

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209512Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 209512
Review #1**

Drug Name/Dosage Form	Norvir (ritonavir) Oral Powder
Strength	100 mg (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	12/07/16	All
Quality Amendment	2/02/17	Product Quality
Labeling Amendment	2/15/17	Multiple
Quality Amendment	2/24/17	Product Quality
Quality Amendment	3/14/17	Product Quality
Quality Amendment	3/21/17	Product Quality
Multiple Categories	3/31/17	Multiple
Quality Amendment	4/14/17	Product Quality
Quality Amendment	4/20/17	Product Quality
Quality Amendment	4/24/17	Product Quality
Labeling Amendment	5/01/17	Multiple
Withdrawal Request	5/05/17	Multiple
Labeling Amendment	5/10/17	Multiple
Quality Amendment	5/22/17	Product Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	NA	NA
Drug Product	William McCalmont	Stephen Miller
Process	Sateesh Kumar Sathigari	Steven Frisbee
Microbiology	Sateesh Kumar Sathigari	Steven Frisbee

CDER Facility	Cassandra Abellard	Derek Smith
Biopharmaceutics	Fang Wu	Kimberly Raines
CDRH Device	Rong Guo	Alan Stevens
CDRH Facility	Crystal Lewis	Jamie Kamon-Brancazio
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	AC	Sufficient information in NDA	
	Type III			AC	Sufficient information in NDA	(b) (4)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Norvir Tablets	NDA 22417	Same (b) (4) Process
NDA for Norvir Oral Solution	NDA 20659	Ritonavir drug substance information

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH Device Eval	Complete	Approval	5/02/17	R. Guo
CDRH Facility Eval	Complete	Approval	5/04/17	C. Lewis
Clinical	NA			
Other	NA			

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Executive Summary

I. Recommendations and Conclusion on Approvability

From the product quality perspective this NDA is recommended for approval.

This product was developed (b)(4), room temperature stable, (b)(4)

Note that on May 19, 2017, FDA conveyed a recommendation to AbbVie to change the proposed name, (b)(4) to Norvir (ritonavir) Oral Powder. This is described further under section C of this Executive Summary.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	In combination with other antiretroviral agents for the treatment of pediatric patients with HIV-1 infection
Duration of Treatment	Chronic
Maximum Daily Dose	1200 mg per day is the adult dosage for treatment; more commonly, lower doses are used for raising the PK of other HIV agents
Alternative Methods of Administration	Mixed with soft food such as apple sauce or vanilla pudding, or mixed with liquids such as water, chocolate milk, or infant formula

B. Quality Assessment Overview

The information on the ritonavir drugs substance is cross-referenced to NDA 20659, which supports other approved NDAs from this applicant. As a result, there is no need for a separate drug substance evaluation as part of this review.

The drug product is a course powder contained in an aluminum (b) (4) (100 mg of ritonavir (b) (4); 30 (b) (4) per carton). It is prepared by (b) (4)

the manufacture of Norvir (ritonavir) tablets (NDA 22417). The information on the manufacturing process (b) (4) is included in NDA 22417, which is cross-referenced by NDA 209512.

An important aspect of the product quality review of the oral powder is the theoretical potential (b) (4)

(b) (4)

Biopharmaceutics: The oral powder shows very rapid dissolution. (b) (4)

The proposed soft foods and liquids (apple sauce, vanilla pudding, chocolate milk, infant formula and water) were studied, and shown not to impact the dissolution behavior over an incubation time of two hours. The dissolution method for the oral powder is adequately supported with developmental studies, including evaluation of rotational speed and discriminating ability relative to large particle size (b) (4). Based on FDA recommendations, the acceptance criterion agreement was revised to “NLT (b) (4) % (Q) of the labeled amount of ritonavir dissolved in 15 minutes.” While a (b) (4) powder formulation was studied during development, the proposed commercial formulation of the oral powder is the same as that used in the pivotal BE study, so no bridging information was required.

Process: The manufacturing process for the oral powder includes manufacture (b) (4)

(b) (4)

CDER Evaluation of Manufacturing Facilities: The most recent inspection of the (b) (4)

With this modification, AbbVie Latina Italy will be the facility that produces (b) (4)
ritonavir API for NDA 209512.

The AbbVie Latina Italy site is an existing facility for manufacture of ritonavir. (b) (4)

Under this situation, and given that AbbVie/Abbott developed the ritonavir synthesis, no additional data is needed to support use of the AbbVie Latina Italy facility for manufacture of ritonavir API for NDA 209512, including the manufacture of (b) (4). With the removal of (b) (4) all manufacturing, testing and packaging/labeling facilities in NDA 209512 are acceptable.

(b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

In consideration that a significant use of this product will be as a mixture with food, the dosage form name, “Oral Powder” is recommended. AbbVie was informed of this recommendation on May 19, 2017, and requested to change the name of the product to Norvir (ritonavir) Oral Powder throughout the labeling including the container labels. From the product quality perspective, this name is appropriate as the product title within the highlights section of the prescribing information.

Several additional edits were recommended from the product quality perspective (see Labeling Review #2). These were discussed with OND and will be conveyed to AbbVie as part of the labeling recommendations.

D. Final Risk Assessment (see Attachment I at the end of this review)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209512

Date: May 23, 2017



Stephen
Miller

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LABELING

Review #2

Because of clinical concerns with the procedures that a care-giver must follow to prepare (b) (4) doses of 100 mg and multiples of 100 mg. (b) (4) As a result, the package insert, Instructions for Use (IFU), and carton labels have been revised.

The revised package insert and carton labels are reviewed below from the product quality perspective. The evaluation of the revised IFU is included in the clinical and DMEPA reviews.

