

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209512Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209512 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Norvir Established/Proper Name: ritonavir Dosage Form: Oral powder		Applicant: AbbVie, Inc. Agent for Applicant (if applicable):
RPM: Nina Mani		Division: Division of Antiviral Products
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><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></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 <u>June 7, 2017</u> 		<input 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 _____		<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):
 (*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 checked="" 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:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• 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 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)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ 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 (<i>approvals only</i>)	<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: Approval; June 7, 2017
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> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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 type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" 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> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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 	<input checked="" type="checkbox"/> Included
❖ 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> 	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> January 25, 2017 & June 7, 2017 DMEPA: <input checked="" type="checkbox"/> May 16, 2017 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> May 30, 2017 OPDP: <input checked="" type="checkbox"/> May 30, 2017 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> May 23, 2017 Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	January 26, 2017
❖ 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>	<input checked="" type="checkbox"/> Completed (Do not include)
❖ 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 <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: 	The product has Orphan designation for the indication.
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<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>) 	
<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>	
❖ 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>)	See AP file
❖ 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)	See AP file
❖ 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 type="checkbox"/> N/A
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> June 30, 2014
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input 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>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> May 9, 2017
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)		May 9, 2017
• Social scientist review(s) (if OTC drug) (indicate date for each review)		<input type="checkbox"/> 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 (indicate date of review/memo)		In Clinical Review, Page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵		<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		<input type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 		<input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		<input type="checkbox"/> None requested
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input checked="" type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)		<input checked="" type="checkbox"/> May 9, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> February 16, 2017

⁵ [REDACTED] (b) (4), 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).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> May 1, 2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 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>)	<input checked="" type="checkbox"/> May 24, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> CDRH; May 24, 2017
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Pg. 28 of Drug Product Review; April 13, 2017
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	May 24, 2017 <input checked="" type="checkbox"/> Acceptable <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) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <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 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ 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	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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

/s/

NINA MANI
06/09/2017

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 209512
NDA 20659/S-67
NDA 22417/S-19

Name of Drug: NORVIR (ritonavir) oral powder, 100 mg
NORVIR[®] (ritonavir) oral solution, 80 mg/mL (NDA 20659)
NORVIR[®] (ritonavir) tablets, 100 mg (NDA 22417)

Applicant: Abbvie Inc.

Labeling Reviewed

Submission Date: June 5, 2017

Receipt Date: June 5, 2017

Background and Summary Description:

Abbvie submitted an original NDA for a new oral powder dosage form and is indicated for use in combination with other antiretroviral products for the treatment of pediatric HIV-1 infection. This dosage form is free of alcohol and propylene glycol, both of which are present in the currently marketed Norvir oral solution, making it safer for use in this patient population.

Abbvie also submitted supplements for the Norvir tablet and Norvir oral solution since they share labeling with the new Norvir oral powder dosage form.

This review focuses on the changes proposed by the Sponsor and the Agency to the Full Prescribing Information, Patient Information and Instructions for Use (only needed for the oral powder).

The sponsor's final draft labeling, submitted on June 5, 2017 is being compared to the last approved labeling dated December 22, 2016.

Review

GENERAL

Throughout the labeling, minor editorial changes were made, such as changes in punctuation, removing trailing zeros, spelling, and changes in formatting such as spacing adjustments, font

and font size, italicization, underlining sub-headings, etc. Changes in the labeling are in track changes.

HIGHLIGHTS

1. The oral solution and powder **dosage forms** are updated as follows:

NORVIR (ritonavir) oral solution, (b) (4)
NORVIR (ritonavir) oral powder

2. The **Boxed Warning** is updated as follows:

(4) (b) (4) .1) (b) (4)

3. The **RECENT MAJOR CHANGES** section is updated as follows:

Indications and Usage (1)

6/2017

Dosage and Administration (2)

(b) (4) 6/2017

7

- General Dosing and Administration Recommendations (2.1)

6/2017

- Recommended Adult Dosage (2.2)

6/2017

- Recommended Pediatric Dosage (2.3)

6/2017

- Preparation of Norvir Oral Powder (2.4)

6/2017

- Dose Modification due to Drug Interaction (2.5)

6/2017

4. The **INDICATIONS AND USAGE** section is updated as follows:

NORVIR (b) (4) tablets and oral solution are HIV protease (b) (4) inhibitors indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1)

NORVIR oral powder is indicated in combination with other antiretroviral agents for the treatment of pediatric patients with HIV-1 infection (1)

5. The **DOSAGE AND ADMINISTRATION** section is updated as follows:

- Adult patients: 600 mg twice-day with meals (2.42)
- Pediatrics patients: The recommended twice daily dose for children greater than one month of age is based on body surface area and should not exceed 600 mg twice daily with meals (2.23)
- NORVIR oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 44 weeks has been attained (2.23, 5.2)
- NORVIR oral powder can only be used for dosing increments of 100 mg (2.3)

- [Instructions for Use should be followed for preparation and administration of NORVIR oral powder \(2.4\)](#)

6. The **DOSAGE FORMS AND STRENGTHS** section is updated as follows:

- Tablet: 100 mg (b) (4) (3)
- Oral solution: 80 mg (b) (4) per milliliter (3)
- [Oral Powder: 100 mg per packet \(3\)](#)

7. The **WARNINGS AND PRECAUTIONS** section is updated as follows:

- [Hepatotoxicity](#) (b) (4): Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations (5.3, 8.6)

8. The **revised** date was updated as follows:

Revised: (b) (4) [06/2017](#)

FULL PRESCRIBING INFORMATION: CONTENTS*

This section is revised as follows:

(b) (4)

[2 DOSAGE AND ADMINISTRATION](#)

- [2.1 General Dosing and Administration Recommendations](#)
- [2.2 Recommended Adult Dosage](#)
- [2.3 Recommended Pediatric Dosage](#)
- [2.4 Preparation of Norvir Oral Powder](#)
- [2.5 Dose Modification due to Drug Interaction](#)

[5 WARNINGS AND PRECAUTIONS](#)

- (b) (4)
- [5.3 Hepatotoxicity](#)

[10 OVERDOSAGE](#)

(b) (4)

[16 HOW SUPPLIED/STORAGE AND HANDLING](#)

(b) (4)

FULL PRESCRIBING INFORMATION

The **BOXED WARNING** is updated as follows:

[see Contraindications

(b) (4)

4), *Warnings and Precautions (5.1)*].

INDICATIONS AND USAGE is updated as follows:

(b) (4) [NORVIR tablets and oral solution are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.](#)

[NORVIR oral powder](#) is indicated in combination with other antiretroviral agents for the treatment of [pediatric patients with](#) HIV-1 infection.

DOSAGE AND ADMINISTRATION is updated as follows and with information regarding administration of Norvir Powder:

2.1 General Dosing and Administration Recommendations

- [NORVIR must be used in combination with other antiretroviral agents.](#)
- [NORVIR oral powder should be mixed with soft food such as apple sauce or vanilla pudding, or mixed with liquid such as water, chocolate milk, or infant formula \[see Dosage and Administration \(2.4\) and Instructions for Use\]. The bitter aftertaste of NORVIR oral powder may be lessened if administered with food.](#)

General Dosing Guidelines

2.12 Recommended Adult (b) (4) Dosage

Recommended Dosage for Treatment of HIV-1:

The recommended dosage of (b) (4) [NORVIR](#) is 600 mg twice daily by mouth to be taken with meals. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. (b) (4) [NORVIR](#) should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. The maximum dose of 600 mg twice daily should not be exceeded upon completion of the titration.

2.23 Recommended Pediatric (b) (4) Dosage

(b) (4) [NORVIR must](#) be used in combination with other antiretroviral agents [*see Dosage and Administration (2)*]. The recommended dosage of (b) (4) [NORVIR in pediatric patients older](#) than 1 month is 350 to 400 mg per m² twice daily by mouth to be taken with meals and should not exceed 600 mg twice daily. (b) (4) [NORVIR](#) should be started at 250 mg per m² twice daily and increased at 2 to 3 day intervals by 50 mg per m² twice daily. If patients do not tolerate 400 mg per m² twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered.

Pediatric Dosage Guidelines for Oral Solution

NORVIR oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 44 weeks has been attained [*see Warnings and Precautions (5.2)*].

NORVIR oral solution contains (b) (4) (v/v) alcohol and (b) (4) % (w/v) propylene glycol. Special attention should be given to accurate calculation of the dose of NORVIR, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, and overdose. This is especially important for young children. Total amounts of alcohol and propylene glycol from all medicines that are to be given to pediatric patients 1 to 6 months of age should be taken into account in order to avoid toxicity from these excipients [*see Warnings and Precautions (5.2) and Overdosage (10)*]. (b) (4)

Table 1. Pediatric Dosage Guidelines for Oral Solution*

Body Surface Area (m ²)	Twice Daily Dose 250 mg per m ²	Twice Daily Dose 300 mg per m ²	Twice Daily Dose 350 mg per m ²	Twice Daily Dose 400 mg per m ²
0.20	0.6 mL (50 mg)	0.75 mL (60 mg)	0.9 mL (70 mg)	1.0 mL (80 mg)
0.25	0.8 mL (62.5 mg)	0.9 mL (75 mg)	1.1 mL (87.5 mg)	1.25 mL (100 mg)
0.50	1.6 mL (125 mg)	1.9 mL (150 mg)	2.2 mL (175 mg)	2.5 mL (200 mg)
0.75	2.3 mL (187.5 mg)	2.8 mL (225 mg)	3.3 mL (262.5 mg)	3.75 mL (300 mg)
1.00	3.1 mL (250 mg)	3.75 mL (300 mg)	4.4 mL (350 mg)	5 mL (400 mg)
1.25	3.9 mL (312.5 mg)	4.7 mL (375 mg)	5.5 mL (437.5 mg)	6.25 mL (500 mg)
1.50	4.7 mL (375 mg)	5.6 mL (450 mg)	6.6 mL (525 mg)	7.5 mL (600 mg)

*The concentration of the oral solution is 80 mg per mL.

Body surface area (BSA) can be calculated as follows¹:



Pediatric Dosage Guidelines for Oral Powder

NORVIR oral powder should be used only for dosing increments of 100 mg. NORVIR powder should not be used for doses less than 100 mg or for incremental doses between 100 mg intervals. NORVIR oral solution is the preferred formulation for patients requiring doses less than 100 mg or incremental doses between 100 mg intervals.

When NORVIR oral powder is used with other protease inhibitors (e.g. atazanavir, darunavir, fosamprenavir, or tipranavir), prescribers should consult the full prescribing information and clinical study information of these protease inhibitors [see Warnings and Precautions (5.1), and

(b) (4)



Drug Interactions (7)

1. When NORVIR oral powder is used as the sole protease inhibitor in a regimen, refer to Table 1 for dosing recommendations.

2.4 Preparation of Norvir Oral Powder

For details on the preparation and administration of NORVIR oral powder, see *Instructions for Use*. NORVIR oral powder should only be used for dosing increments of 100 mg.

Prepare the dose using the required number of packets. For example, use one packet for doses of 100 mg and two packets for doses of 200 mg). Pour and mix the entire contents of each packet over soft food or liquid. All of the powder mixed with soft food or liquid should be administered within 2 hours of preparation.

The prescribed dose of NORVIR oral powder can be administered via a feeding tube after being mixed with water (see *Instructions for Use*). Follow the instructions for the feeding tube to administer the medicine.

2.5 Dose Modification due to Drug Interaction

Dose reduction of NORVIR is necessary when used with other protease inhibitors: atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir.

Prescribers should consult the full prescribing information and clinical study information of these protease inhibitors if they are co-administered with a reduced dose of ritonavir [see *Warnings and Precautions (5.1)*, and *Drug Interactions (7)*].

DOSAGE FORMS AND STRENGTHS is updated with information about Norvir Powder:

- NORVIR Oral Powder

Beige/pale yellow to yellow powder in child-resistant packet. Each packet contains 100 mg of ritonavir.

