CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209512Orig1s000

CLINICAL REVIEW(S)

Clinical and Cross-Discipline Team Leader (CDTL) Review

Date	May 14, 2017
From	Regina Alivisatos, MD Medical Officer Division of Antiviral Products/Office of Antimicrobial Products
Through	Adam Sherwat, MD Medical Team Leader
Subject	Clinical and CDTL Review
NDA #	209512 (000)
Applicant	Abbvie
Date of Submission	December 7, 2016
PDUFA Goal Date	June 7, 2017
Proprietary Name / Non-Proprietary Name	Norvir (ritonavir [RTV])
Dosage form(s) / Strength(s)	Oral Powder
Applicant Proposed Indication(s)/Population(s)	NORVIR Powder for Oral Suspension is indicated in combination with other antiretroviral agents for the treatment of pediatric HIV-1 infection.
Recommendation on Regulatory Action	Approval for doses of 100 mg (i.e., the full sachet dose) and increments of 100 mg.
Recommended Indication(s)/Population(s) (if applicable)	Norvir is indicated in combination with other antiretroviral (ARV) agents for the treatment of human immunodeficiency virus (HIV)-1 infection (adults and children greater than one month of age in whom doses greater or equal to 100 mg are appropriate).

1. Introduction

This New Drug Application (NDA) submission for a new RTV powder formulation for oral administration is based on the demonstrated bioequivalence of the powder to the approved oral solution at a dose of 100 mg. Because the formulations are bioequivalent, the previously reviewed preclinical and clinical studies that supported the approval of the oral solution are applicable to the approval of the powder in both adults and pediatric patients. Therefore, this NDA is supported by the safety and efficacy information included in the Norvir Capsules, Oral Solution, and Tablets NDA (020945, 020659, and 022417 respectively) and the BA/BE clinical data included in the NDA submission.

Pertinent to this clinical review there are no new clinical efficacy or safety studies submitted as part of the application.

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This New Drug Application (NDA) includes CMC, Human Factors and User Testing, and three BA and BE studies in healthy adult subjects (Studies M11-472, M12-279, M11-475) that were evaluated for safety in the clinical review.

NORVIR (RTV) is a peptidomimetic human immunodeficiency virus (HIV) type 1 (HIV-1) protease inhibitor that selectively inhibits the virus-specific processing of viral Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature infectious virions. This mechanism of action is similar to that of other protease inhibitors used in the treatment of HIV-1 infection. NORVIR is approved worldwide for the treatment of HIV-1 infections at a dose of 600 mg PO twice daily in combination with other antiretroviral agents. In the USPI it is indicated "in combination with other ARV agents for the treatment of HIV-1 infection in adults and children greater than one month of age."

Unique however to RTV is its enhanced ability to inhibit cytochrome P450-mediated metabolism as compared to other protease inhibitors. This enables it to be used at reduced doses of 100 mg once daily to 200 mg twice daily with protease inhibitors, including lopinavir (co-formulated), atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir in order to increase their exposure and therefore their antiviral activity. RTV is primarily used at these lower doses and rarely or not at all at the 600 mg twice daily approved adult dose.

Three formulations are currently marketed: a 100 mg soft gelatin capsule (SGC), an 80 mg/mL oral solution and the 100 mg tablet formulation (b) (4)

Rationale for the development of the powder formulation is that it provides for an alcohol and propylene glycol (PG) free formulation that will be safer to use in pediatric patients. The currently marketed oral solution contains ((b) (4) alcohol and (b) (4) PG). Other potential benefits of the new powder formulation include increased shelf life through reduced degradation rates; greater ease in transporting it to underserved areas; the ability to administer it in various liquid or soft food vehicles thus improving administration flexibility in those who cannot take a tablet; and palatability. (b) (4)

AbbVie received Orphan Drug designation for the Norvir Powder for Oral Solution in December, 2016 for use in pediatric HIV-1 infected patients.

2. Background

The United States Centers for Disease Control (CDC) reported the first clinical evidence of Acquired Immunodeficiency Syndrome (AIDS) in June 1981. Shortly thereafter the link between HIV-1 infection and AIDS was discovered. Since that time HIV/AIDS has been recognized as a global epidemic with an estimated 65 million

people being infected and over 25 million deaths from the disease. In 2012, over 35 million people worldwide were living with HIV infection and 1.6 million people died from HIV/AIDS.