Highlighted font indicates a change in the label made after Labeling Review #1

I. Package Insert

1. Highlights of Prescribing Information

NORVIR (ritonavir) tablet, for oral use
 NORVIR (ritonavir) **oral solution** (b) (4)
 NORVIR (ritonavir) **oral powder** (b) (4)

DOSAGE AND ADMINISTRATION -----

- Dose modification for NORVIR is necessary when used with other protease inhibitors (2)
- Adult patients: 600 mg twice-day with meals (2.2)
- 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 (2.3)
- 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 (2.3, 5.2)
- Instructions for Use should be followed for preparation and administration of Norvir **oral powder** (b) (4) (2.4)

DOSAGE FORMS AND STRENGTHS -----

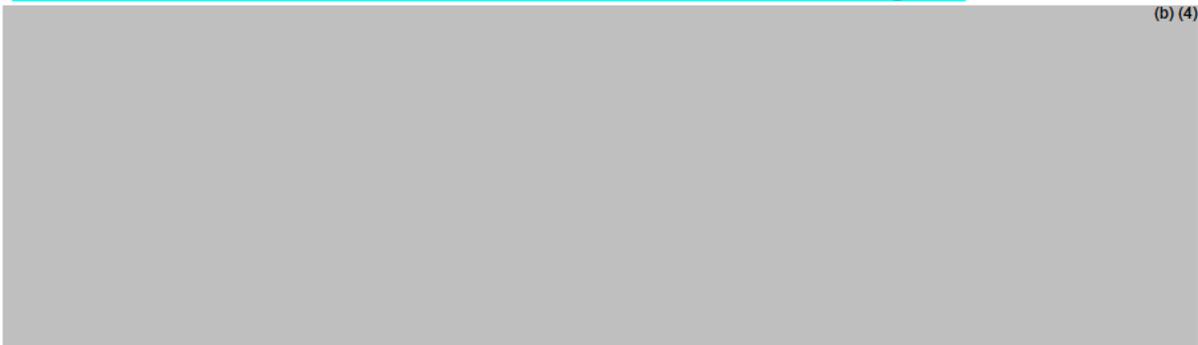
- Tablet: 100 mg (b) (4)
- Oral solution: 80 mg (b) (4) per milliliter
- **Oral Powder** (b) (4): 100 mg (b) (4) **per packet.**

Item	Information Provided in NDA
Product Title (Labeling Review Tool	and 21 CFR 201.57(a)(2))
Proprietary name and established	Acceptable with edits

name	
Dosage form, route of administration	Acceptable with edits
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Acceptable with edits

2. Section 2 Dosage and Administration

- NORVIR must be used in combination with other antiretroviral agents.



(b) (4)

2.4 Preparation of Norvir Oral Powder (b) (4)

For details on the preparation and administration of NORVIR oral powder (b) (4), see *Instructions for Use*. (b) (4)
 (b) (4) NORVIR oral powder (b) (4) should only be used for dosing increments of 100 mg. All of the powder mixed with soft food or liquid should be administered within 2 hours of preparation.



(b) (4)

(b) (4)

The prescribed dose of **Norvir** **NORVIR oral powder** (b) (4) 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.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Adequate. From the Product Quality perspective, the description of the preparation in Section 2.4 is a reasonable summary of the more detailed description in the Instructions for Use (IFU) document, and the statement about administration via a feeding tube is supported by data that is evaluated in the Drug Product Chapter of the Product Quality review.

3. Section 3 Dosage Forms and Strengths

- **NORVIR Tablets**
White film-coated ovaloid tablets debossed with the "a" logo and the code NK providing 100 mg ritonavir.

- **NORVIR Oral Solution**
Orange-colored liquid containing 600 mg ritonavir per 7.5 mL marked dosage cup (80 mg per mL).

- **NORVIR Oral Powder** (b) (4)
Beige/pale yellow to yellow powder in child-resistant packet. Each packet contains 100 mg of ritonavir.

contains 19.2 grams of ritonavir. NORVIR oral solution also contains 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** (b) (4) 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.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Acceptable with edit to dosage form and for expression of strength
Active moiety expression of strength with equivalence statement (if applicable)	Not a salt, so no equivalence statement is needed. Edit recommended regarding strength per packet.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Adequate
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Adequate

5. Section 16 How Supplied/Storage and Handling

- **16.1 NORVIR Tablets, 100 mg Ritonavir**
- NORVIR (ritonavir) tablets are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.
- Bottles of 30 tablets each (NDC 0074-3333-30).
- Recommended Storage
- Store at or below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for seven days permitted. Dispense in original container or USP equivalent tight container (60 mL or less). For patient use: exposure of this product to high humidity outside the original or USP equivalent tight container (60 mL or less) for longer than 2 weeks is not recommended.
- **16.2 NORVIR Oral Solution, 80 mg per mL Ritonavir**
- NORVIR (ritonavir) oral solution is an orange-colored liquid, supplied in amber-colored, multi-dose bottles containing 600 mg ritonavir per 7.5 mL marked dosage cup (80 mg per mL).
- 240 mL bottles (NDC 0074-1940-63).
- Recommended Storage
- Store at room temperature 20°-25°C (68°-77°F). Do not refrigerate. Shake well before each use. Use by product expiration date.
- Product should be stored and dispensed in the original container.
- Avoid exposure to excessive heat. Keep cap tightly closed.
- **16.3 NORVIR Oral Powder** (b) (4), 100 mg Packet
- NORVIR (ritonavir) oral powder (b) (4) 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) (b) (4)
- Recommended Storage
- Store at or below 30°C (86°F).

End of Section 17:

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

**NORVIR oral powder (b) (4) is manufactured for:
AbbVie Inc.
North Chicago, IL 60064 USA**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	N/A
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer’s Assessment of Package Insert: Adequate

From the product quality labeling perspective the dosage form “oral powder” is recommended for this product. This is felt to be appropriate because a significant use of the product will be by mixing the drug product with soft food. Additionally, including the word “Powder” is recommended from the clinical perspective in order to help differentiate it from the other approved pediatric dosage form (ritonavir oral solution). The PI is combined, and includes tablets, oral solution, and the new powder for oral suspension. Additionally, there are some statements in the PI which recommend when the oral solution should be used instead of the powder.