WARNINGS AND PRECAUTIONS, subsection 5.3 is updated as follows:

5.3 (b) (4) **Hepatotoxicity**

DRUG INTERACTIONS, Table 5 is updated as follows:

Concomitant Drug Class: Drug Name	Effect on Concentration of Ritonavir or Concomitant Drug	Clinical Comment
PDE5 Inhibitors: avanafil sildenafil, tadalafil, vardenafil	↑ avanafil ↑ sildenafil ↑ tadalafil ↑ vardenafil	The following dose adjustments are recommended for use of tadalafil ^{(b) (4)} Adcirca® with ritonavir:

OVERDOSAGE is updated with removal of sub-section numbers:

[10.1 Acute Overdosage - Human Overdose Experience](#)

[10.2 Management of Overdosage](#)

DESCRIPTION is updated with information about Norvir Powder:

[NORVIR oral powder is beige/pale yellow to yellow and is available for oral administration as a packet containing 100 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, and colloidal silicon dioxide.](#)

CLINICAL PHARMACOLOGY is updated as follows with information about the Norvir Powder:

1. In sub-section 12.3, Pharmacokinetics:

Absorption

[After administration of a single 100 mg dose under fed conditions \(617 Kcal, 29% calories from fat\), ritonavir oral powder \$AUC_{\(0-\infty\)}\$ and \$C_{max}\$ are bioequivalent to the oral solution.](#)

Effect of Food on Oral Absorption

[^{\(b\) \(4\)} The bioavailability of NORVIR tablet, oral solution ^{\(b\) \(4\)} and oral powder is decreased under ^{\(b\) \(4\)} fed conditions as compared to fasted conditions.](#)

Following the administration of a 100 mg tablet dose of NORVIR, C_{max} and AUC_{inf} of ritonavir were decreased by 21-23% under moderate fat (857 Kcal, 30% from fat) or high fat conditions (917 Kcal, 60% calories from fat) relative to fasting conditions (b) (4)

Following the (b) (4) administration of a 600 mg dose NORVIR oral solution, C_{max} and AUC_{inf} of ritonavir were decreased by 23% and 7 (b) (4)%, respectively, under nonfasting conditions (514 Kcal, 10% from fat) relative to fasting conditions. Dilution of the oral solution, within one hour of administration, with 240 mL of chocolate milk, Advera[®] or Ensure[®] did not significantly affect the extent and rate of ritonavir absorption (b) (4)

(b) (4)

(b) (4)

Following the administration of a 100 mg dose of NORVIR oral powder, C_{max} and AUC_{inf} of ritonavir were decreased by 23-49% under moderate fat (617 Kcal, 29% calories from fat) or high fat conditions (917 Kcal, 60% calories from fat) relative to fasting conditions.

(b) (4)

Cardiac Electrophysiology

HOW SUPPLIED/STORAGE AND HANDLING is updated as follows and with information about the Norvir Powder:

[REDACTED] (b) (4)
[REDACTED] ÷

16.1 NORVIR Tablets, 100 mg Ritonavir

16.2 NORVIR Oral Solution, 80 mg per mL Ritonavir

Recommended Storage

Store [REDACTED] (b) (4) at room temperature 20°-25°C (68°-77°F).

NORVIR Oral Powder, 100 mg Packet

NORVIR (ritonavir) oral powder is beige/pale yellow to yellow, supplied in packets containing 100 mg of ritonavir.

30 foil/laminate, child-resistant packets per carton (NDC 0074-3399-30).

Recommended Storage

Store at or below 30°C (86°F).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

[REDACTED] (b) (4)

General Information Dosing and Preparation Information

- ^{(b) (4)} Advise patients and caregivers to pay special attention to accurate preparation and administration of their dose to minimize the risk of accidental overdose or underdose of NORVIR.
- ^{(b) (4)} For Norvir oral powder, advise patients or caregivers to read and follow the Instructions for Use for preparing the correct dose.
- Advise caregivers to inform their healthcare provider if their children's weight changes in order to make sure that the child's NORVIR dose is ^{(b) (4)} adjusted as needed.
- ^{(b) (4)} Advise patients to take NORVIR with meals.
- ^{(b) (4)} For adult patients taking NORVIR tablets, the maximum dose of 600 mg twice daily by mouth with meals should not be exceeded.

^{(b) (4)}

- ^{(b) (4)} Advise patients to remain under the care of a physician while using NORVIR ^{(b) (4)} and to take NORVIR and other concomitant antiretroviral therapy every day as prescribed. NORVIR must always be used in combination with other antiretroviral drugs. ^{(b) (4)} Advise patients not to alter the dose or discontinue therapy without consulting with their ^{(b) (4)} healthcare provider. If a dose of NORVIR is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

- Continued NORVIR therapy at a dose of 600 mg twice daily following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.
 NORVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using NORVIR.

^{(b) (4)}

Drug Interactions

- NORVIR may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's Wort.
- Instruct patients receiving combined hormonal contraception to use an effective alternative contraceptive method or an additional barrier method during therapy with NORVIR because hormonal levels may decrease [*see Drug Interactions (7.3), Use in Specific Populations (8.3)*].

Hepatotoxicity

Pre-existing liver disease including Hepatitis B or C can worsen with use of NORVIR. This can be seen as worsening of transaminase elevations or hepatic decompensation. (b) (4)

Advise patients that their liver function tests will need to be monitored closely especially during the first several months of NORVIR treatment and that they should notify their healthcare provider if they develop the signs and symptoms of worsening liver disease including loss of appetite, abdominal pain, jaundice, and itchy skin. [*see Warnings and Precautions (5.3)*].

Pancreatitis

Pancreatitis, including some fatalities, has been observed in patients receiving NORVIR therapy.

(b) (4) Advise patients (b) (4) to notify their healthcare provider of signs and symptoms (nausea, vomiting, and abdominal pain) that might be suggestive of pancreatitis. [*see Warnings and Precautions (5.4)*].

Allergic Reactions/Hypersensitivity

Skin rashes ranging in severity from mild to Stevens-Johnson syndrome have been reported in patients receiving NORVIR. (b) (4) [Advise patients](#) to contact their healthcare provider if they develop a rash while taking NORVIR. (b) (4)

(b) (4) [\[see Warnings and Precautions \(5.5\)\]](#).

(b) (4)

[PR Interval Prolongation](#)

NORVIR may produce changes in the electrocardiogram (e.g., PR prolongation). (b) (4) [Advise patients to](#) consult their (b) (4) [healthcare provider](#) if they experience symptoms such as dizziness, lightheadedness, abnormal heart rhythm or loss of consciousness. [\[see Warnings and Precautions \(5.6\)\]](#).

(b) (4)

[Lipid Disorders](#)

[Advise patients that treatment](#) with NORVIR therapy can result in substantial increases in the concentration of total cholesterol and triglycerides. [\[see Warnings and Precautions \(5.7\)\]](#).

(b) (4) [Diabetes Mellitus/Hyperglycemia](#)

[Advise patients that new](#) onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported. (b) (4) [and](#) to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or unusual weight loss and/or an increased blood sugar while on NORVIR as they may require a change in their diabetes treatment or new treatment. [\[see Warnings and Precautions \(5.7\)\]](#).

☐ Immune Reconstitution Syndrome

Advise patients that immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including NORVIR- [see Warnings and Precautions (5.9)].

☐ Fat Redistribution

Advise patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time- [see Warnings and Precautions (5.10)].

☐ Patients with Hemophilia

Advise patients with hemophilia that they may experience increased bleeding when treated with protease inhibitors such as NORVIR- [see Warnings and Precautions (5.11)].

NORVIR Oral Solution Not Recommended During Pregnancy

Advise pregnant women that use of NORVIR oral solution during pregnancy is not recommended due to its alcohol content [see Dosage and Administration (2.1) and Use in Specific Population (8.1)].

Pregnancy Exposure Registry

Inform patients that there is an antiretroviral pregnancy registry that monitors fetal outcomes of pregnant women exposed to NORVIR [see Use in Specific Populations (8.1)].

(b) (4)

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk [see Use in Specific Populations (8.2)].

Manufacturing information at the end of the USPI is updated as follows:

NORVIR oral powder is manufactured for:

AbbVie Inc.

North Chicago, IL 60064 USA

(b) (4)

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Patient Information

The Patient Labeling Team recommended reformatting and updating the Patient Information section as follows:

<u>Patient Information</u>		
<u>NORVIR®</u> <u>(NOR-VEER)</u> <u>(ritonavir)</u> <u>Tablet</u>	<u>NORVIR®</u> <u>(NOR-VEER)</u> <u>(ritonavir)</u> <u>Oral Solution</u>	<u>NORVIR®</u> <u>(NOR-VEER)</u> <u>(ritonavir)</u> <u>Oral Powder</u>
<u>What is the most important information I should know about NORVIR?</u> <ul style="list-style-type: none"><u>NORVIR can interact with other medicines and cause serious side effects. It is important to know the medicines that should not be taken with NORVIR. See the section "Who should not take NORVIR?"</u>		
<u>What is NORVIR?</u> <ul style="list-style-type: none"><u>NORVIR tablets and oral solution are prescription medicines that are used with other antiviral medicines to treat people with human immunodeficiency virus (HIV-1) infection.</u><u>NORVIR oral powder is a prescription medicine that is used with other antiviral medicines to treat children with HIV-1 infection.</u> <u>HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).</u>		

Do not take NORVIR if you or your child:

- are allergic to ritonavir or any of the ingredients in NORVIR. See the end of this leaflet for a complete list of ingredients in NORVIR.
- take any of the following medicines:
 - alfuzosin (UROXATRAL[®])
 - amiodarone (CORDARONE[®], NEXTERONE[®], PACERONE[®])
 - cisapride (PROPULSID[®], PROPULSID QUICKSOLV[®])
 - colchicine (COLCRYS[®], COL-PROBENECID[®], Probenecid and Colchine)
 - dronedarone (MULTAQ[®])
 - ergot-containing medicines, including:
 - dihydroergotamine (D.H.E. 45[®], MIGRANAL[®])
 - ergotamine tartrate (CAFERGOT[®], MIGEROT[®], ERGOSTAT[®], MEDIHALER ERGOTAMINE[®], WIGRAINE[®], WIGRETTES[®])
 - methylergonovine maleate (ERGOTRATE[®], METHERGINE[®])
 - flecainide (TAMBOCOR[®])
 - lovastatin (ADVICOR[®], ALTOPREV[®], MEVACOR[®])
 - lurasidone (LATUDA[®])
 - midazolam, when taken by mouth
 - pimozide (ORAP[®])
 - propafenone (RYTHMOL[®])
 - quinidine (NUEDEXTA[®], QUINAGLUTE[®], RADIOQUIN[®], QUINIDEX[®], and others)
 - sildenafil (REVATIO[®]) only when used for treating the lung problem, pulmonary arterial hypertension (PAH)
 - simvastatin (SIMCOR[®], VYTORIN[®], ZOCOR[®])
 - St. John's Wort (Hypericum perforatum) or a product that contains St. John's wort
 - triazolam (HALCION[®])
 - voriconazole (VFEND[®]) if your NORVIR dose is 400 mg every 12 hours or greater

Serious problems can happen if you or your child takes any of these medicines with NORVIR.

Before taking NORVIR, tell your healthcare provider about all of your medical conditions, including if you or your child

- have liver problems, including Hepatitis B or Hepatitis C
- have heart problems
- have high blood sugar (diabetes)
- have bleeding problems or hemophilia
- are pregnant or plan to become pregnant.
 - NORVIR oral solution contains alcohol. You should not take NORVIR oral solution during pregnancy because there is no known safe level of alcohol exposure during pregnancy. Tell your healthcare provider if you become pregnant during treatment with NORVIR.
 - NORVIR may reduce how well hormonal birth control works. Females who may become pregnant should use another effective form of birth control or an additional barrier method of birth control during treatment with NORVIR.
 - **Pregnancy Registry:** There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take NORVIR.**
 - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
 - NORVIR may pass into your breastmilk.
 - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with NORVIR. Keep a list of your medicines to show our healthcare provider and pharmacist.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with NORVIR.
- Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take NORVIR with other medicines.

How should I take NORVIR?

See the detailed Instructions for Use for information about how to give or take a dose of NORVIR oral powder.

