: April 30, 2019

Long Term Follow-up Study

- a. Protocol Submission: December 1, 2015
- b. Study Completion: April 30, 2022

- 4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
- 5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

The components for treatment for Hepatitis C in these studies are paratapravir, ritonavir, ombtasvir and dasabuvir. Paratapravir, ritonavir and ombitasvir are co-formulated as parts of a single pill in the 3DAA and 3OD formulations, and dasabuvir is formulated as a stand-alone tablet. The dasabuvir component is now included in the 3OD formulation. (b)(4)

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

Division comments on product safety:

Are there any safety concerns currently being assessed? **Yes** **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? **Yes** **No**

Will a DSMB be required? **Yes** **No**

Other comments:

Division comments on product efficacy:

The efficacy (SVR₁₂) of the 3 DAA regimen of parataprevir, ritonavir, ombitasvir with dasabuvir + ribavirin ranges from 90-100%, depending on treatment history and presence or absence of cirrhosis.

Division comments on sponsor proposal to satisfy PREA:

The proposal is acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE K STRAYHORN
05/24/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/17/2016 03:36:30 PM
To: sherie.masse@abbvie.com
CC: Suzanne.Strayhorn@fda.hhs.gov
BCC: Bamidele.aisida@fda.hhs.gov
Subject: NDA 208624 INFORMATION REQUEST

Please see attached and confirm receipt.

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 |Bamidele.aisida@fda.hhs.gov



NDA 208624

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA77, Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

Please refer to your New Drug Application (NDA) dated and received September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (3QD) Film-Coated Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by March 31, 2016. A partial response at that date with a timeline for the remaining questions is also acceptable.

1.

(b) (4)

2.

(b) (4)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/25/2016 04:07:50 PM
To: sherie.masse@abbvie.com
CC:
BCC: Bamidele.aisida@fda.hhs.gov
Subject: NDA 208624 INFORMATION REQUEST

Please see attached and confirm receipt.

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 |Bamidele.aisida@fda.hhs.gov



NDA 208624

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, CMC Regulatory Affairs
1 North Waukegan Road
Dept. PA77, Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

Please refer to your New Drug Application (NDA) dated and received September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (3QD) Film-Coated Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by March 9, 2016. A partial response at that date with a timeline for the remaining questions is also acceptable.

We have the following questions regarding the formulation optimization studies, which required a total of 15 prototype formulations:

- a) Were all 15 formulations planned typically in a formal design of experiments or one formulation at a time?
- b) What were the objectives of specific formulation changes for the ER and IR layers in each study? Summarize in a single table the important tablet characteristics, test results and conclusions. If test results pertain to dissolution/bioavailability, provide study outcome with reference to location of the data in the submission.
- c) Provide the physical characteristics, e.g., particle size, viscosity range etc., of the excipients and/or Certificate of Compliance from the vendors for the development of extended release tablet layer. If knowledge gained from the prototype studies lead to identification of excipient characteristics that are important for either the IR or ER layer in the final commercial product, summarize that information.

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F.
Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.1001.1-200170330
s, cn=Bamidele F. Aisida -A
Date: 2016.02.25 16:06:03 -0500

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208624

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA77, Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

Please refer to your New Drug Application (NDA) dated and received September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (3QD) Film-Coated Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by Feb 7, 2016. A partial response at that date with a timeline for the remaining questions is also acceptable.

1. Provide complete dissolution profile data (individual, mean, SD, profiles) for Ombitasvir, Paritaprevir, and Ritonavir. Specifically, in addition to the time points included, provide the percentage dissolved at time less than 0.5 hr (b)(4) and at the 1.5 hr time point.

2. (b)(4)

3. In your Manufacturing Process Development Report (Section 3.2.P.2.3, Page 44), you have stated that (b)(4).

(b)(4)