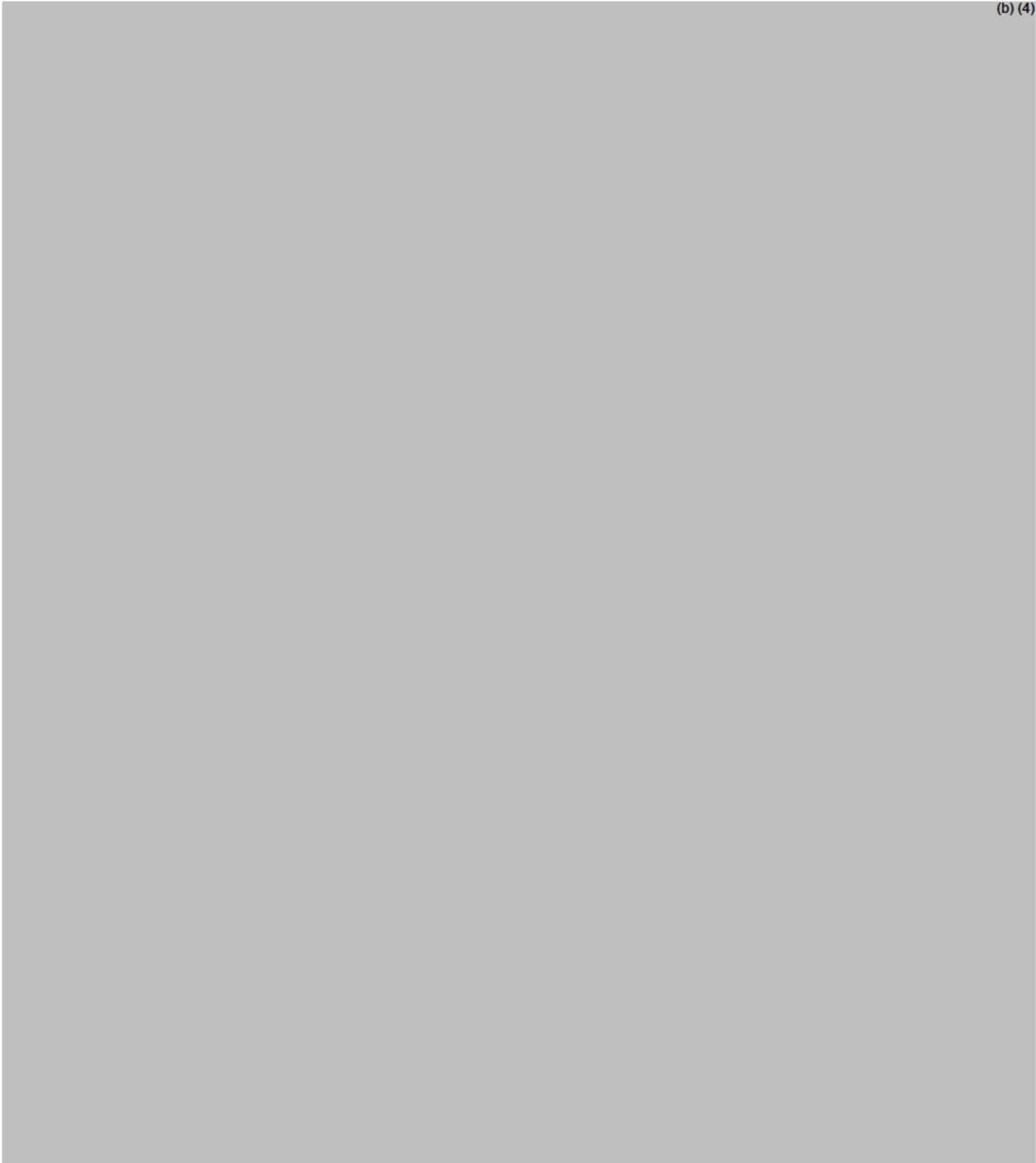
On May 19th this recommended change in the name of the dosage form was conveyed to the applicant, along with a request to update the container label. The change to “oral powder” throughout the PI (including the product title), PPI and IFU will be made during the labeling negotiations.

Additional edits are recommended from the Product Quality perspective in the Dosage Forms and Strengths section of the Highlights and in Section 11. These are listed at the end of this review.

II. Labels:

1. *Container and Carton Labels*

Carton Label



Packet Label



Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Acceptable, edit has been conveyed to applicant	Acceptable, edit has been conveyed to applicant
Dosage strength	Adequate	Adequate
Net contents	Adequate	Adequate
“Rx only” displayed prominently on the main panel	Adequate	Rx only is small font that is displayed beneath the (b) (4) suggest making it more prominent (perhaps larger font and left justified on same line as strength)
NDC number (21 CFR 207.35(b)(3)(i))	Adequate	Adequate
Lot number and expiration date (21 CFR 201.17)	See DEMPA review for more information.	See DEMPA review for more information.
Storage conditions	N/A	Adequate
Bar code (21CFR 201.25)	Adequate	Adequate
Name of manufacturer/distributor	Adequate	Adequate
And others, if space is available		

Reviewer’s Assessment of Container and Carton Labels: adequate

The carton label was modified (b) (4)

(b) (4)

Based upon the recommendations from the product quality labeling perspective the dosage form name used on the container labels is recommended to be “oral powder”. See the comments in the reviewer’s assessment of the Package Insert, above, for additional information.

List of Deficiencies: There are no deficiencies which would prevent approval from the Product Quality perspective. The following recommendations should be conveyed to the clinical division for consideration during labeling negotiations:

- 1. In the Highlights section of the Prescribing Information please edit the Dosage Forms and Strength summary to read:
“Oral Powder: 100 mg ritonavir per packet.”***
- 2. Please edit the following sentence in the Descriptions section to read:
“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.”***
- 3. For consideration by DMEPA reviewer: From the Product Quality perspective, we recommend that the Carton Label be modified by increasing the font of “Rx only” and moving it to a more prominent location (perhaps left justified beside strength). Update: Abbvie has centered the “Rx only” wording on their new label for Norvir and is sufficient to address the earlier concerns of it not being prominent enough.***

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date:

William McCalmont, Ph.D.
14 May 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Stephen Miller, Ph.D.
16 May 2017



William
McCalmont

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Stephen
Miller

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BIOPHARMACEUTICS**NDA: 209512****Drug Product Name/Strength: Norvir® (Ritonavir) Powder for Oral Suspension/ 100 mg per unit****Route of Administration: Oral****Applicant Name: ABBVIE INC****Submission:**

AbbVie is submitting an NDA, Norvir® (Ritonavir) Powder for Oral Suspension. (b) (4)

This NDA is supported by the safety and efficacy information included in the Norvir® Capsules, Oral Solution, and Tablets NDAs (020945, 020659, and 022417 respectively) and the BA/BE clinical data included in this NDA submission. The BA/BE clinical data show that Norvir® Powder is equivalent to the approved Norvir® Oral Solution. Reference is made to the Pre-NDA meeting information package submitted to IND 043718 on May 16, 2014, the June 27, 2014 FDA preliminary responses (Ref ID 3533782) and the June 30, 2014 meeting minutes (Ref ID 3601489).