- Take NORVIR exactly as your healthcare provider tells you to take it.
- You should stay under a healthcare provider's care during treatment with NORVIR. Do not change your dose of NORVIR or stop your treatment without talking with your healthcare provider first.
- If your child is taking NORVIR, your child's healthcare provider will decide the right dose based on your child's height and weight. Tell your healthcare provider if your child's weight changes. If your child does not tolerate NORVIR oral solution or NORVIR oral powder, ask your child's healthcare provider for advice.
- Swallow NORVIR tablets whole. Do not chew, break, or crush tablets before swallowing. If you cannot swallow NORVIR tablets whole, tell your healthcare provider. You may need a different medicine.
- Take NORVIR with meals.
- **NORVIR oral solution is peppermint or caramel flavored.**
 - You can take it alone, or may improve the taste by mixing it with 8 ounces of chocolate milk, Ensure[®], or Advera[®].
 - NORVIR oral solution should be taken within 1 hour after mixing with these fluids.
 - Ask your healthcare provider, nurse or pharmacist about other ways to improve the taste of NORVIR oral solution.
- Do not run out of NORVIR. Get your NORVIR prescription refilled from your healthcare provider or pharmacy before you run out.
- If you miss a dose of NORVIR, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, wait and take the next dose at the regular time. Do not double the next dose.
- If you take too much NORVIR, call your local poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of NORVIR?

NORVIR can cause serious side effects including:

- **See "What is the most important information I should know about NORVIR?"**
- **Liver problems.** Some people taking NORVIR in combination with other antiviral medicines have developed liver problems which may be life-threatening. Your healthcare provider should do regular blood tests during your combination treatment with NORVIR. If you have chronic hepatitis B or C infection, your healthcare provider should check your blood tests more often because you have an increased chance of developing liver problems. Tell your healthcare provider right away if you get any of the following signs and symptoms of liver problems:
 - loss of appetite
 - yellowing of your skin or whites of your eyes
 - pain or tenderness on your right side below your ribs
 - itchy skin
- **Inflammation of your pancreas (pancreatitis).** NORVIR can cause serious pancreas problems, which may lead to death. Tell your healthcare provider right away if you have signs or symptoms of pancreatitis such as:
 - nausea
 - vomiting
 - stomach (abdomen) pain
- **Allergic reactions.** Sometimes these allergic reactions can become severe and require treatment in a hospital. Call your healthcare provider right away if you develop a rash. Stop taking NORVIR and get medical help right away if you have any of the following symptoms of a severe allergic reaction:

- trouble breathing
- wheezing
- dizziness or fainting
- throat tightness or hoarseness
- fast heartbeat or pounding in your chest
(tachycardia)
- sweating
- swelling of your face, lips or tongue
- muscle or joint pain
- blisters or skin lesions
- mouth sores or ulcers

Changes in the electrical activity of your heart called PR prolongation. PR prolongation can cause irregular heartbeats. Tell your healthcare provider right away if you have symptoms such as:

- dizziness
- lightheadedness
- feel faint or pass out
- abnormal heart beat

• **Increase in cholesterol and triglyceride levels.** Treatment with NORVIR may increase your blood levels of cholesterol and triglycerides. Your healthcare provider should do blood tests before you start your treatment with NORVIR and regularly to check for an increase in your cholesterol and triglycerides levels.

• **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including NORVIR can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often during treatment with NORVIR.

• **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.

• **Change in body fat** can happen in some people who taking HIV-1 medicines. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.

• **Increased bleeding for hemophiliacs.** Some people with hemophilia have increased bleeding with protease inhibitors including NORVIR.

The most common side effects of NORVIR include:

- diarrhea
- nausea
- vomiting
- upper and lower stomach (abdominal) pain
- tingling feeling or numbness in hands or feet or around the lips
- rash
- feeling weak or tired

NORVIR oral solution contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of NORVIR, it could make him/her sick from too much alcohol. Go to the nearest emergency room right away if this happens.

These are not all of the possible side effects of NORVIR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NORVIR?

- Store NORVIR tablets and NORVIR oral solution in the original container given to you by the pharmacist.
- Use NORVIR tablets, NORVIR oral solution, and NORVIR oral powder by the expiration date.

Store NORVIR tablets:

- Store below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for seven days permitted.
- Exposure to high humidity outside the original container for longer than 2 weeks is not recommended.

Store NORVIR oral solution:

- At room temperature between 20°C to 25°C (68°F to 77°F).
- Do not refrigerate.
- Shake well before each use.
- Keep away from heat.
- Keep bottle cap tightly closed.

Store NORVIR oral powder:

- At or below 30°C (86°F).

Keep NORVIR and all medicines out of the reach of children.

General information about the safe and effective use of NORVIR

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use NORVIR for a condition for which it was not prescribed. Do not give NORVIR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about NORVIR that is written for healthcare professionals.

What are the ingredients in NORVIR?

Active ingredient: ritonavir

Inactive ingredients:

NORVIR tablet: copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The film coating contains: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, polyethylene glycol 3350, 3350, colloidal silicon dioxide, and polysorbate 80.

NORVIR oral solution: ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C Yellow No. 6.

NORVIR oral powder: copovidone, sorbitan monolaurate, and colloidal silicon dioxide.

NORVIR tablets and NORVIR oral solution are manufactured by: AbbVie Inc., North Chicago, IL 60064 USA

NORVIR oral powder is manufactured for: AbbVie Inc., North Chicago, IL 60064 USA

For more information, call 1-800-633-9110.

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: (b) (4) June 2017

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

Recommendations

It will be conveyed to the applicant that labeling is acceptable, and an approval letter should be sent. Please refer to the clinical and clinical pharmacology, reviews and addenda for additional information.

Nina Mani

Regulatory Project Manager

Date

Karen Winestock

Chief, Project Management Staff

Date

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/s/

NINA MANI
06/07/2017

KAREN D WINESTOCK
06/07/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512: USPI Revisions
Date: Friday, June 02, 2017 2:02:12 PM

Thank you Nina, we have received the changes and will respond by the due date.

Regards,
Sherie

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

abbvie

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From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Friday, June 02, 2017 12:51 PM
To: Masse, Sherie V
Subject: NDA 209512: USPI Revisions

Hi Sherie:

Attached are our latest USPI/PPI revisions. The IFU revisions and rationale submitted on June 1, 2017 are acceptable.

The following revisions are being recommended in the USPI/PPI:

1. HL/D & A
2. Revised language in Section 2.4

3. Two comments in the PPI

Please accept all changes you are in agreement with and document your agreement by some mechanism; only keep in track changes those that need further discussion.

Kindly acknowledge receipt of this communication and please submit revised labeling by **10:00 am, Monday, June 5, 2017**.

Regards,
Nina

Nina Mani
Senior Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
06/02/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512: IFU Revisions
Date: Wednesday, May 31, 2017 12:57:10 PM
Attachments: [image012.png](#)
[image013.png](#)
[image014.png](#)
[image015.emz](#)
[image017.png](#)
[image018.png](#)
[image019.png](#)
[image020.png](#)
[image021.png](#)
[image001.png](#)

Thank you Nina! I received both this comment and the previous hepatotoxicity comment.

Regards,
Sherie

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



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From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, May 31, 2017 11:35 AM
To: Masse, Sherie V
Subject: RE: NDA 209512: IFU Revisions

Hi Sherie:

DMEPA has added information to Step 2. No additional Figures are needed for Steps 1 and Step 8.

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

Kindly acknowledge receipt and submit IFU by **COB Thursday, June 1, 2017** together with the USPI and PPI.

Regards,
Nina

From: Mani, Nina
Sent: Wednesday, May 31, 2017 12:23 PM

To: 'Masse, Sherie V'
Subject: RE: NDA 209512

Hi Sherie:

Also, in the USPI, in HL, W& P [REDACTED] (b) (4) ” has been changed to “Hepatotoxicity”. For consistency, please make similar changes in FPI’s, TOC, W& P, section 5, sub-section 5.3, and in the Patient Counseling section.

Thanks,
Nina

From: Mani, Nina
Sent: Wednesday, May 31, 2017 12:21 PM
To: 'Masse, Sherie V'
Subject: RE: NDA 209512

Hi Sherie:

Please submit the USPI and PPI as planned. I am waiting to hear back about the IFU from the Patient Labeling and DMEPA teams and will get back to you shortly.

Thanks,
Nina

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Tuesday, May 30, 2017 4:54 PM
To: Mani, Nina
Subject: RE: NDA 209512

Thank you Nina – I have received the comments and we will respond accordingly.

Regards,
Sherie

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

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From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Tuesday, May 30, 2017 3:27 PM
To: Masse, Sherie V
Subject: RE: NDA 209512

Hi Sherie:

Attached are our latest labeling revisions. Please note that the PPI and IFU have been extensively revised and contain Division and Patient labeling comments. Please do **not** make revisions in the PPI attached to the USPI; make them in the standalone PPI.

Kindly accept all changes you are in agreement with and document your agreement by some mechanism; only keep in track changes those that need further discussion.

Kindly acknowledge receipt of this communication and please submit all revised labeling by **COB Thursday, June 1, 2017**.

Regards,
Nina

Nina Mani
Senior Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

Please specify if the expiry date is on both carton and packet.

Section 2.4 of the PI states to "administer within 2 hours of preparation". Please clarify if this instruction should remain as currently

presented or be changed to “within 2 hours of preparation”.

Figures (illustrations, diagrams or photos) should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related step.

1) Based on the below instructions for administering 100 mg and 200 mg doses [REDACTED] (b) (4)

[REDACTED]

2) Please increase the font size of the text below each picture as it may be difficult for patients with poor vision to read.

Please increase the font size of the text below each picture as it may be difficult for patients with poor vision to read.

Please clarify if a [REDACTED] (b) (4).

Be sure to label each figure in the table along with the above figures alphabetically.

5/31/17:

No human factors validation testing will be necessary for this added language and figure since it has already been determined that preparation of doses 100 mg and 200 mg was well understood and because the added language aligns with the USPI and PPI. This will be sufficient from a medication error perspective.

We recommend that this instruction be added to section 2.4 of the PI.

We recommend that this instruction be added to section 2.4 of the PI.

Applicant to issue month and year upon approval.

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/s/

NINA MANI
06/01/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512: USPI HL Revisions
Date: Wednesday, May 31, 2017 7:55:33 PM

Thank you Nina – we acknowledge receipt.

Regards,
Sherie

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

abbvie

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: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Wednesday, May 31, 2017 5:47 PM
To: Masse, Sherie V
Subject: RE: NDA 209512: USPI HL Revisions

Hi Sherie:

In the USPI we are recommending the following change: Highlights/Recent Major Changes/ Dosage and Administration (2.1, 2.2, 2.3, 2.4)

Kindly acknowledge receipt.

Regards,
Nina

Nina Mani
Senior Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
06/01/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512
Date: Tuesday, May 30, 2017 4:54:46 PM

Thank you Nina – I have received the comments and we will respond accordingly.

Regards,
Sherie

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

abbvie

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From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Tuesday, May 30, 2017 3:27 PM
To: Masse, Sherie V
Subject: RE: NDA 209512

Hi Sherie:

Attached are our latest labeling revisions. Please note that the PPI and IFU have been extensively revised and contain Division and Patient labeling comments. Please do **not** make revisions in the PPI attached to the USPI; make them in the standalone PPI.

Kindly accept all changes you are in agreement with and document your agreement by some mechanism; only keep in track changes those that need further discussion.

Kindly acknowledge receipt of this communication and please submit all revised labeling by **COB Thursday, June 1, 2017**.

Regards,
Nina

Nina Mani
Senior Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

58Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NINA MANI
05/30/2017

From: Mani, Nina
To: "[Masse, Sherie V](#)"
Subject: RE: NDA 209512 (Norvir Oral Powder)
Date: Tuesday, May 23, 2017 11:15:00 AM
Attachments: [image002.png](#)

Hi Sherie:

Thank you for your agreement to changing the name of the product to "Oral Powder".

We recognize AbbVie's concern that it could cause confusion for patients and care-givers if the name of this product "Oral Powder" would need to be changed once instructions [REDACTED] (b) (4)

[REDACTED] Even after that change, because preparation of higher doses by directly mixing the powder with soft foods would still remain as a significant use, FDA believes that the dosage form name, Oral Powder, would continue to be appropriate.