4. You have performed studies on content uniformity/assay testing by using stratified sampling over the course of the tablet process during your manufacturing process development. However, it was not clear what the frequency of your stratified sampling for uniformity of dosage (for Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir) will be throughout a commercial tableting run. Please provide a detailed description of your stratified sampling plan for content uniformity testing of your tablets and please give the frequency of sample collection to be performed through the tableting process.
5. In your Batch Formula for the drug product (Section 3.2.P.3.2), you have provided the amounts of each component of the ER layer and (b)(4) for the IR layer for a commercial sized batch (b)(4). However, the Batch Formulas for the (b)(4) to be produced on the commercial scale has not been provided. We referred back to Section 3.2.P.3.2, but we were unable to locate the Batch Formulas for (b)(4) for a commercial-batch production. Please provide a Batch Formula for (b)(4) to be produced for a commercial-level batch of tablets.
6. We noticed that you have calculated yield reconciliation for each unit operation step of your exhibit batch (RD-14-011). Please establish step-wise yield limits for each unit operation for your commercial-level batches. The step-wise yields should also be included in your intended commercial batch records.
7. Please submit a table comparing the frequency of your proposed in-process tests for the submitted exhibit batch (Batch #14-005926) and future commercial batches of Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir Tablets. If there are any differences of in-process testing frequency between the exhibit batch and the commercial batches, please provide justifications for these differences.

8.

(b)(4)

If you have questions, call me at (240) 402-2691.

Sincerely,

**Bamidele F.
Aisida -A**

Digitally signed by Bamidele F. Aisida -A
DN: cn=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001703308,
cn=Bamidele F. Aisida -A
Date: 2016.01.21 12:12:46 -05'00'

**Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research**



NDA 208624

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AbbVie, Inc.
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

ATTENTION: Sherrie Masse, M.S., RAC
Director, Regulatory Affairs

Dear Ms. Masse:

Please refer to your New Drug Application (NDA) dated and received September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir Extended-release Tablets, 200 mg/8.33 mg/50 mg/33.33 mg.

We also refer to your correspondence dated and received October 26, 2015, requesting review of your proposed proprietary name, Viekira XR. We have completed our review of the proposed proprietary name Viekira XR, and have concluded it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 26, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Suzanne Strayhorn, at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AZEEM D CHAUDHRY
01/19/2016

TODD D BRIDGES
01/19/2016



NDA 208624

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA77, Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

Please refer to your New Drug Application (NDA) dated and received on September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for dasabuvir, ombitasvir, paritaprevir, and ritonavir (200 mg/ 8.33 mg/ 50 mg/ 33.33 mg) tablets.

We also refer to your amendments dated October 21 and 26, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 28, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 30, 2016.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Antiviral Products (DAVP). Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Suzanne Strayhorn, Regulatory Project Manager, at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
11/27/2015



NDA 208624

NDA ACKNOWLEDGMENT

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA77, Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (3QD) Film-Coated Tablets, (200 mg / 8.33 mg / 50 mg / 33.33 mg)

Date of Application: September 28, 2015

Date of Receipt: September 28, 2015

Our Reference Number: NDA 208624

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-4247 or via the Division's main line at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Suzanne Strayhorn, MS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
10/15/2015



IND 122839

**MEETING REQUEST-
WRITTEN RESPONSES**

AbbVie Inc.
Attention: Sherie Masse, MS, RAC
Associate Director, Regulatory Affairs CMC
1 N. Waukegan Road, Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Masse:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dasabuvir, obmitasvir, paritaprevir and ritonavir fixed-dose combination tablets.

We also refer to your submission dated February 9, 2015, containing a Type C meeting request. The purpose of the requested meeting was to discuss chemistry, manufacturing, and controls topics, including the intended stability data package for the NDA and dissolution method development.

Further reference is made to our Meeting Granted letter dated February 26, 2015, wherein we stated 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 March 25, 2015 background package.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Balajee Shanmugam, PhD
Branch Chief Branch III (Acting)
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

IND 122839
Page 2

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Chemistry
Application Number: IND 122839
Product Name: dasabuvir, obmitasvir, paritaprevir and ritonavir fixed-dose combination tablets
Indication: Treatment of genotype 1 chronic hepatitis C virus infection
Sponsor/Applicant Name: AbbVie Inc.

1.0 BACKGROUND

The purpose of this Type C meeting is to gain the FDA's agreement on the adequacy of the stability data package in support of a New Drug Application (NDA) submission and feedback regarding the development of the dissolution method for this immediate release/extended release bilayer tablet.

2.0 QUESTIONS AND RESPONSES

Question 1: –Stability Data

AbbVie has presented the formulation comparison and the stability data package intended to be included in the NDA, including stability studies conducted on tablets manufactured with both the (b)(4) and pale yellow (b)(4) film-coating. Does the FDA agree that the proposed stability data package is sufficient to support the pale yellow film-coated 3QD tablets as the intended marketed formulation?