Ritonavir (Norvir®) is a peptidomimetic inhibitor of the human immunodeficiency virus Type 1 (HIV-1) protease. Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children older than 1 month of age in the US and 2 years of age and older in the EU. Norvir® is currently available globally in 3 commercial dosage forms: Norvir® Oral Solution, Norvir® Capsule, and Norvir® Tablet.

The proposed Norvir® Oral Powder was developed without including excipients present in the Norvir® Oral Solution, such as alcohol and propylene glycol solvents, that could potentially cause toxicities in the younger pediatric population.

Review Summary: ADEQUATE**List Submissions being reviewed (table):**

Submitted data	Description	Submission Date
Module 3.2.P.2 Pharmaceutical Developments	Dissolution method development part	12/07/2016

	Drug Product Part	12/07/2016
	Compatibility Part	12/07/2016
Module 3.2.P.5 Control of Drug Product	Specification Batch Analysis	12/07/2016, 2/24/2017

The biopharmaceutics assessment focuses on the dissolution method and dissolution acceptance criteria/criterion for this NDA. In summary:

The Applicant developed an in-house *in vitro* dissolution testing method. The Applicant investigated the dissolution medium and rotation speed during their dissolution method development to support their proposed dissolution method. Based on the submitted data, the proposed *in vitro* dissolution testing method (*see below*) for Norvir® (Ritonavir) Powder for Oral Suspension (100 mg/unit) is adequate.

Based on the dissolution data shown in Table 8 of this review, the proposed dissolution specification of “*NLT* ^{(b) (4)} % (*Q*) of the labeled amount of ritonavir dissolved in ^{(b) (4)}” is permissive for the proposed drug product. Therefore, the data-driven dissolution acceptance criterion “*NLT* ^{(b) (4)} % (*Q*) of the labeled amount of ritonavir dissolved in 15 minutes” was recommended. In the responses dated 2/24/2017, the Applicant accepted FDA recommended dissolution acceptance criterion and updated the relevant parts in their NDA submission.

The dissolution method shown in the following table is ADEQUATE and the recommended acceptance criterion is accepted by the Applicant.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Recommended Acceptance Criterion
I (basket 100 mesh)	100 rpm	900 mL	37°C ± 0.5°C	0.1 M hydrochloric acid	Amount of Ritonavir Dissolved: ^{(b) (4)} (<i>Q</i>) at 15 minutes

Concise Description Outstanding Issues Remaining:

n/a

BCS Designation

The Applicant claims BCS Class IV designation.

Table 1: Ritonavir Solubility Profile

Solvent	Solubility (mg/ml)	
	(b) (4)	
Water	<0.001	<0.001
Acetonitrile	18.9	-
Acetonitrile/water (1/1, v/v)	66.4	-
Methanol	573	-
Ethanol	165	55
Isopropyl alcohol	41.7	-
Ethyl acetate	15	5.4
Heptane	0.1	-
Tetrahydrofuran	456	-
Methylene chloride	602	-
Chloroform	675	-
Dimethylformamide (DMF)	593	-
Toluene	2.2	-
0.05 M KH ₂ PO ₄ pH 3.0	<0.001	-
0.05 M KH ₂ PO ₄ pH 6.0	<0.001	-
0.05 M KH ₂ PO ₄ pH 9.1	<0.001	-

Reviewer’s Assessment:

Ritonavir (b) (4) in relevant solvents such as ethanol, ethyl acetate and various formulations are shown in Table 1. The solubilities vary from highly soluble in, for example, methanol and tetrahydrofuran, to practically insoluble in, for example, water and 0.05 M potassium phosphate solution. (Refer to Table 1 in 3.2.S.1.3 General Properties).

Solubility: The solubility of Ritonavir (b) (4) is shown in **Table 1**.

Permeability:

Experimental permeability data were not provided in the submission.

Dissolution Method and Acceptance Criteria

Reviewer’s Assessment:

1. Drug Product Composition Information

The proposed Norvir® Powder for Oral Suspension was developed without including excipients present in the Norvir® Oral Solution, such as alcohol and propylene glycol solvents. According to the Applicant, that could potentially cause toxicities in the younger pediatric population. Ritonavir has been formulated as a powder for oral administration that contains 100 mg per unit. The quantitative composition of Proposed Norvir® Powder for Oral Suspension is shown in Table 2 (refer to Module 3.2.P.1 Description and Composition of the Drug Product), which is the same as the primary stability and pivotal bioequivalence lot. For comparison, the composition for earlier clinical formulations, stability lots formulation and the formulation used in pivotal BE study is shown in Table 3 (refer to Module 3.2.P.2 Pharmaceutical Development), further indicating that the commercial formulation is the same as that used in pivotal BE study and primary stability study.

Table 2: Composition of the Proposed Norvir® Powder for Oral Suspension

Component	Quality Standard	Function	Amount (mg)/Unit
Ritonavir	USP/Ph. Eur.	Drug Substance	100.0
Copovidone (b) (4)	NF/Ph. Eur.	(b) (4)	(b) (4)
Colloidal silicon dioxide (b) (4)	NF/Ph. Eur.		
Sorbitan monolaurate (b) (4)	NF/Ph. Eur.		
Total			666.7

Table 3: Composition of the Proposed Norvir® Powder for Oral Suspension for Clinical Supplies, Pivotal Bioavailability and Primary Stability Lots/Commercial formulation

Table 1. Composition of Norvir Oral Powder Clinical Supplies, Pivotal Bioavailability, and Primary Stability Lots

(b) (4)



In order to improve oral bioavailability, a solid dispersion formulation of ritonavi (b) (4)

2. Information about listed approved drug product and USP in vitro dissolution testing method

The listed approved drug product, Ritonavir Oral Solution (NDA020659) manufactured by ABBVIE INC was approved on March 1, 1996. It has no in vitro dissolution testing method as it is formulated as a homogeneous solution.