Kindly acknowledge receipt of this communication and we look forward to receiving the revised labelings by the dates mentioned below.

Regards,
Nina

From: Masse, Sherie V [mailto:Sherie.Masse@abbvie.com]
Sent: Monday, May 22, 2017 1:35 PM
To: Mani, Nina
Cc: Winestock, Karen
Subject: RE: NDA 209512 (Norvir Powder [REDACTED] (b) (4)): FDA Revised labeling

Hi Nina:

Following on my voicemail from this morning –

Upon additional assessment, AbbVie believes that we can agree to changing the name of the product [REDACTED] (b) (4) to "Oral Powder". [REDACTED] (b) (4)

(b) (4) In the interest of avoiding patient confusion, we would not intend to change the name of the product although (b) (4) additional instructions may be added to the product. Does the FDA agree with this general approach?

We are currently on track to provide the changes to the USPI and IFU for the requested timeline of May 24th. It is likely that the carton, cover note, and foil will likely be ready on Tuesday, May 30th.

Regards,
Sherie

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

abbvie

AbbVie, Inc.
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From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Friday, May 19, 2017 2:59 PM
To: Masse, Sherie V
Cc: Winestock, Karen
Subject: RE: NDA 209512 (Norvir Powder (b) (4)): FDA Revised labeling

Hi Sherie:

The Office of Product Quality has the following recommendation and request for your consideration:

We recommend that instead of (b) (4) the preferred dosage form term for this product would be "Oral Powder".

This name is appropriate because a significant use will be by mixing the powder with food.

When you submit revised labeling, as requested below, please update all labeling, including that for the container labels with the new term.

Kindly acknowledge receipt of this communication.

Regards,
Nina

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, May 17, 2017 11:59 AM
To: Masse, Sherie V
Subject: NDA 209512 (Norvir Powder [REDACTED] (b) (4)): FDA Revised labeling

Hi Sherie:

Kindly acknowledge receipt of the attached recommended revisions to the USPI, PPI and IFU. Please accept all changes you are in agreement with, and document your agreement by some mechanism.

Only leave in track changes those that need further discussion.

In addition, we also have the following recommendation regarding the **Carton** labeling:

A section designated for the expiration date and lot number is missing from the immediate carton labeling. Ensure the expiration date and lot number are included on the carton per 21 CFR 201.17 and 21 CFR 201.10(i)(1), respectively.

Please submit all revised labeling by Wednesday, **May 24, 2017**.

Thanks,
Nina

Nina Mani, PhD, MPH

Senior Regulatory Project Manager

FDA/CDER/OND/OAP

Division of Antiviral Products

10903 New Hampshire Avenue, Building 22

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Silver Spring, MD 20993-0002

Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov



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/s/

NINA MANI
05/24/2017

From: Rivera, Luz E (CDER)
To: Masse, Sherie V
Subject: RE: INFORMATION REQUEST NDA 209512
Date: Monday, May 22, 2017 11:34:00 AM
Attachments: [image002.png](#)
[image003.png](#)
[image004.png](#)

Hello Sherie,

Thank you,
Luz

From: Masse, Sherie V [mailto:Sherie.Masse@abbvie.com]
Sent: Monday, May 22, 2017 10:40 AM
To: Rivera, Luz E (CDER)
Subject: RE: INFORMATION REQUEST NDA 209512

Luz;

Enclosed please find a courtesy copy of the cover letter and form that will be included in today's electronic submission to the NDA to remove the ^{(b) (4)} manufacturing site and provide the CMC updates.

Regards,
Sherie

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



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From: Rivera, Luz E (CDER) [<mailto:Luz.E.Rivera@fda.hhs.gov>]
Sent: Thursday, May 18, 2017 12:37 PM
To: Masse, Sherie V
Subject: RE: INFORMATION REQUEST NDA 209512

Good afternoon Sherie,

The Product Quality team has reviewed your communication and have the following comments and information request:

- Please do not remove the (b)(4) site from the 356h but rather mark it withdrawn. Otherwise the changes seem appropriate to remove (b)(4) from the supply chain for NDA 209512 without impacting the approved applications using this drug substance source.

Thank you,
Luz

Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting) Div I/Branch I
Office of Program and Regulatory Operations
FDA/CDER/OPQ
luz.e.rivera@fda.hhs.gov
301 796 4013



From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Tuesday, May 16, 2017 10:31 AM
To: Rivera, Luz E (CDER)
Cc: Mani, Nina
Subject: RE: INFORMATION REQUEST NDA 209512
Importance: High

Luz;

Per my email yesterday, enclosed is the draft letter for the review team's comments. Please let me know if there will be feedback quickly – we can be prepared to submit all of the CMC updates on Friday May 19th if this plan is agreeable.

Regards,
Sherie

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



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From: Masse, Sherie V
Sent: Monday, May 15, 2017 3:46 PM
To: Rivera, Luz E (CDER)
Subject: RE: INFORMATION REQUEST NDA 209512

Dear Luz;

Based on our discussion on Thursday, the FDA team asked to review our plan for removal of the (b) (4) manufacturing site from the application prior to an official submission to the NDA, and requested the response within a week of the teleconference. We have drafted the plan for the withdrawal of (b) (4) in the form of a letter, which I expect to be able to provide to you early tomorrow via email. We could be prepared to submit the updates officially to the NDA as early as Friday, depending on the timing of the feedback from the review team. Please let me know if you think this is sufficient to satisfy the review team's request.

Regards,
Sherie

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



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Regulatory Affairs

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One North Waukegan Road
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From: Rivera, Luz E (CDER) [<mailto:Luz.E.Rivera@fda.hhs.gov>]
Sent: Thursday, May 11, 2017 1:28 PM
To: Masse, Sherie V
Subject: RE: INFORMATION REQUEST NDA 209512

Hello Sherie,

The FDA attendees were:

1. Cassandra Abellard, Product Quality Reviewer, OPF/OPQ
2. Derek Smith, Branch Chief, OPF/OPQ
3. Steve Miller, Team Lead, ONDP/OPQ
4. Adam Sherwat, DAVP/OND, Team Lead
5. Nina Mani, DAVP/OND, Senior RPM
6. Karen Winestock, DAVP/OND, CPMS
7. Jeffrey Murray, DAVP/OND, Deputy Director
8. Debra Birnkrant, Director, DAVP
9. Regina Alivisatos, Medical Officer, DAVP

Thank you,
Luz

Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting) Div I/Branch I
Office of Program and Regulatory Operations
FDA/CDER/OPQ
luz.e.rivera@fda.hhs.gov
301 796 4013

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Thursday, May 11, 2017 9:33 AM
To: Rivera, Luz E (CDER)
Subject: RE: INFORMATION REQUEST NDA 209512

Luz;

Here are the AbbVie attendees. Could you please also send me the list for the FDA attendees?

Sherie Masse, Director Global Regulatory Strategy
Donna Helms, Director Global Regulatory Strategy
Vlad Liberman, Director CMC Regulatory
Michael Smith, Director Product Quality
Rebecca Hopkins, Manger Quality Operations

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: Rivera, Luz E (CDER) [<mailto:Luz.E.Rivera@fda.hhs.gov>]
Sent: Thursday, May 11, 2017 8:24 AM
To: Masse, Sherie V
Subject: RE: INFORMATION REQUEST NDA 209512

Good morning Sherie,

Can you send me the list of AbbVie's participants during our teleconference this morning.

Thank you,
Luz

From: Masse, Sherie V [mailto:Sherie.Masse@abbvie.com]
Sent: Wednesday, May 10, 2017 3:33 PM
To: Rivera, Luz E (CDER)
Subject: RE: INFORMATION REQUEST NDA 209512

Good afternoon Luz.

I wanted to check in and find out if you could provide an update on the specific questions for the teleconference tomorrow?

I have also included the information for the teleconference line, below:

Phone number [REDACTED] (b) (4) United States Toll Free

Meeting number (access code): [REDACTED] (b) (4)

Regards,
Sherie

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



AbbVie, Inc.
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Bldg. AP30-1 Dept. PA72
One North Waukegan Road
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CELL [REDACTED] (b) (6)
EMAIL sherie.masse@abbvie.com

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computer.

From: Rivera, Luz E (CDER) [<mailto:Luz.E.Rivera@fda.hhs.gov>]
Sent: Monday, May 08, 2017 12:37 PM
To: Masse, Sherie V
Subject: RE: INFORMATION REQUEST NDA 209512

Good afternoon Ms. Masse,

The Product Quality team would like to schedule a teleconference with your team. I will call you today to schedule during this week a teleconference to discuss the manufacturing and testing facilities.

Thank you,
Luz

Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting) Div I/Branch I
Office of Program and Regulatory Operations
FDA/CDER/OPQ
luz.e.rivera@fda.hhs.gov
301 796 4013



From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Friday, April 14, 2017 1:55 PM
To: Rivera, Luz E (CDER); Mani, Nina
Subject: RE: INFORMATION REQUEST NDA 209512

Mrs. Rivera;

AbbVie confirms that we are in contact with our contract manufacturing facilities, and the facilities are required to notify AbbVie under our Quality Technical Agreements of any inspections or 483's that have been issued.

Regards,
Sherie

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

AbbVie, Inc.

Regulatory Affairs

Bldg. AP30-1 Dept. PA72

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OFFICE +1 847-938-9250

CELL (b) (6)

EMAIL sherie.masse@abbvie.com

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-----Original Message-----

From: DoNotReply@fda.hhs.gov [<mailto:DoNotReply@fda.hhs.gov>]

Sent: Monday, April 10, 2017 12:44 PM

To: Masse, Sherie V

Cc: luz.e.rivera@fda.hhs.gov; Nina.Mani@fda.hhs.gov

Subject: INFORMATION REQUEST NDA 209512

NDA 209512

INFORMATION REQUEST

AbbVie, Inc.

Attention: Sherie VL Massé

Director, Global Regulatory Strategy

1 N. Waukegan Road

Dept. PA72/Bldg. AP30, North Chicago ILL 60064

Dear Ms. Massé:

Please find the Product Quality team comment for NDA 209512:

- Per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations. Please confirm that you are in contact with your contract manufacturing facilities, and that you are aware of any inspections or 483's that have been issued.

We request that you acknowledge this communication upon receipt.

Best regards,
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Mani, Nina
To: ["Masse, Sherie V"](#)
Cc: [Winestock, Karen](#)
Subject: RE: NDA 209512 (Norvir Powder [REDACTED] (b) (4)): FDA Revised labeling
Date: Friday, May 19, 2017 3:59:00 PM
Attachments: [image002.png](#)

Hi Sherie:

The Office of Product Quality has the following recommendation and request for your consideration:

We recommend that instead of [REDACTED] (b) (4) the preferred dosage form term for this product would be "Oral Powder". This name is appropriate because a significant use will be by mixing the powder with food.

When you submit revised labeling, as requested below, please update all labeling, including that for the container labels with the new term.

Kindly acknowledge receipt of this communication.

Regards,
Nina

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, May 17, 2017 11:59 AM
To: Masse, Sherie V
Subject: NDA 209512 (Norvir Powder [REDACTED] (b) (4)): FDA Revised labeling

Hi Sherie:

Kindly acknowledge receipt of the attached recommended revisions to the USPI, PPI and IFU. Please accept all changes you are in agreement with, and document your agreement by some mechanism.

Only leave in track changes those that need further discussion.

In addition, we also have the following recommendation regarding the **Carton**

labeling:

A section designated for the expiration date and lot number is missing from the immediate carton labeling. Ensure the expiration date and lot number are included on the carton per 21 CFR 201.17 and 21 CFR 201.10(i)(1), respectively.

Please submit all revised labeling by Wednesday, **May 24, 2017**.

Thanks,
Nina

Nina Mani, PhD, MPH

Senior Regulatory Project Manager

FDA/CDER/OND/OAP

Division of Antiviral Products

10903 New Hampshire Avenue, Building 22

Room 6317

Silver Spring, MD 20993-0002

Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov



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/s/

NINA MANI
05/19/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512 (Norvir Powder [REDACTED] (b) (4)): FDA Revised labeling
Date: Wednesday, May 17, 2017 1:06:31 PM
Attachments: [image003.png](#)

Thank you Nina, I have received the comments and we will work to provide a response by the requested date.