FDA Response to Question 1: We concur with the proposal to include 12 mo on 3 batches of (b)(4) ER-12 tablets and 9 mo on 3 batches of the yellow (commercial image) ER-12 tablets. This will include data from the long-term stability condition of 30°C/75%RH as well as accelerated and other appropriate stability data.

Question 2: – Dissolution Method

Significant developmental studies investigating in vitro dissolution and exploration of IVIVC were completed in an attempt to establish a dissolution method that could distinguish the differences between the formulations studied.

Question 2a: Does the FDA agree that the dissolution method for the ER layer (dasabuvir) is suitably discriminating?

FDA Response to Question 2a: The proposed dissolution method shows discriminating capability towards formulation changes of the ER layer ((b) (4)) with regards to the dissolution of the dasabuvir component.

Question 2b: Does the FDA agree that the dissolution method for the IR layer (ombitasvir/paritaprevir/ritonavir) is suitably discriminating?

FDA Response to Question 2b: The proposed dissolution method shows discriminating capability towards the tested formulation changes (ER-7 and ER-8 vs. ER-12) with regards to dissolution of the IR layer components, ombitasvir, paritaprevir, and ritonavir. Clarify why in (b)(4)

It is noted that data regarding the discriminating ability of the proposed dissolution method (b)(4)

Additionally, provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution of the ER and IR layers components.

Question 2c: Since predictive Level (b) (4) correlation could not be established, an alternative approach (without IVIVC) to establish dissolution specifications is being pursued. Does the FDA agree with AbbVie's approach to set (b)(4) dissolution acceptance criteria for both the ER and IR layers?

FDA Response to Question 2c: Your approach to set (b)(4) dissolution acceptance criteria for both the ER and IR components appears reasonable. The dissolution acceptance criteria will be reviewed under the NDA.

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/s/

STEPHEN MILLER
04/24/2015
For B. Shanmugam



IND 122,839

MEETING PRELIMINARY COMMENTS

AbbVie Inc.
Attention: Jamie Austin, MS, RAC
Manager, Regulatory Affairs
1 North Waukegan Road
Dept. PA77 / Building AP30
North Chicago, IL 60064-6194

Dear Ms. Austin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dasabuvir, ombitasvir, paritaprevir, and ritonavir tablets.

We also refer to your January 9, 2015, correspondence requesting an End-of-Phase 2 meeting to discuss the adequacy of current bioavailability data and exposure-response modeling to support an NDA. You also proposed to discuss a planned clinical trial to evaluate dasabuvir, ombitasvir, paritaprevir and ritonavir tablets with low-dose, once daily ribavirin (RBV).

We also refer to our initial preliminary comments sent on March 12, 2015 and your correspondence of March 13, 2015 agreeing to reschedule the End-of-Phase 2 teleconference to allow the Agency time to review newly available data from your fasted bioavailability (BA) and food effect trial, M14-240.

Following review of your March 24, 2015 submission, our additional responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-1182 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

IND 122,839

Page 2

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: April 16, 2015 2:00 PM – 3:00 PM EDT
Meeting Location: Teleconference

Application Number: IND 122,839
Product Name: dasabuvir, ombitasvir, paritaprevir and ritonavir tablets
Indication: Treatment of genotype 1 chronic hepatitis C virus (HCV) infection
Sponsor/Applicant Name: AbbVie Inc.

FDA ATTENDEES (tentative)

Division of Antiviral Products

Debra Birnkrant, Division Director
Jeffrey Murray, Deputy Director
Russell Fleischer, Clinical Reviewer
Linda Lewis, Clinical Team Leader
Jules O'Rear, Clinical Virology Team Leader
Patrick Harrington, Clinical Virology Reviewer
Hanan Ghanous, Pharmacology/Toxicology Team Leader
Mark Seaton, Pharmacology/Toxicology Reviewer
Elizabeth Thompson, Chief, Project Management Staff
Katherine Schumann, Regulatory Project Manager

Office of Clinical Pharmacology

Islam Younis, Clinical Pharmacology Team Leader
Vikram Arya, Clinical Pharmacology Reviewer
Jeffry Florian, Pharmacometrics Team Leader
Luning Zhuang, Pharmacometrics Reviewer