The USP dissolution method and acceptance criteria for Ritonavir Capsules is shown in the following table.

Table 4 USP Monograph Ritonavir Capsules - Dissolution Testing Method and Tolerance

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Approved Acceptance Criterion
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II (paddle)	50 rpm with sinker	900 mL	37°C ± 0.5°C	0.1 N hydrochloric acid with 25 mM polyoxyethylene 10 lauryl ether	NLT ^(b) ₍₄₎ % (Q) of the labeled amount of ritonavir is dissolved within 30 minutes
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The USP dissolution method and acceptance criterion for Ritonavir Tablets is shown in the following table.

Table 5 USP Monograph Ritonavir Tablets - Dissolution Testing Method and Tolerance

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Approved Acceptance Criterion
II (paddle)	75 rpm	900 mL	37°C ± 0.5°C	0.06 M polyoxyethylene 10 lauryl ether	NLT ^(b) ₍₄₎ % (Q) of the labeled amount of ritonavir is dissolved within 120 minutes

3. Dissolution Method

The proposed dissolution method (refer to Table 6 in Module 3.2.P.2.2 Drug Product) was shown below:

Table 6 Proposed In Vitro Dissolution Testing Method

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Sampling Time
I (basket 100 mesh)	100 rpm	900 mL	37°C ± 0.5°C	0.1 M hydrochloric acid	15 minutes

During development, [REDACTED] ^(b)₍₄₎

[REDACTED] Later in development the proposed method described above was utilized.

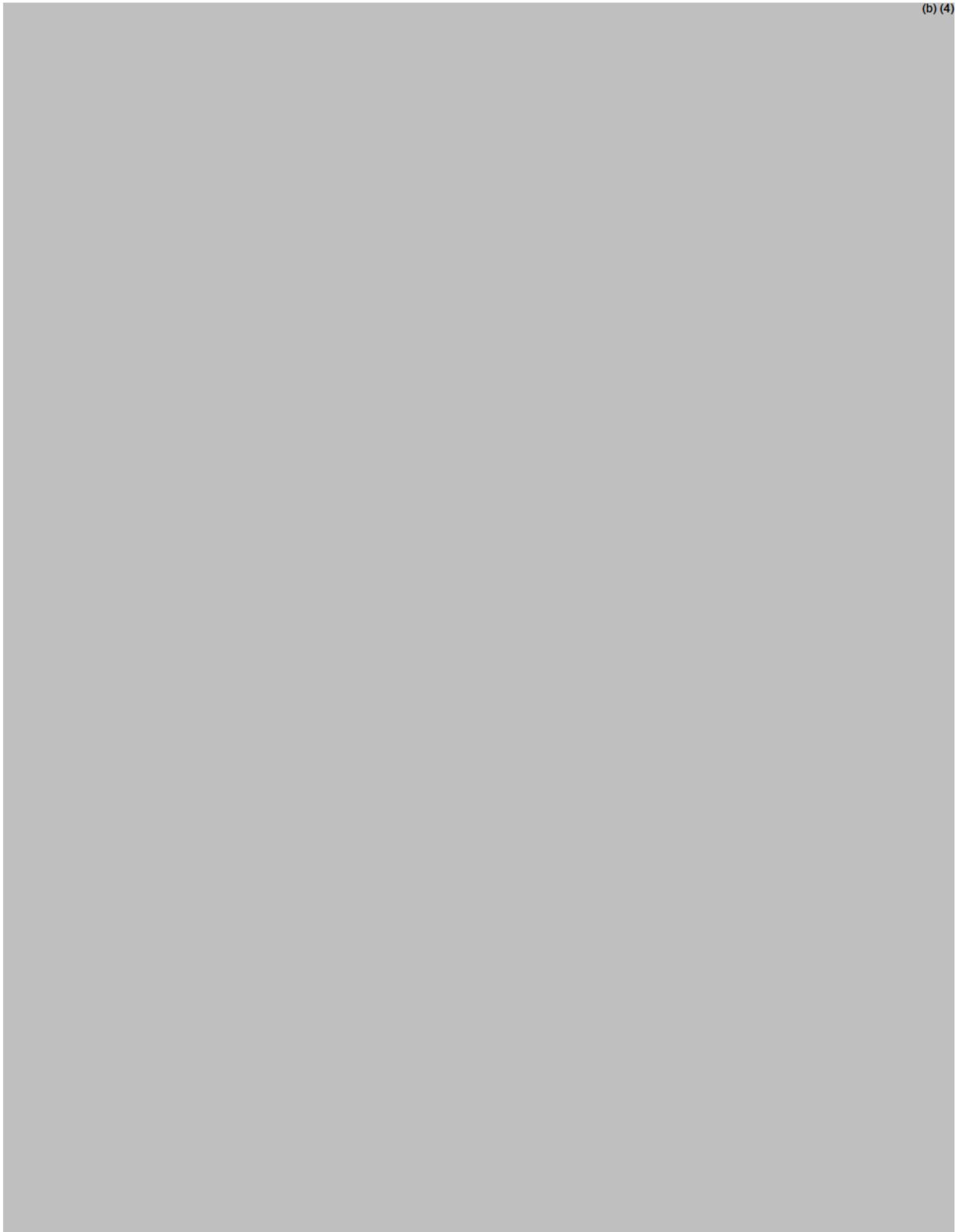
3.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The dissolution method was evaluated to determine the effect of medium and apparatus selection would have on the in vitro drug release. For more details, refer to pharmaceutical development¹.