Regards,
Sherie

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

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CELL [REDACTED] (b) (6)
EMAIL sherie.masse@abbvie.com

abbvie.com

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From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, May 17, 2017 11:59 AM
To: Masse, Sherie V
Subject: NDA 209512 (Norvir Powder [REDACTED] (b) (4)): FDA Revised labeling

Hi Sherie:

Kindly acknowledge receipt of the attached recommended revisions to the USPI, PPI and IFU. Please accept all changes you are in agreement with, and document your agreement by some mechanism.

Only leave in track changes those that need further discussion.

In addition, we also have the following recommendation regarding the **Carton** labeling:

A section designated for the expiration date and lot number is missing from the immediate carton labeling. Ensure the expiration date and lot number are included on the carton per 21 CFR 201.17 and 21 CFR 201.10(i)(1), respectively.

Please submit all revised labeling by Wednesday, **May 24, 2017**.

Thanks,
Nina

Nina Mani, PhD, MPH

Senior Regulatory Project Manager

FDA/CDER/OND/OAP

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e-mail: Nina.Mani@fda.hhs.gov



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/s/

NINA MANI
05/17/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512 (Norvir) Carton and Container
Date: Thursday, May 04, 2017 3:43:13 PM

Nina –

I have received the request. We had already started working on that update – I will get back to you as soon as I know when it will be ready.

Regards,

Sherie

SHERIE VL MASSE, M.S., RAC

Director, Regulatory Affairs
Global Regulatory Strategy - Antiviral

abbvie

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: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Thursday, May 04, 2017 2:39 PM
To: Masse, Sherie V
Subject: RE: NDA 209512 (Norvir) Carton and Container

Hi Sherie:

Since [REDACTED] (b) (4) doses will now be in the USPI, please submit ASAP revised carton/container labels.

Kindly acknowledge receipt do this request.

Regards,

Nina

From: Mani, Nina
Sent: Thursday, May 04, 2017 12:36 PM
To: Masse, Sherie V (Sherie.Masse@abbvie.com)
Subject: NDA 209512 (Norvir) Withdrawal Letter

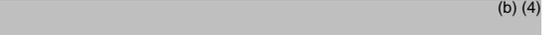
Hi Sherie:

My responses are in red font.

Regards,
Nina

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Wednesday, May 03, 2017 3:22 PM
To: Mani, Nina
Subject: NDA 209512 (Norvir) Letter

Nina;

I have a couple of procedural questions regarding  (b) (4)



 (b) (4)

Thanks!

Regards,
Sherie

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

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/s/

NINA MANI
05/04/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 2, 2017
Application Number: NDA 209512
Product Name: Norvir (ritonavir) Powder (b) (4) 100 mg
Sponsor/Applicant Name: AbbVie Inc.
Subject: Clarifications on DAVP's April 26, 2017 communication

FDA Participants

Debra Birnkrant, Director, DAVP
Jeffrey Murray, Deputy Director, DAVP
Adam Sherwat, Clinical Team Lead, DAVP
Regina Alivisatos, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Mangement Staff, DAVP
Nina Mani, Senior Regulatory Project Manager, DAVP

Sponsor/Applicant Participants

Andrew Storey, VP Global Regulatory Strategy
Donna Helms, Therapeutic Area Lead, Established Products
Sherie VL Massé, Director, Global Regulatory Strategy

1.0 BACKGROUND:

AbbVie has developed a Norvir powder formulation for use in HIV-1 infected pediatric patients. The new formulation does not contain ethanol or propylene glycol, which are found in their currently marketed Norvir oral solution formulation (ritonavir 80 mg/mL). Doses of Norvir powder for oral suspension require preparation with soft food or liquid prior to administration. With their NDA application the Sponsor submitted results from a human factors (HF) validation study including Knowledge Task Assessment, Instructions for Use (IFU), draft packet label, carton labeling, cover note to patients, and prescribing information (PI). DMEPA reviewed the results and concluded that the Sponsor's HF study results showed multiple failures across multiple critical tasks, and that it did not support the safe and effective (b) (4). DMEPA recommended that the Sponsor should consider conducting another Human Factor study, with a list of recommendations for improving the IFU, carton label and cover note. (b) (4)

(b) (4)

(b) (4)

(b) (4)

The Sponsor was advised that since the product has Orphan Designation they are exempt from any PREA PMRs.

(b) (4)

2.0 DISCUSSION:

(b) (4)

3.0 POST CALL FOLLOW-UP: None

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/s/

NINA MANI
05/03/2017



NDA 209512

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Global Regulatory Strategy
1 N. Waukegan Road
Dept. PA72/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

Please refer to your New Drug Application (NDA) dated and received December 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Norvir (ritonavir) powder for suspension, 100 mg packet.

We also refer to your April 20, 2017 and April 24, 2017 submissions, containing your responses to our Advice Letter sent on April 7, 2017 recommending that you conduct a new Human Factors study along with improvements to the Instructions for Use (b) (4).

We are in general agreement with the approach outlined in your April 24, 2017 submission. (b) (4)

Please resubmit labeling (in Microsoft Word format) by May 1, 2017, limiting the information related to the pediatric powder formulation (b) (4). The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

If you have any questions, please contact Nina Mani, Senior Regulatory Project Manager, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, MD, MPH
Deputy Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
04/26/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 12, 2017
Application Number: NDA 209512
Product Name: Norvir (ritonavir) Powder for oral suspension, 100 mg
Sponsor/Applicant Name: AbbVie Inc.
Subject: Human Factors Study

FDA Participants

Nina Mani, Senior Regulatory Project Manager, DAVP

Sponsor/Applicant Participants

Sherie VL Massé, Director, Global Regulatory Strategy

1.0 BACKGROUND:

AbbVie has developed a Norvir powder formulation for use in HIV-1 infected pediatric patients. The new formulation does not contain ethanol or propylene glycol, which are found in their currently marketed Norvir oral solution formulation (ritonavir 80 mg/mL). Doses of Norvir powder for oral suspension require preparation with soft food or liquid prior to administration. With their NDA application the Sponsor submitted results from a human factors (HF) validation study including Knowledge Task Assessment, Instructions for Use (IFU), draft packet label, carton labeling, cover note to patients, and prescribing information (PI). DMEPA reviewed the results and concluded that the Sponsor's HF study results showed multiple failures across multiple critical tasks and that it did not support the safe and effective (b) (4)

(b) (4) DMEPA recommended that the Sponsor should consider conducting another Human Factor study, with a list of recommendations for improving the IFU, carton label and cover note. (b) (4)

(b) (4) On April 7, 2017 these recommendations and concerns were communicated to the Sponsor via electronic correspondence, with a request that by April 14, 2017 they provide us the date by which they believe they could submit results from a follow-up HF study for Agency review.

2.0 DISCUSSION:

Today, the Sponsor called to inform me that they will need more time to submit their response. The Sponsor wanted to discuss the FDA's specific concerns regarding the use of this product, which I told them were quite well elucidated in the April 7, 2017 IR, and the Sponsor concurred. In particular, they do not believe that another HF study will provide much improvement on the results already observed (according to the Sponsor, 4 studies have already been conducted with the last 2 showing similar results). (b) (4)

AbbVie

does not see the benefit of conducting another HF study, though it is still on the table. In the end, we agreed that they will submit their response in the latter half of the week of April 17, 2017. Following review of the information we may hold a follow up t-con with the Sponsor.

3.0 POST CALL FOLLOW-UP:

None

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/s/

NINA MANI
04/12/2017

RECORD OF ELECTRONIC MAIL CORRESPONDENCE



Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: April 7, 2017
TO: Sherie VL Massé, Director, Global Regulatory Strategy
FROM: Nina Mani, Senior Regulatory Project Manager, DAVP
SPONSOR: AbbVie, Inc.
SUBJECT: NDA 209512

Please refer to your New Drug Application (NDA) dated and received December 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Norvir (ritonavir) powder for suspension, 100 mg packet. The review of the application is ongoing, but we have identified the following human factors related and device-related deficiencies.

Simulated Use – Human Factors (HF) Validation Study and Knowledge Task Assessment Study

The Simulated Use and the Knowledge Task Assessment Study results showed multiple failures across multiple critical tasks and across the two user groups that could result in medication errors. These results and associated root cause analyses indicate that the user interface does not support safe and effective (b) (4) We note you did not implement any additional mitigation to address failures observed during the HF validation study. Please address the following comments related to product design, Instructions for Use, Carton Labeling, and Cover Note.

Product Design

We have identified a product design concern (b) (4)

[Redacted]

[Redacted] (b) (4)

Instructions for Use

We recommend you make the following changes to the **Instructions for Use** to address failures observed during the HF validation study:

(b) (4)

In addition, we have the following recommendations for the Carton Labeling and Cover Note:
Carton Labeling

17. Relocate the net quantity statement to appear away from the product strength, for example to the bottom of the principal display panel (PDP), to mitigate the risk of numerical confusion between the strength and net quantity which increases when the net quantity statement is located in close proximity to the strength statement.

Additional Risk Mitigations Considerations

21. We are concerned about the ability of risk mitigation strategies that are primarily focused on the IFU to resolve the residual risk that exists with your product. (b) (4)
- (b) (4) and we would like to know what other mitigation strategies you plan to put in place (e.g., training, education, etc.) to further reduce the risk for errors.

As outlined above, the deficiencies related to the HF study, Knowledge Task Assessment Study, (b) (4) raise significant concerns as to the approvability of the pediatric powder formulation. We recommend that you: (a) address the above concerns, (b) modify the user interface of the proposed product including the instructions and (if feasible) the product design, and (c) provide additional HF validation data to demonstrate that you have effectively addressed the use errors, and that the proposed product can be used safely and effectively by intended users.

Please provide by **April 14, 2017**, a realistic estimate for when results from a follow-up HF study could be submitted to the Agency for our review.

Please contact me at (240) 402-0333 or via email at Nina.Mani@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Nina Mani, PhD, MPH
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
04/07/2017



NDA 209512

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Global Regulatory Strategy
1 N. Waukegan Road
Dept. PA72/Bldg. AP30, North Chicago ILL 60064

Dear Ms. Massé:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvir (ritonavir) Powder for Oral Suspension.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a written response by COB **Friday, April 14, 2017**, in order to continue our evaluation of your NDA. If it is not possible to respond completely by that date, please provide a partial response, with the timeline for submission of the remainder.

- The Agency recommends that a

(b) (4)

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 4/04/2017 05:58:49PM
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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: March 28, 2017
TO: Sherie VL Massé, Director, Global Regulatory Strategy
FROM: Nina Mani, Regulatory Project Manager, DAVP
SPONSOR: AbbVie, Inc.
SUBJECT: NDA 209512 – Human Factors Study

Please refer to your New Drug Application (NDA) dated and received December 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Norvir (ritonavir) powder for suspension, 100 mg packet. We have the following request for information with regard to the human factors (HF) study.

Confirmed doses of Norvir outside of your protocol-based acceptable range of (b) (4) % were produced by some of the caregivers and health care providers participating in the HF study. Please provide an assessment of the specific preparation errors that occurred in subjects with confirmed doses of Norvir that fell below the study's goal dose. Please provide the breakdown of errors in three categories based on how far the actual dose was from the goal dose, namely, 15-25%, 25%-50%, and > 50% from the goal dose. Please provide potential mitigation strategies to reduce these errors.

Please e-mail me the information by **March 31, 2017**, and subsequently submit it formally to the NDA.

Please contact me at (240) 402-0333 or via email at Nina.Mani@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Nina Mani, PhD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
03/28/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512: Clinical Pharmacology
Date: Thursday, March 23, 2017 10:55:07 AM
Attachments: [image002.png](#)

Thank you!

Regards,
Sherie

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

abbvie

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: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Thursday, March 23, 2017 9:33 AM
To: Masse, Sherie V
Subject: RE: NDA 209512: Clinical Pharmacology

Hi Sherie:

It is for the pivotal BA study, M11-475.

Thanks,
Nina

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Thursday, March 23, 2017 9:44 AM
To: Mani, Nina
Subject: RE: NDA 209512: Clinical Pharmacology

Nina;

I have received the request I do have one question - can you clarify if this question refers to results from a specific clinical study?