Office of Biostatistics

Greg Soon, Biostatistics Team Leader
Karen Qi, Biostatistics Reviewer

Office of New Drug Products

Steve Miller, CMC-Lead
Angelica Dorantes, Acting Biopharmaceutics Branch Chief

Elsbeth Chikhale, Acting Biopharmaceutics Lead

SPONSOR ATTENDEES

Barry M. Bernstein, Divisional Vice President, Infectious Disease Development
Daniel E. Cohen, Senior Medical Director, Clinical Project Team
Barbara Da Silva-Tillmann, Senior Medical Director, HCV Product Safety Lead
Melanie Gloria Director, Infectious Diseases Clinical Program Development
Amit Khatri, Assistant Director, Clinical Pharmacology and Pharmacometrics
Martin King, Director, Statistics
Patrick Marroum, Director, Clinical Pharmacology and Pharmacometrics
Sherie Masse, Associate Director, CMC Regulatory Affairs
Kevin McDonald Director, Regulatory Affairs, Global Product Strategy
Rajeev M. Menon, Senior Director, Clinical Pharmacology and Pharmacometrics
John Morris Director, CMC Project Management
Thomas J. Podsadecki, Project Director, Antiviral Clinical Project Team
Andrew Sansone, Sr. Director, Regulatory Affairs, US and Canada
Sara Siggelkow, Program Lead I, HCV Clinical Program Development
Yijie Zhou, Associate Director, Statistics
Troy ZumBrunnen, Director, Regulatory Affairs, US and Canada
Jamie Austin Manager, Regulatory Affairs, US and Canada

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for March 16, 2015 between AbbVie Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

AbbVie Inc. is developing the fixed-dose combination of dasabuvir, ombitasvir, paritaprevir and ritonavir (3QD tablet) for the treatment of genotype 1 chronic hepatitis C virus (HCV) infection.

This fixed-dose combination tablet is an alternative formulation of the currently-approved drug product Viekira Pak (NDA 206619), consisting of ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets. AbbVie has requested an End-of-Phase 2 meeting to discuss the adequacy of current bioavailability data and exposure-response modeling to support an NDA without the need for additional safety and efficacy trials. In addition, AbbVie would like to discuss their proposal for updating the 3QD prescribing information with data from ongoing trials with Viekira Pak. Finally, AbbVie is requesting DAVP feedback on the design of their proposed clinical trial [REDACTED] ^{(b)(4)} as an alternative to the currently recommended weight-based, twice daily dosage of RBV.

2.0 DISCUSSION

AbbVie's questions are shown below in ***bold italicized*** font. The Division's preliminary responses of March 12, 2015 are shown in standard font. The teleconference initially scheduled for March 16, 2015 was subsequently rescheduled for April 16, 2015 due to the receipt on March 11, 2015 of high level summary data from M14-240. Following review of data from M14-240 submitted on March 24, 2015, the Division is providing additional responses to Questions 1 and 2, shown in *italicized* font below.

2.1. Clinical/Clinical Pharmacology

Question 1:

Does the FDA agree that the results from the pivotal bioavailability study (Study M14-566) and the exposure-response analyses are sufficient to support an NDA for the 3QD tablet and that no additional clinical studies or additional modeling/simulations are required to establish the similarity of the safety and efficacy profiles between the 3QD and reference 3-DAA formulations?

March 12 FDA Response to Question 1:

We received high level summary of data from trial M14-240 on March 11, 2015. Based on a preliminary analysis of the summary data and our review of the meeting package, the clinical relevance of changes in dasabuvir exposures observed in the Fed BE Trial (trial M14-566) and Fasted BE trial (M14-240) may be assessed by the available exposure-response analysis.

We are very concerned about the significantly higher exposures of paritaprevir and dasabuvir observed under fed (high fat) conditions and the potential effect of these higher exposures on the safety profile of paritaprevir and dasabuvir. This new information has significant bearing on our interpretation of your proposal for NDA submission and we request that you address the comments below under 3.0 Additional Comments, 3.1 Clinical Pharmacology. We will review your responses and provide a response to questions 1 and 2.

April 13 FDA Response to Question 1:

Based on the review of the additional information provided on March 24, 2015, we agree that the results of trial M14-566 and the exposure-response analysis can support the NDA for the 3QD tablet. The adequacy of all the information provided in the NDA will be assessed during the review of the NDA.