The Applicant developed the dissolution testing method through investigating the following parameters:

(b) (4)

¹ <\\cdsesub1\evsprod\NDA209512\0000\m3\32-body-data\32p-drug-prod\norvir-oral-powder-all\32p2-pharm-dev\drug-product-usdev.pdf>



3.2 What data are available to support the discriminating power of the method?

Different particle size distribution

A series of experiments (b) (4) of different particle size distribution was conducted under rotation speed of (b) (4) 100 rpm. The results are shown in Figure 3 and Figure 4:

Figure 3. Dissolution Profile Comparison for (b) (4) Ritonavir (b) (4) 0.1 M HCl with Different Particle Size Distribution using Different Rotation Speeds

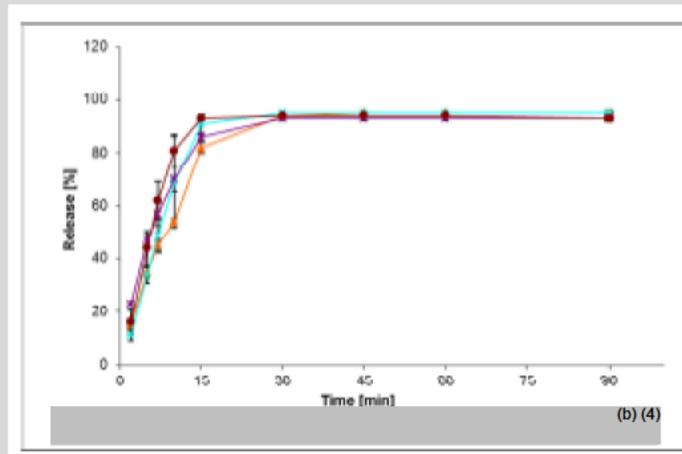
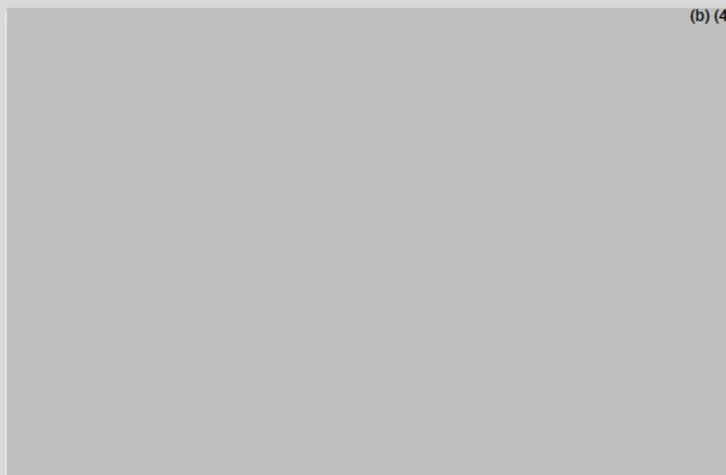


Figure 4. Dissolution Profile Comparison for (b) (4) Ritonavir (b) (4) Compared to 2 mm Mini-tablets ((b) (4) Ritonavir) in 0.1 M HCl



Reviewer’s Comments:

- Under the rotation speed of (b) (4) 100 rpm, only minor differences are shown for the release rates (b) (4) with a PSD of (b) (4) um and those with PSD of (b) (4) um.

- According to the Applicant, the dissolution method can discriminate (b) (4) with a particle size distribution defined by the process parameters and larger particles, e.g., (b) (4) (Figure 4). However, the discriminating capability of the dissolution method was normally investigated on changes on the critical material attributes or critical process parameters of formulations with the same dosage forms. Therefore, the following IR was communicated to the Applicant in the Information Request dated January 19th, 2017.

IR #1 (Issued dated January 19, 2017)

“We acknowledge that you study the release (b) (4) with different properties (particle size distribution, stressed samples) using different dissolution media and rotation speeds to investigate the discriminating power of the method. Provide further evidence showing the discriminating capability of the proposed dissolution method by comparing the dissolution differences using formulation with (b) (4) % changes in key excipients such as surfactant included in the powder formulation”.

(b) (4)

(b) (4)



Reviewer's Comments:

- The Applicant's Responses dated 02/02/2017 to IR #1 issued on 01/19/2017 is acceptable.
- As Norvir® Powder for Oral Suspension exhibits rapid release of the drug substance from the (b) (4) formulation and the drug has good solubility in the 0.1M HCl dissolution medium, it is not expected to see significant differences in the Norvir® Powder for Oral Suspension dissolution profile as a result of minor (e.g. (b) (4)%) changes in the surfactant amount.
- The method is capable of determining differences (b) (4) with a particle size distribution defined by the process parameters and larger particles (b) (4) (Figure 4). This indicated that the in vitro dissolution testing method can be used as a quality control tool to assure batch-to-batch reproducibility during manufacturing.

3.3 Is the proposed dissolution/release method biorelevant? What data including but not limited to IVIVC are available to support this claim?

There is no information included in the submission to indicate that the in vitro dissolution testing method is biorelevant. Also, according to the Applicant, as expected for BCS class IV compound, the in vitro dissolution method is not correlated to in vivo performance of the product. For example, Norvir Powder is bioequivalent to the other commercial formulations (tablet and capsule formulation) with respect to AUC while their dissolution behavior are not in the same release pattern (refer to page 37 in Module 3.2.P.2 Drug Product submitted on 02/24/2017). Therefore, the in vitro dissolution testing method is a quality control tool to assure batch-to-batch reproducibility during manufacturing. There is no data suggesting the dissolution method and acceptance criterion can qualify a BE batch.

3.4 Overall assessment on dissolution method

Based on the above assessment, the in vitro dissolution testing method is ADEQUATE.