Regards,

Sherie

SHERIE VL MASSE, M.S., RAC

Director, Regulatory Affairs

Global Regulatory Strategy - Antiviral

abbvie

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: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]

Sent: Thursday, March 23, 2017 8:34 AM

To: Masse, Sherie V

Subject: NDA 209512: Clinical Pharmacology

Hi Sherie:

Kindly acknowledge receipt of the following Clinical Pharmacology request for information.

*We noticed that observed QC concentrations in certain runs were consistently lower than the nominal concentrations (3rd QC batch in Runs # 10, 11, 13, and 14, run dates from 17-Apr-2013 to 18-Apr-2013) by ~ 50%, suggesting potential errors during sample preparation or analysis, such as incorrect dilution of samples or internal standards. Please provide feedback on possible explanations and submit chromatograms to support your explanation. Please provide your response by **March 31, 2017**.*

Regards,

Nina

Nina Mani, PhD, MPH

Senior Regulatory Project Manager

FDA/CDER/OND/OAP

Division of Antiviral Products

10903 New Hampshire Avenue, Building 22

Room 6317

Silver Spring, MD 20993-0002

Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov



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Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

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/s/

NINA MANI
03/23/2017

From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512: Feeding Tubes
Date: Thursday, March 23, 2017 12:08:22 PM
Attachments: [image003.png](#)

Thank you Nina; I have received the request.

Regards,
Sherie

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

abbvie

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: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Thursday, March 23, 2017 11:02 AM
To: Masse, Sherie V
Subject: NDA 209512: Feeding Tubes

Hi Sherie:

We require additional information in order to assess your labeling proposal related to the use of Norvir Powder for Oral Suspension with feeding tubes. Given that the vehicle is water, we believe that this evaluation can be limited to whether there is a significant loss of ritonavir (absorption or blockage). Please develop a standardized approach including the volume of the suspension, the process for reconstitution, and the volume of water rinse(s). Please use feeding tubes which cover the range of available (b) (4) types, tube types (e.g., nasogastric tubes, gastrostomy tubes, gastrojejunal tubes, etc.), (b) (4)

(b) (4)

Kindly acknowledge receipt of this request for information and provide your response by **April 6, 2017**.

Regards,
Nina

Nina Mani, PhD, MPH

Senior Regulatory Project Manager

FDA/CDER/OND/OAP

Division of Antiviral Products

10903 New Hampshire Avenue, Building 22

Room 6317

Silver Spring, MD 20993-0002

Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov



NOTICE:

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/s/

NINA MANI
03/23/2017



NDA 209512

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Global Regulatory Strategy
1 N. Waukegan Road
Dept. PA72/Bldg. AP30, North Chicago ILL 60064

Dear Ms. Massé:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvir (ritonavir) Powder for Suspension.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a written response to Question 1 by **Tuesday, March 14, 2017**, and responses to the remaining questions by **Tuesday, March 21, 2017**.

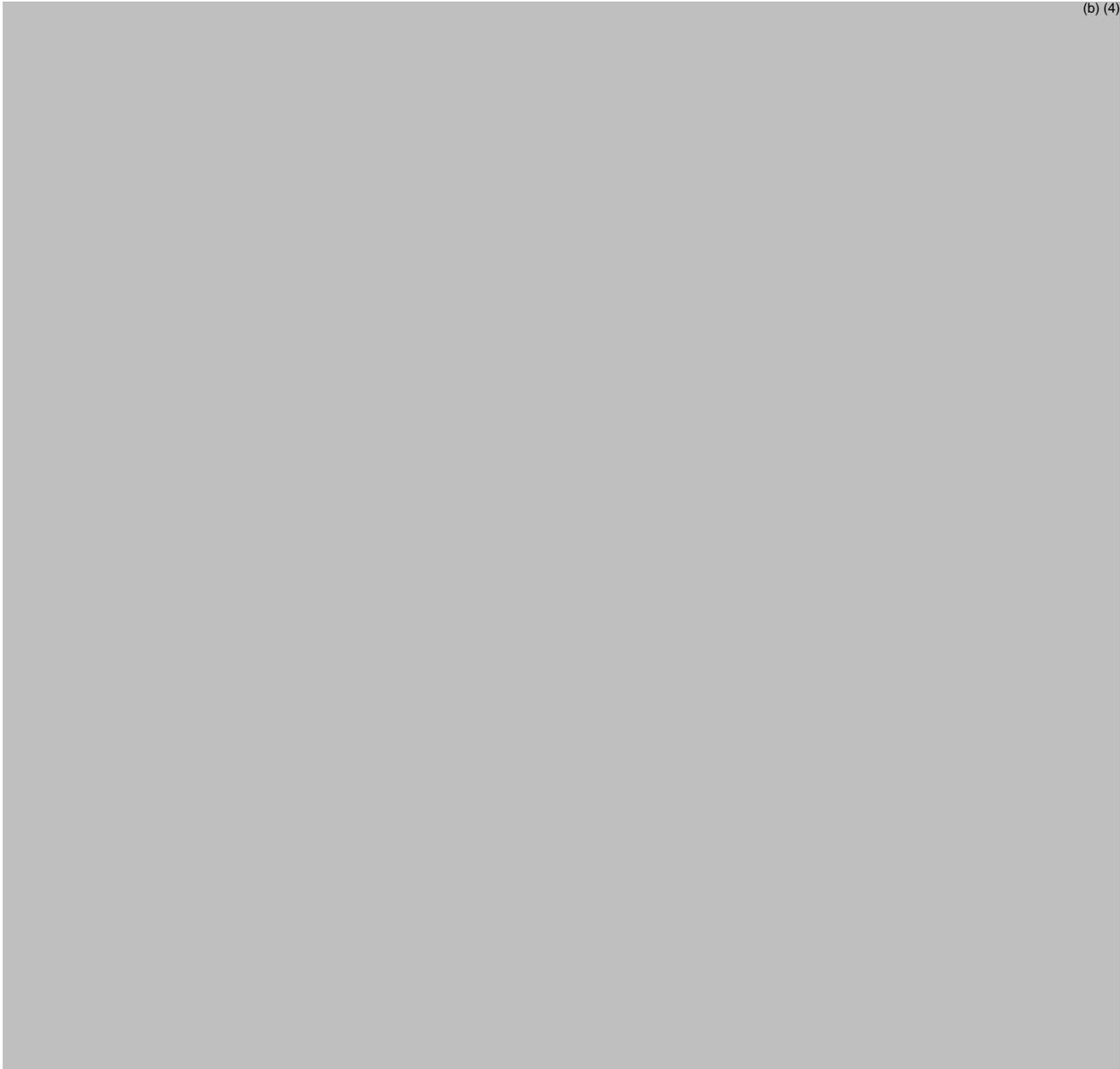
1. Dose accuracy data were provided in “3.2.P.2.4 Container Closure System for Norvir Oral Powder” and Section 5.3.5.4 (Part 8.3.3: Dosing Accuracy Results).
 - a) For the studies in Section 3.2.P.2.4, please indicate how you prepared the suspension, i.e. if you exactly followed the instruction for use in the proposed labeling. (b) (4)

 - b) Provide a detailed protocol how you performed the dosing accuracy study (Section 3.2.P.2.4).
 - c) For the Dosing Homogeneity results summarized in Tables 5 and 6 in Section 3.2.P.2.4, please present histograms of the mg of ritonavir for the (b) (4)
target doses. Please indicate the mean, min, max and % standard deviation.
 - d) Please present a similar display of the data on Ritonavir Content (by HPLC) in the doses prepared by participants in Section 5.3.5.4 (Part 8.3.3: Dosing Accuracy

Results). Please present the results from the Health Care Providers and the Care Givers separately. Please analyze whether there is a correlation between the Ritonavir Content of individual doses and the observations made on that participant during the mixing phase of dose preparation.

- e) Please describe how you determined that the mixing time [REDACTED] (b) (4) was necessary. When the Norvir Powder for Oral Suspension is reconstituted in this way with water, what is the nature of the ritonavir in that preparation [REDACTED] (b) (4) [REDACTED] ?
 - f) When we reproduced the reconstitution procedure with water, a large amount of foam was still present [REDACTED] (b) (4), which made it very difficult to see where liquid ended and foam began. We found significantly less foaming when we used a full-fat chocolate milk. Are there vehicle factors that cause more or less foaming? Given that this product will be given to young infants, what were your observations when reconstituting with infant formula?
2. Provide [REDACTED] (b) (4) [REDACTED]
 3. The stability testing did not include the essential performance requirements [REDACTED] (b) (4) [REDACTED]
 4. Please provide an explanation of how future changes [REDACTED] (b) (4) will be handled to assure ongoing safety and effectiveness of the product.
 5. We note you have not included in-process [REDACTED] (b) (4) [REDACTED]

(b) (4)



Provide information to support a conclusion that Norvir delivery risks (e.g., inconsistent dose accuracy associated with dosing precision identified in the draft labeling), are adequately mitigated without compliance to 21 CFR 4.4(b)(1). Alternatively, provide the following information regarding your compliance with 21 CFR 4.

9. The information provided by your firm has inadequately addressed the requirements of 21 CFR (b) (4) . (b) (4)



[REDACTED] (b) (4)

10. The information provided by your firm has inadequately addressed the requirements of [REDACTED] (b) (4)

11. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.50, purchasing controls. The submission did not specify the controls applicable to your firm’s suppliers. This would include any contract design, service or contract manufacturers [REDACTED] (b) (4) Please provide a description of your procedures for Purchasing Controls. Please explain how your firm will ensure that changes made by contractors/suppliers will not affect the final [REDACTED] (b) (4) product.

12. The information provided by your firm has inadequately addressed the requirements of [REDACTED] (b) (4)

You may find useful information regarding the information to provide for [REDACTED] (b) (4) Guidance for Industry and FDA Staff: “Current Good Manufacturing Practice Requirements [REDACTED] (b) (4) Products” accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances> [REDACTED] (b) (4)

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 3/06/2017 10:10:41 PM
GUID: 502abbaa000025b89fdb52a977a3d336



From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512: Human Factors Engineering Usability Report
Date: Thursday, February 23, 2017 9:37:04 AM
Attachments: [image003.png](#)

Nina;
I have received the request and will get the team working on the response.
Thanks.

Regards,
Sherie

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

abbvie

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: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Thursday, February 23, 2017 8:34 AM
To: Masse, Sherie V
Subject: NDA 209512: Human Factors Engineering Usability Report

Hi Sherie:

We refer to your NDA 209512 for Norvir Powder for Oral Suspension and your Human Factors (HF) Engineering – Usability Engineering Report submitted on December 7, 2016. To assist us in our review, please provide the following:

1. We note some feedback was provided by the users in Table 19 and Table 20. We would like to review the transcript of subjective feedback provided during the debriefing sessions. We consider the subjective data to be critical in our review of your HF study report. As such,

please provide all user comments obtained at the completion of the usability study. To promote an efficient review process, we ask that this information is placed in a tabular format which details the use task relating to the user comment.

2. Table 18 entitled “Knowledge Task Assessment Results” provides the list of knowledge task assessment questions that were asked during the study and the number of participants who answered the questions successfully or unsuccessfully and the number of participants whose answers were close calls. We note that participant answers/subjective feedback and root-cause analysis were not provided for the incorrectly answered questions from this study. Participant responses/subjective feedback and root-cause analysis, are useful for providing important information that could be used to further identify any additional user interface issues. As such, please provide a transcript of participant responses/subjective feedback and root-cause analysis for the knowledge tasks failures and close calls. To promote an efficient review process, we ask that this information is placed in a tabular format detailing the participants’ incorrect responses/ subjective feedback, and root-cause analysis for all failure and close call responses.

Kindly acknowledge receipt of this request and submit your response by **COB Monday, February 27, 2017**.