Question 2:

Does the FDA agree that [REDACTED] (b) (4)

March 12 FDA Response to Question 2:

Please refer to the response to Question 1 above.

April 13 FDA Response to Question 2:

The Division agrees that if the 3QD tablet is approved based on pharmacokinetic data, [REDACTED] (b) (4)

Question 3:

March 12 FDA Responses to Question 3:

Does the FDA agree that the proposed design of clinical Study [REDACTED] (b)(4) ***is sufficient to support a post-approval efficacy supplement to amend the RBV dosing recommendations from weight-based BID dosing to low dose QD dosing in all genotype 1 subpopulations that require RBV?***

[REDACTED] (b) (4)

[REDACTED] (b) (4)



b. Does the FDA agree with the proposed primary efficacy endpoint?

The Division agrees that SVR12 is an acceptable endpoint for this trial. Please ensure that available SVR24 and SVR48 data from study participants are included in a supplemental filing.



April 13 FDA Response to Question 3:

We acknowledge your March 24, 2015 response to the comments above stating that the advice was received and no additional discussion regarding (b)(4) is necessary.

3.0 ADDITIONAL COMMENTS

3.1 Clinical Pharmacology

1. Please provide all available pharmacokinetic data (individual data and summary) from trials M14-566 and (b)(4) and populate the following table for paritaprevir, ombitasvir, and dasabuvir.

Condition		C_{max} Median (range)	AUC Median (range)
Fasting	3-DAA		
	3-QD		
Standardized Breakfast [Caloric and fat content]	3-DAA		
	3-QD		
High Fat Breakfast [Caloric and fat content]	3-DAA		
	3-QD		

2. Please provide a graph which shows the distribution of paritaprevir exposures (C_{max} and AUC) after administration of 3-DAA and 3-QD under fasting conditions, standardized breakfast, and high fat conditions. In the same graph, include the distribution of paritaprevir exposures from the Phase III trials of the 3-DAA regimen.
 - a. Please create similar graphs for ombitasvir and dasabuvir.
3. Based on the exposure-response analysis conducted for the 3-DAA, a 0.5-2 fold change in mean exposures of all the components of the 3-DAA was not anticipated to be clinically relevant. The summary of food effect data on the 3-QD (trial M14-240) suggests that the mean exposures of paritaprevir in the fed state (high fat conditions) may increase by 4.6-6 fold and the mean exposure of dasabuvir may increase by at least 6-fold. Hence, please explain how the anticipated increase in exposures of paritaprevir and ombitasvir from the 3-QD in the fed state (high fat conditions) are supported by the available exposure-response (safety) analysis.
4. Please statistically compare the PK data collected on the various components of the 3-DAA under high fat conditions as "reference" and the PK data collected on the various components of the 3-QD regimen under high fat conditions as "test" treatment. The comparison will help with assessing the magnitude of increase in the PK parameters for

the various components of the 3-QD as compared to the exposures of the various components of the 3-DAA.

5. Please provide the caloric and fat content of the “standardized breakfast” used in trial M14-566.

We acknowledge your responses to the Clinical Pharmacology comments submitted on March 24, 2015 and have no further questions. Please refer to the response to Question 1 above.

3.2 Biopharmaceutics

6. Based on the Code of Federal Regulations, [21 CFR 320.25 (f)], since a part of your FDC drug product includes an extended-release component, you should provide the data supporting the approval of the extended-release claim made for your FDC product.
7. Evaluate the alcohol induced dose dumping of the ER component of your FDC product, by first conducting an *in vitro* alcohol dose dumping test. Depending on the result of the *in vitro* testing you may have to follow-up with an *in vivo* alcohol-dose dumping study. Note that if the results show an interaction of the ER component of your FDC product with alcohol, you should discuss these results with FDA prior to NDA submission.

The following points should be considered during the evaluation of the *in vitro* alcohol-induced dose dumping of the ER component of your FDC product:

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
- In general;
 - If the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.
 - If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.
 - If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
 - If the dissolution of the ER component of your FDC product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.

- The shape of the dissolution profiles should be compared to determine if the extended release characteristics are maintained, especially in the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).

The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

We acknowledge your responses to the Biopharmaceutics comments submitted on March 24, 2015. The provided information is currently under review.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors

regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

6.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

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/s/

KATHERINE SCHUMANN
04/14/2015