4. Dissolution Acceptance Criterion**4.1 What are the dissolution data of the biobatches used in the pivotal clinical trial?**

Dissolution profiles for three Norvir® Powder for Oral Suspension primary stability lots and one clinical lot (13-000335) used for the pivotal BE study are presented in Table 8 (refer to Module 3.2.P.2.2 Drug Product)

Table 8. Summary of Dissolution Data for the Primary Stability Lots and One Bio-batch (Batch No 13-000335) of Norvir® Powder for Oral Suspension

Protocol	Lot number	Mean % Label Amount Released (Range) ^a		
		5 min	15 min	30 min
Primary stability lot	12-003343	57 (45-71)	89 (71-97)	98 (93-100)
Primary stability lot	12-003344	56 (52-58)	92 (83-95)	99 (96-101)
Primary stability lot	12-003345	62 (47-76)	93 (82-100)	99 (96-101)
Clinical lot (used for Pivotal BE Study))	13-000335	52 (46-64)	91 (84-96)	98 (97-100)

a Dissolution data from initial testing from the formal stability study.

The dissolution profiles of the Norvir Oral Powder primary stability batches (lots 12-003343, 12-003344, and 12-003345), the pivotal bioequivalence batch (lot 13-000335) and the two demo batches (lots 7683586, 7683574) are shown in **Figure 6**.

Figure 6. Dissolution Profiles of Primary Stability Batches, Pivotal Bioequivalence Batch (Batch CTS) and Demo Batches for Norvir Powder for Oral Suspension



Based on the dissolution data shown in Table 8 for biobatches for Norvir® Powder for Oral Suspension, the proposed dissolution specification of “NLT $\frac{(b)}{(4)}\%$ (Q) of the labeled amount of ritonavir dissolved in $\frac{(b)}{(4)}$ ” is permissive for the proposed drug product. 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”. Therefore, the following IR was communicated to the Applicant in the Information Request IR#2 dated February, 12, 2017.

IR #2 (Issued dated February 12, 2017)

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.

Summary of the Applicant’s Responses dated February 24th, 2017 to IR#2

The drug product dissolution acceptance criterion of Q = $\frac{(b)}{(4)}\%$ of the labeled amount of ritonavir dissolved in 15 minutes will be adopted. The documents in the table below have been updated.

Table 9. Updated Sections in the submission

Section	Title	Description of Change
3.2.P.5.1	Pharmaceutical Development	Updated section 3.2.P.2.2.3 to reflect the dissolution acceptance criterion of Q = $\frac{(b)}{(4)}\%$ in 15 minutes
3.2.P.2.2	Specifications	Updated dissolution acceptance criterion to Q = $\frac{(b)}{(4)}\%$ in 15 minutes
3.2.P.5.6	Analytical Procedures	Update dissolution analytical procedure RTM.C5232 to reflect 15 minute sampling point
3.2.P.5.2	Justification of Specification	Updated the dissolution section to reflect the dissolution acceptance criterion of Q = $\frac{(b)}{(4)}\%$ in 15 minutes

Reviewer’s Comments:

The Applicant adopted the recommended acceptance criterion “NLT $\frac{(b)}{(4)}\%$ (Q) of the labeled amount of ritonavir dissolved in 15 minutes” and updated the drug product specification table and other relevant sections of the NDA, which is satisfactory.

The original proposed and the recommended/adopted dissolution acceptance criterion is shown in the following table.

Original Proposed Acceptance Criterion	Recommended Acceptance Criterion
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	(Adopted by the Applicant)
Amount of Ritonavir Dissolved:	Amount of Ritonavir Dissolved:
(b) (4) % (Q) at (b) (4)	(b) (4) % (Q) at 15 minutes

Stability test

Reviewer’s Assessment:

In Module 3.2.P.8.1 (submitted on 12/07/2016) Stability Summary and Conclusion, the Applicant indicated that no meaningful change in the dissolution of ritonavir has been observed in the stability data for samples stored (b) (4) at all storage conditions tested including the long-term storage condition for up to 36 months (for primary stability test). Dissolution results from Norvir® Powder for Oral Suspension stored (b) (4) meet the originally proposed dissolution shelf-life specification (Q (b) (4) % a (b) (4)) at all storage conditions and all time points.

Dissolution specification will be met at the time of product release through the time of use or expiration dating period. The Applicant did not include dissolution specification in their final stability test, which is acceptable due to the following reasons.

- According to the Applicant, a series of experiments with (b) (4) different particle size distribution was conducted under rotation speed of 75 rpm or 100 rpm, only minor differences are shown for the release rates (b) (4) with a PSD of (b) (4) um and those with PSD of (b) (4).
- The Norvir® Powder for Oral Suspension exhibits relatively rapid release of the drug substance from the high surface area (b) (4) formulation and the drug has good solubility in the 0.1M HCl dissolution medium.
- (b) (4)

In-Vitro Soft-food Interaction Study

The Applicant performed a study to evaluate the impact of the administration vehicles on the release of ritonavir from Norvir® Powder for Oral Suspension. The vehicles intended to be included in the product labeling are water, chocolate milk, and infant formula for suspension preparation, and apple sauce and vanilla pudding for sprinkle preparation.

10 mL of the prepared suspension in liquid vehicles was incubated for 0, 30 and 120 minutes at ambient conditions. After incubation the suspension was transferred into the dissolution vessel and analyzed by the test method RTM.C5232 (dissolution method for quality control). The sprinkle preparation in the soft foods was incubated for 0, 30, and 120 minutes at ambient conditions. After incubation the sprinkle preparation was analyzed by the test method RTM.C5232 (b) (4)

The results showed that when the Norvir® Powder for Oral Suspension is prepared as a suspension in chocolate milk, water and infant formula, a release of more than 94%, 98% and 98% of ritonavir occurs after 5 minutes, respectively (refer to Module 3.2.P.2 Compatibility). Also, it was shown that the release of ritonavir is independent of the holding time after suspension preparation for the above three mixtures.

When the Norvir® Powder for Oral Suspension is prepared as a sprinkle preparation in apple sauce and vanilla pudding, a release of more than 87% and 94% of ritonavir occurs after 5 minutes. Also, it was shown that the release of ritonavir is independent of the holding time after suspension preparation for the above two mixtures.