Regards,
Nina

Nina Mani, PhD, MPH

Regulatory Project Manager

FDA/CDER/OND/OAP

Division of Antiviral Products

10903 New Hampshire Avenue, Building 22

Room 6317

Silver Spring, MD 20993-0002

Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov



NOTICE:

Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

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/s/

NINA MANI
02/23/2017

DATE: 2/13/2017

TO: Division of Antiviral Products
Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209512

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	PPD Phase 1 Clinic	7551 Metro Center Drive, Suite 200, Austin, TX

MEMORANDUM

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

DATE: 1/24/2017

TO: Division of Antiviral Products
Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209512

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

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

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/s/

SHILA S NKAH
02/16/2017



NDA 209512

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Global Regulatory Strategy
1 N. Waukegan Road
Dept. PA72/Bldg. AP30, North Chicago ILL 60064

Dear Ms. Massé:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvir (ritonavir) Powder for Suspension.

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 **Friday, February 24, 2017**, in order to continue our evaluation of your NDA.

1. Based on the submitted in vitro dissolution data for the clinical lot used for the Pivotal BE study, the proposed dissolution acceptance criteria of “NLT $\frac{(b)}{(4)}$ % (Q) of the labeled amount of ritonavir dissolved in $\frac{(b)}{(4)}$ ” is too permissive for Norvir Powder for Oral Suspension. Therefore, the following data-driven dissolution acceptance criterion is recommended: “NLT $\frac{(b)}{(4)}$ % (Q) of the labeled amount of ritonavir dissolved in 15 minutes”. Update the drug product specification table and other relevant sections of your NDA accordingly.
2. You have provided summary-level results for cytotoxicity test, sensitization and irritation tests. However, no full test reports for any of these tests can be found in the submission. In order for the Agency to fully evaluate the safety and effectiveness of your product, please provide full reports from the original test facilities.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

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From: [Masse, Sherie V](#)
To: [Mani, Nina](#)
Subject: RE: NDA 209512 - Indication
Date: Tuesday, February 07, 2017 11:12:53 AM

Thank you Nina, we will make the submissions accordingly.

Regards,
Sherie

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

abbvie

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: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Tuesday, February 07, 2017 10:07 AM
To: Masse, Sherie V
Subject: RE: NDA 209512 - Indication

Thanks, Sherie for this update.

Please submit updated labeling to **NDA 209512** by **Wednesday, February 15, 2017**.
As discussed during our T-con on February 3, 2017, please also submit supplements to the Norvir Tablet and Norvir Oral Solution NDAs to update those labelings. Please submit these by **February 22, 2017**.

Kindly acknowledge receipt of this communication.

Regards,
Nina

From: Masse, Sherie V [<mailto:Sherie.Masse@abbvie.com>]
Sent: Tuesday, February 07, 2017 8:24 AM
To: Mani, Nina
Subject: NDA 209512 - Indication

Nina;

In response to the feedback from the Office of Orphan Products Development on the labeled indication for Norvir Powder for Oral Suspension, AbbVie has decided on how we would like to proceed.

We will update Section 1 INDICATIONS AND USAGE in the current label to change the indication for Norvir Powder for Oral Suspension to reflect the use in pediatric HIV-1. Our proposed change is below (new text in red). We will also make the same changes to the Highlights section and any other relevant part of the USPI to be consistent with the indication.

Please let me know when we would need to have the updated labelling submitted to the NDA application, or if there is anything needed from me to facilitate the user fee refund.

1 INDICATIONS AND USAGE

NORVIR Tablets and (b) (4) Oral Solution is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

NORVIR (b) (4) is indicated in combination with other antiretroviral agents for the treatment of pediatric HIV-1 infection.

Regards,

Sherie

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

abbvie

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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/s/

NINA MANI
02/07/2017

MEMORANDUM OF TELECON

DATE: February 3, 2017

APPLICATION NUMBER: NDA 209512

BETWEEN:

Name: Sherie Masse
Phone: 847-938-9250
Representing: AbbVie, Inc.

AND

Name: Nina Mani
Division of Antiviral Products, Office of Antimicrobial Products

SUBJECT: User fee refund based on Orphan Designation

BACKGROUND

1. NDA 209512 was submitted on 12/07/16.
2. AbbVie paid a user fee \$1,019,050.00 (NDA without Clinical Data) on 11/22/16.
3. On January 11, 2017 Norvir powder for oral suspension was granted Orphan Designation for treatment of pediatric HIV-1 infection.

Search Orphan Drug Designations and Approvals

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Results for All Designations

[Return to Orphan Products Designation Search Page](#)

1 - 25 of 1

#	Generic Name	Orphan Designation
1	Ritonavir powder for oral suspension	Use with other antiretroviral agents for the treatment of pediatric HIV-1 infect

4. On January 27, 2017 AbbVie submitted user fee refund request for this NDA based on the Orphan Designation.
5. According to the User Fee Staff, based on the current labeling in DARRTS, AbbVie just added powder for oral suspension as a new dosage form, but the indication statement did not change. It was kept as “NORVIR is an HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection”, which is for a broad patient population and outside of the scope of the orphan designation.
6. The User Fee Staff (Jun Wang) reached out to me on February 2, 2017 regarding the discrepancy in the Indication statement for the labeling submitted for the new dosage form in the NDA and the indication for which Orphan designation has been granted.
7. I spoke with the User Fee’s Jun Wang, who told me that I can communicate their

concerns and options to the Sponsor.

SUMMARY OF TELEPHONE CONVERSATION

During today's call with the Sponsor representative I provided the above background and the following options to the Sponsor:

1. Adjust indication in current labeling to restrict the powder dosage form to pediatric patients (in this case they will also have to submit PAS's for the Norvir tablet and oral solution NDAs since they share labeling with the powder),
2. Submit stand-alone labeling for the powder dosage form to be used only in pediatric patients for this NDA, and
3. Keep the labeling as is, which includes all patient populations for powder dosage form. User Fee team will deny the refund request.

The Sponsor was informed that they will need to submit revised labeling by the end of the month. This will be used for labeling discussions and would be shared with the User Fee Staff to aid in their final determination regarding the Sponsor's refund request.

By Friday, February 10, 2017, the Sponsor will let us know which option they'd like to pursue.

Nina Mani
Regulatory Project Manager
DAVP/OAP

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/s/

NINA MANI
02/03/2017



NDA 209512

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

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Global Regulatory Strategy
1 N. Waukegan Road
Dept. PA72/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Massé:

Please refer to your New Drug Application (NDA) dated and received December 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Norvir (ritonavir) powder for suspension, 100 mg packet

We also refer to your amendment dated January 19, 2017.

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 **Priority**. Therefore, the user fee goal date is June 7, 2017.

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 requirement/commitment requests by May 17, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

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 patient PI. 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 patient PI, 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.

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

If you have any questions, call Nina Mani, Regulatory Project Manager, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEFFREY S MURRAY
02/01/2017



NDA 209512

INFORMATION REQUEST

AbbVie, Inc.
Attention: Sherie VL Massé
Director, Global Regulatory Strategy
1 N. Waukegan Road
Dept. PA72/Bldg. AP30, North Chicago ILL 60064

Dear Ms. Massé:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvir (ritonavir) Powder for Suspension.

We are reviewing the Chemistry, Manufacturing and Control sections of your submission and have the following comments and information requests. We request a written response by **Thursday, February 2, 2017**, in order to continue our evaluation of your NDA. A partial response on that date with a timeline for the remaining responses is acceptable.

Regarding your submission, NDA 209512, the proposed final drug product (b) (4)

[Redacted]

[Redacted] (b) (4)

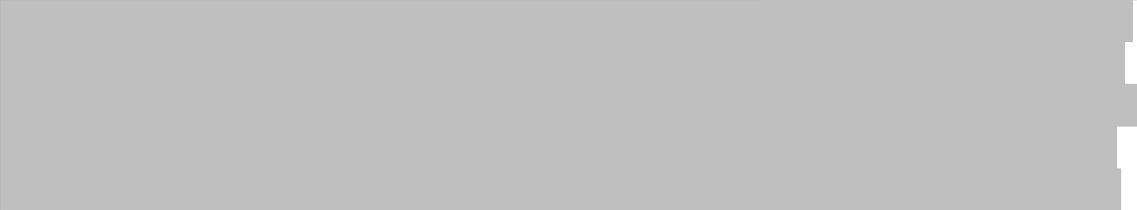
(b) (4)



We have the following additional information requests related to the drug product.

5. Provide an assessment, with data as appropriate, of the risk

(b) (4)



(b) (4)

8. With regard to our email request (Jan 12) that you submit an updated 356h form by Jan 19, we have the following clarification. Please include on the 356h all facilities involved in the manufacturing process including the drug substance manufacturers and any facilities associated with the drug substance manufacturing (specifying which (b) (4) (b) (4) are conducted at each facility).

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



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IND 43718

MEETING MINUTES

AbbVie, Inc.
Attention: Matthew Kuntz, PharmD, MBA, RAC
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Kuntz:

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

We also refer to the telecon between representatives of your firm and the FDA on June 30, 2014. The purpose of the meeting was to discuss and obtain Agency feedback on the format and content of the proposed NDA submission for the new Norvir oral powder formulation.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager at (301) 796-0759 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 30, 2014 9:00 AM – 10:30 AM
Meeting Location: Teleconference

Application Number: IND 43718
Product Name: Norvir (ritonavir)
Indication: treatment of HIV-1 infection
Sponsor/Applicant Name: AbbVie, Inc.

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Linda C. Onaga, MPH

FDA ATTENDEES

1. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
3. M. Regina Alivisatos, MD, Clinical Reviewer, DAVP
4. Prabha Viswanathan, MD, Clinical Reviewer, DAVP
5. Adam Sherwat, MD, Clinical Team Lead, DAVP
6. Linda Lewis, MD, Clinical Team Lead, DAVP
7. Su-Young Choi, PharmD, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCPIV)
8. Shirley Seo, PhD, Clinical Pharmacology Team Lead (DCPIV)
9. Rajiv Agarwal, PhD, Chemistry, Manufacturing and Controls (CMC) Reviewer, Division of New Drug Quality Assessment I (DNDQAII)
10. Okpo Eradiri, Ph.D., Biopharmaceutics Reviewer, Office of New Drug Quality Assessment
11. Stephen Miller, PhD, CMC Lead, DNDQAII
12. Karen Winestock, Chief, Project Management Staff, DAVP
13. Monica Calderon, PharmD, BCPS, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
14. Irene Z. Chan, PharmD, BCPS, Associate Director, DMEPA
15. Robert Pratt, PharmD, Risk Management Analyst, Division of Risk Management (DRISK)
16. Jamie Wilkins Parker, PharmD, Team Lead, DRISK
17. Linda C. Onaga, MPH, Senior Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. Angela Nilius, PhD, Project Director, Virology, Research and Development
2. Neddie Zadeikis, MD, MBA Senior Medical Director, Virology, Research and Development
3. Ariel Porcalla, MD, MPH, Medical Director, Global Pharmacovigilance
4. Yi-Lin Chiu, PhD, Director, Department of Biometrics, Research and Development
5. Cheri Enders Klein, PhD, ARF, Senior Director, Clinical Pharmacokinetics and Pharmacodynamics,
6. Research and Development
7. Matthew Kuntz, PharmD, RPh, MBA, RAC, Director, United States (US) and Canada Regulatory Affairs
8. Alan McEmber, MS, Senior Director, Therapeutic Area Head, US and Canada Regulatory Affairs
9. Daniel Larkins, MS, QA/RA, Global Regulatory Lead, Global Product Strategy, Regulatory Affairs
10. David McCann, PhD, Associate Director, Regulatory Affairs CMC
11. John Morris, PhD, CMC Scientific Director, Research and Development
12. Bill Bracken, PhD, Director, Preclinical Safety, Research and Development
13. Ed Israelski, PhD, Director, Human Factors
14. James Duhig, PhD, Manager, CMC Regulatory Affairs (Human Factors)
15. Diana Green, PhD, Associate Director, CMC Coordination

1.0 BACKGROUND

AbbVie, Inc. is developing a new oral powder formulation for NORVIR[®] for the treatment of HIV-1 infection. (b) (4)

(b) (4) Norvir oral powder eliminates the alcohol and propylene glycol (b) (4) increases the commercial shelf life through reduced degradation rates, and provides the ability to use with several food and liquid vehicles so as to increase administration flexibility and palatability to meet patient preferences.