Reviewer's Assessment:

- Different incubation time up to 2 hours² of the drug product food mixtures have no impact on the dissolution behavior of the Norvir® Powder for Oral Suspension. The investigated soft food vehicles do not impact the release of ritonavir from the drug product over an incubation time of two hours.
- No crystalline ritonavir was detected in any of the Norvir® Powder for Oral Suspension samples mixed with chocolate milk, infant formula, vanilla pudding and apple sauce dose vehicles or water after a 2 hour hold time (For additional details, refer to Drug Product Assessment)

Bridging of Formulations

Reviewer's Assessment:

The to-be-marketed product formulation is the same as the one used in primary stability studies, which is also the same as the formulation used in M11-475 (Pivotal Bioequivalence Study, Bulk Product lot number: 13-000335, Finishing Lot Number 13-000920) (See Table 3 of this review).

² Labeling statement: *All of the powder mixed with soft food or liquid should be administered within 2 hours of preparation.*

Bioavailability of Norvir® Powder for Oral Suspension was assessed in 3 studies: Study M11-472, M12-279 and M11-475.

M11-472 compared the relative bioavailability of 3 test regimens of 2 ritonavir powder formulations to the marketed Norvir® Oral Solution. Based on the results of this study, the uncoated powder formulation was chosen as the proposed Norvir® Powder for Oral Suspension.

M12-279 compared the bioavailability of the proposed Norvir® Powder for Oral Suspension in 3 different vehicles (water, infant formula, and applesauce) relative to the marketed Norvir® Oral Solution.

Study M11-475 was conducted to establish the bioequivalence of the proposed Norvir® Powder for Oral Suspension to the reference marketed Norvir® Oral Solution under moderate-fat conditions. (Bio-batch No: Bulk Product lot number: 13-000335, Finishing Lot Number 13-000920).

The commercial batch size is the same as the bio-batch size (b) (4) (Refer to Table 1 in Module 3.2. P.5.4 Batch Analysis), therefore, no bridging data is needed.

List of Deficiencies:

Biopharmaceutics Comments for IR #1:

1. We acknowledge that you study the release (b) (4) with different properties (particle size, stressed samples) using different dissolution media and rotation speeds to investigate the discriminating power of the method. Provide further evidence showing the discriminating capability of the proposed dissolution method by comparing the dissolution differences using formulation with (b) (4) 0% changes in key excipients such as surfactant included in the powder formulation.

The above deficiency was communicated to the Applicant on 01/19/2017 and the Agency received the Applicant's responses on 02/02/2017. The responses are acceptable.

Biopharmaceutics Comments for IR #2:

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* (b) (4) % (*Q*) of the labeled amount of ritonavir dissolved in (b) (4) " is too permissive for Norvir Powder for Oral Suspension. Therefore, the following data-driven dissolution acceptance criterion is recommended: "*NLT* (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.

The above deficiency was communicated to the Applicant on 02/12/2017 and the Agency received the Applicant's responses on 02/24/2017. The Applicant accepted the FDA recommended dissolution acceptance criterion and updated the drug product specification table for release test and other relevant sections of their NDA accordingly, which are acceptable.

Primary Biopharmaceutics Reviewer Name and Date:

Fang Wu, Ph. D.

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drugs Products

Date:

3/3/2017

4/21/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur with the biopharmaceutics assessment.

Kimberly Raines, Ph. D.

Secondary Biopharmaceutics Reviewer
& Branch Chief (acting)
Division of Biopharmaceutics
Office of New Drugs Products

Date: *04/04/2017*

Date: *04/21/2017*



Kimberly
Raines

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Fang
Wu

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date: February 20, 2017 (**Updated 5/4/2017**)

To: ICCR Lead-Center Contact, Office, Location, E-mail:

CC: Office of Combination Product at: combination@fda.gov
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Date: 2017.05.12 08:19:36 -0400

From: Crystal Lewis, REGO/DMQ/OC, CDRH, WO 66, Rm 3452, E-mail:
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1 N. Waukegan Road
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North Chicago, Illinois 60064
FEI: 3009751352

Submission (Type & Number): NDA209512

Combination Product Name: Norvir (ritonavir) powder for oral suspension

Combination Product Intended Use: Product is intended for the treatment of patients with HIV infection.

Device Constituent (Type): (b) (4)

ICCR Number:

RECOMMENDATION

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

- (2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

**Crystal
Lewis -A**
Crystal Lewis

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ou=FDA, ou=People, cn=Crystal Lewis -
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Prepared: CLewis: 2/20/2017, 5/4/2017

Reviewed: JKamon-Brancazio: 2/28/2017, 5/12/2017

CTS No.: (b) (4)

NDA 209512

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 209512

Final Risk Table for Norvir (ritonavir) Oral Powder

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations/ Comments
Assay, Stability		L		Acc	
Physical stability (solid state)		M	See factors described in Exec Summary	Acc	
Content uniformity		M	In-process controls (b) (4)	Acc	Future investigator could assess if (b) (4) filing yields are appropriate.
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV		M	Timepoint for AC tightened to 15 min. Studies supporting dosing in liquid and soft foods.	Acc	
Bead size for sprinkles		L	Controls on (b) (4) s give D90 values in the range of (b) (4).	Acc	
Patient Use Considerations	(b) (4)	M	Dosing accuracy studies in laboratory settings. Recover studies for administration by feeding tubes.	Acc	
Safety of Device Materials of Construction		L		Acc	



Stephen
Miller

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GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Intercenter Consult Memorandum

Device Constituent Part Design Review: CDER NDA 209512 - CDRH (b) (4)

Date: April, 2017

To: Stephen Miller
Branch III (NDPBIII)
Division of New Drug Products I (DNDPI)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

From: Rong Guo
General Hospital Devices Branch (GHDB)
Division of Anesthesiology, General Hospital Device, Respiratory, Infection
Control, & Dental Device (DAGRID)
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)

Re: NDA 209512

Subject: Device Constituent Part Design Review: CDER NDA 209512 - CDRH
ICC1600870; CDER review of Norvir powder for suspension; (b) (4)

Recommendation: CDRH recommends approval (b) (4)

I. Recommendation and Summary

(b) (4)



X. Concurrence Table

Digital Signature Concurrence Table	
Reviewer Sign-Off	Rong Guo -S (Affiliate) 2017.05.02 09:44:43 -04'00'
Branch Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2017.05.02 09:46:06 -04'00'