AbbVie intends to submit a 505(b)(1) new drug application (NDA) with bioequivalence studies to support the new oral powder formulation.

The purpose of this meeting is to obtain guidance and agreement on the format and content of the planned NORVIR[®] oral powder NDA.

2. DISCUSSION

The Division provided preliminary comments to AbbVie on June 27, 2014. AbbVie requested this teleconference focus on the Agency's responses to Questions 1, 3, 4, and 5. Prior to the teleconference AbbVie agreed to conduct a validation study as requested in the Division's response to Question 4. To guide the discussion, AbbVie provided a table (see Section 7.0) with the key design characteristic of the validation protocol.

2.1. Category/Discipline A

Question 1: *The open-dish and packaged Norvir powder for oral suspension stability studies demonstrate that API in the proposed formulation does not change (b) (4) under the proposed storage conditions, thus AbbVie will not have a specification for (b) (4) in the proposed drug product. Does the Agency agree?*

FDA Response to Question 1: No agreement is made at this time as acceptability of the drug product specification is an NDA review issue. To support the (b) (4)

Additional Biopharmaceutics Comments:

We note that the proposed oral powder is manufactured using (b) (4) as starting material. Since the (b) (4) process involves (b) (4)

(b) (4) We have the following comments regarding the dissolution information that should be provided in your NDA.

- 1) **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a. Solubility data for the drug substance across the physiologic pH range;
 - b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e.*, selection of the equipment/apparatus, *in vitro* dissolution/release media, volume, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. Since the dosage form is a powder for oral suspension, particular, justification should be provided for the choice of equipment, medium's volume, and rotation speed as well as the sampling time points for release testing. We suggest initial sampling time points of 10, 15, 20, 30, 45, 60, 90 and 120 min prior to selection of final profiling time points. The cumulative dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e.*, no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

- c. Provide the complete dissolution profile data (*individual vessel, mean, SD, %CV, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*);
- d. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). [REDACTED] (b) (4)
[REDACTED] In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent; and
- e. Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

- 2) **Dissolution Acceptance Criteria:** For the selection of the dissolution acceptance criterion or criteria of your product, the following points should be considered:
- a. The dissolution profile data from the pivotal clinical batch(es) and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).
 - b. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
 - c. The selection of the specification time point should be where Q=80 % dissolution occurs. However, if you have a slowly dissolving product, specifications at two time points may be adequate for your product. The first time point should be selected during the initial dissolution phase (i.e., [REDACTED] (b) (4) minutes about [REDACTED] (b) (4) % dissolution) and the second time point should be where Q = 80% dissolution occurs.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA review stage. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Discussion:

AbbVie provided the division with a summary of their controls procedure for the new formulation of Norvir. The in-process controls [REDACTED] (b) (4)

[REDACTED] (u) (4)
The company has experience with over [REDACTED] (b) (4) batches and 18 months of stability data on Norvir products. [REDACTED] (b) (4)

2.3. Vehicle Qualification

Question 3a: *Does the Agency agree with the proposed Module 3 submission strategy?*

FDA Response to Question 3a: The CMC data (compatibility and in-use stability) appears reasonable. Please also refer to the response to Question 3b.

Question 3b: *For each selected vehicle, only specificity and accuracy method validation will be performed in support of the compatibility and in-use stability studies. Does the Agency agree with the method validation plan?*

FDA Response to Question 3b: Data from in vitro in-use stability studies should be submitted to demonstrate that the (b) (4) drug product purity/impurity, palatability and its release profile (and any other critical attributes) are unaffected in the sprinkle vehicle (chocolate milk, infant formula, pudding or applesauce) prior to administration. To quantitate the impurities, if the method itself is already fully validated for drug product release/stability, it may be sufficient to perform only specificity and accuracy method validation for in-use stability studies.

Discussion:

AbbVie intends to include impurity and purity data with the in vivo data which will be submitted with the NDA. Given the broad bioavailability in various vehicles proposed, AbbVie does not believe that it will be an issue. As outlined, the Division confirmed that studies are sufficient for an NDA submission.

2.4. Human Factors/User Testing

Question 4a: *Does FDA agree that the (b) (4) % dose accuracy criteria applied in the human factors studies is acceptable?*

FDA Response to Question 4a: The acceptability of the (b) (4) % accuracy criteria will be a review issue.

Question 4b: Does FDA agree the human factors program consisting of the 2 formative studies is adequate to support the NDA submission for review, and no further user testing is needed?

FDA Response to Question 4b: We do not agree. The two formative studies performed are insufficient to support a finding that the product will be safely and correctly used by the intended end users for intended uses and intended use environments. An updated use related risk analysis should be performed, taking into account critical failures encountered during formative testing and the interventions made to address them. We consider overdoses and underdoses to be critical failures that can impact the efficacy of treatment, and acceptability of any margin of error regarding accuracy of the final dose administered will be a review issue. Please note that relying on clinical lab markers (e.g. increased viral load or a decrease in CD4 count) to detect dosing inaccuracies that may have resulted from use error is not acceptable.

Discussion:

Prior to the teleconference, AbbVie agreed to conduct another validation study as recommended by the Division of Medication Error Prevention and Analysis (DMEPA). AbbVie provided the Division and DMEPA with a summary of the key design features for the new study.

Study Size and User Groups:

AbbVie proposed a total of 15 subjects for the Human Factors validation study. The Agency recommended two groups, 15 subjects per arm. One group should be caregivers and the other health care providers (i.e., nurses, pharmacists).

Example of Prescribed Dosing:

AbbVie proposed a single dose of Norvir powder formulation ((b) (4) for the study. (b) (4) The study will test and validate a caregiver's ability to mix the powder and liquid vehicle. DMEPA had no additional comments.

Dose Card:

AbbVie will not provide a patient dose card for the validation study. Instead a simulated pharmacy label will be provided to each participant to communicate that the prepared dose should be 3.2 mL. The goal is to simulate how information will be disseminated to the caregiver and health care provider, which will be done in clinical practice. DMEPA had no additional comments.

Vehicle:

AbbVie proposed a single vehicle of either water or infant formula. DMEPA had no additional comments.

Learning:

AbbVie proposed participants have three practice trials and then measure the fourth trial. AbbVie stated that consistency will get better with time, as this mimics real-life scenarios. DMEPA disagreed with AbbVie's approach and indicated there should be no training or practice trials. If multiple trials are run, then the results should be collected for every trial and reported.

AbbVie agreed to do measurements for all trials, however, they plan to assert that there is a learning curve and accuracy gets better with practice. DMEPA indicated that they can include their position along with their rationale with their submission for review.

Support:

AbbVie will recommend consultation with support number as instructed in the Instructions for USE (IFU). In a separate room, another person acting as a health care provider will answer the call and address any questions that the participant has. This will mimic "real life" situations. DMEPA stressed that the participant should not be prompted to call the support number, nor should it be stressed or highlighted during the study introduction and set up. AbbVie should provide a copy of the script as a part of the protocol submission for review.

Endpoint and Definition of Success:

AbbVie suggested volume as the endpoint with success defined as plus or minus (b) (4) on the fourth trial. DMEPA reiterated that all results for all trials should be collected and reported. Additionally, they can propose their rationale for definition of success, but whether it is acceptable will be a review issue, and the granular data should be submitted to the Agency for review. DMEPA also indicated that mass of (b) (4) should also be collected as part of the study results.

AbbVie proposed a label comprehension study as part of a third formative study prior to the human factors validation study. They indicated the study will incorporate some of the elements of the IFU and is limited to the understanding of the preparation and dosing properties of labeling. The Division agreed to this approach, as it provides an opportunity to optimize the IFU prior to the initiation of the validation study. AbbVie confirmed that the same individuals will participate in the comprehension and validation studies. DMEPA indicated that the participants for the comprehension and validation should be different.

The Division inquired about the acceptance criteria (b) (4) to ensure that there is a full 100 mg by weight. (b) (4)

(b) (4) AbbVie agreed to provide this information with the NDA submission, specifically in Module 3. In addition, the (b) (4) tolerance specification, measurements of mass accuracy and human factors validity protocol will be included.

DMEPA recommended AbbVie submit the full human factors validation protocol for FDA review. Typically, the review goal is 90 days; however, DMEPA will aim to provide comments within 4-6 weeks of receipt of the protocol.

2.5.Specialty Pharmacy Distribution

Question 5a: AbbVie does not intend to [REDACTED] (b) (4)

FDA Response to Question 5a: [REDACTED] (b) (4)

[REDACTED] (b) (4)

Question 5b: Does the Agency agree with the planned approach [REDACTED] (b) (4)

[REDACTED] ***the Norvir Oral Powder as necessary to meet the dosing needs of the patients?***

FDA Response to Question 5b: We do not agree with your approach. [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

Additionally, please further define what is meant by “specialty pharmacies” (i.e., does this include hospital pharmacies, internet pharmacies, select local pharmacy chains, etc.) and comment on the accessibility of the product if only specialty pharmacies are utilized as proposed.

Discussion:

The specialty pharmacies that AbbVie intends to use to distribute Norvir powder formulation

is

(b) (4)

(b) (4)

(b) (4)

¹ Guidance for Industry *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*, accessible at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/>

(b) (4)

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.

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. 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 Pediatric and Maternal Health Staff 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>.

- **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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including: The Final Rule (Physician Labeling Rule) on the content and format of 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.

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.				

6.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

7.0 ACTION ITEMS

Action Item/Description	Owner
Submit the comprehension and human factors validation study protocols for FDA review	AbbVie
Submit general outline of the specialty pharmacy distribution steps of the drug and variations of the process flow model	AbbVie

8.0 ATTACHMENTS AND HANDOUTS

Email of table for discussion.

From: [Kuntz, Matthew](#)
To: [Onaga, Linda](#)
Subject: RE: IND 43718 Pre NDA preliminary Comments
Date: Friday, June 27, 2014 5:57:35 PM
Attachments: [image001.png](#)

Hi Linda,

We've had a chance to review the preliminary comments. We would like to focus the discussion Monday on Questions 1, 3, 4 and 5. There is no reason for further discussion or clarification of any of the other comments.

For Question 4, we agree to conduct a validation study. Please share with the Human Factors reviewers the following table that shows key design characteristics of the validation protocol. We would be very interested in the Agency's thoughts on these Monday if possible.

Norvir Oral Powder – Human Factors Validation Study Design

Characteristics	Study Design
Study Size	N = 15
User Groups	Caregivers with a broad range of literacy
Example of Prescribed Dose	Single dose of [REDACTED] (b) (4)
Dose Card	A patient dose card will not be provided. A simulated pharmacy label will be provided to the participant to communicate that the prepared dose should be 3.2ml.
Vehicle	Single vehicle of either water or infant formula.
Learning	Three practice trials will be allowed and the fourth trial will be measured without any coaching or training by the moderator.
Support	As per the IFU, provide the opportunity for the user to call "their doctor or pharmacist" for support if needed.
Endpoint	Volume
Definition of Success	Plus / minus [REDACTED] (b) (4) on the fourth trial

Best regards,
Matt

MATT KUNTZ, PHARMD, MBA, RAC
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Area & Affiliate - US & Canada



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From: Kuntz, Matthew
Sent: Friday, June 27, 2014 2:17 PM
To: 'Onaga, Linda'
Subject: RE: IND 43718 Pre NDA preliminary Comments

Thanks Linda. I'll share these with the team.

Based on my quick scan of the comments, I'm certain we'll want to meet. I'll try to get you a list of Questions for the call later today.

Please use the following teleconference number:

Dial: [REDACTED] (b) (4)
Code [REDACTED]

Thanks,
Matt

From: Onaga, Linda [<mailto:Linda.Onaga@fda.hhs.gov>]
Sent: Friday, June 27, 2014 2:04 PM
To: Kuntz, Matthew
Subject: IND 43718 Pre NDA preliminary Comments

Good Afternoon Matt,

Please find attached the preliminary comments for the upcoming pre-NDA meeting between AbbVie and the Division of Antiviral Products.

Please let me know if AbbVie would still like to hold the t-con. If so, please provide a call in number.

Thanks

Linda

*Linda C. Onaga, MPH
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/s/

DEBRA B BIRNKRANT
07/30/2014