The CDC's most recent estimate of the US prevalence for HIV infection in 2011, both diagnosed and undiagnosed, is >1.1 million adults and adolescents (447.8 per 100,000) (CDC 2013). The estimated incidence of HIV has remained stable in recent years at about 50,000 new cases per year (US). Within the estimates some groups are more affected than others. Men who have sex with men (MSM) continue to bear the greatest burden of HIV infection, and within race and ethnicities, African Americans continue to be disproportionately affected. Blacks represent approximately 12% of the US population but accounted for 44% of new HIV infections in 2010. Hispanics and Latinos are also disproportionately affected by HIV. They represented 16% of the US population but accounted for 21% of new HIV infections in 2010.

The total estimated number of children and adolescents below the age of 20 living with HIV in 2013 was 8,952, with an estimated 2,037 new infections in 2014. The total estimated number of infected individuals in this age group has steadily declined over the years (2010: 11,673; 2011: 10,789; 2012: 9,964; 2013: 9,092). New infections in this age group have also steadily declined in the USA over time (2010: 2,399; 2011: 2,311; 2012: 2,260), but appears to have remained stable between 2013 (2,026) and 2014 (2,037)

Infection with HIV-1 results in chronic, progressive depletion of T-lymphocytes (CD4+ or helper T-cells) and also affects macrophages and other cells important for immune surveillance. HIV infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function with subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death.

The primary objective of anti-HIV treatment is to suppress viral replication to undetectable levels through the use of a combination of highly active antiretroviral drugs (HAART). Persons with ongoing viral replication are at risk for disease progression and death. The principle reasons for treatment failure include the development of viral resistance, non-adherence, and intolerance to the available medications. HIV RNA levels in plasma correlate with the rate of CD4 decline, with higher plasma viral loads predicting more rapid progression to AIDS and death. Once patients have progressed to AIDS, defined by either diagnosis of one of the AIDS-defining conditions, or by measurement of CD4 levels <200 cells/μL. median survival after a single AIDS-defining condition ranges from 3 to 51 months.

As noted in section 1, RTV inhibits cytochrome P450-mediated metabolism and is used as a pharmacokinetic enhancer as part of the recommended first line HARRT PI based regimen in treatment naive subjects (DRV/r plus TDF/FTC) as well as a component of an alternative PI based regimens (ATV/r plus TDF/FTC). In addition it is a component of other regimen options that include LPV/r and DRV/r.

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RTV is generally used more frequently in pediatric patients as a component of HARRT. Initial regimens in treatment naive children generally include one boosted PI with RTV.

The predominant doses used for ritonavir in all populations are less than 100 mg, 100 mg, or 200 mg per day. Of these dosing regimens, the less than 100 mg dose was estimated to be in use by less than 40 patients in the U.S. in 2013. Consistent with the treatment guideline recommendations and standard of care practice, the percent use of the Norvir Oral Solution product (b) (4) among all patients taking Norvir is less than 1% (0.23%). For further details see APPENDIX 1.

Pertinent to this application are the issues surrounding the target population who will be using the Norvir Powder formulation as opposed to the oral solution, primarily pediatric patients infected with HIV and their ability or the ability of their caregivers to accurately prepare and either self-administer or administer the medicatio (b) (4) These issues need to be counterbalanced with the safety benefit achieved with the new formulation due to the absence of the toxic excipients and the prolonged shelf life.

3. Product Quality

The Norvir Oral Powder is a (b) (4) presentation of the same (b) (4) used in the approved commercial Norvir tablet and contains standard compendia excipients that are utilized in the marketed Norvir tablets and have a known safety profile.

The toxicology profiles of the excipients in the tablet formulation were reviewed by the Agency as part of the Norvir tablet submission and were determined to be generally safe.

Based on a (b) (4) process, the currently approved Norvir tablet formulation contains RTV in a solid form that is chemically and physically stable at room temperature. Similar to the experience with the Norvir tablet, no meaningful increase in degradation products is observed following the (b) (4) Norvir Oral Powder. As such, the Norvir Oral Powder is expected to exhibit similar stability characteristics.

Based on 18-month stability study results, the Norvir Oral Powder product is anticipated to have a packaged shelf life of (b) (4) under global climatic storage conditions (30°C/ (b) (4) % RH). Therefore, the Norvir Oral Powder formulation offers additional stability benefits compared to that of the current marketed Norvir Oral Solution, which has a limited shelf life of (b) (4) at room temperature (25°C/ (b) (4) % RH).

From an environmental assessment perspective, Norvir Oral Powder (b) (4)

(b) (4) Norvir Oral Powder is not anticipated to significantly add to the overall RTV manufacture and thus increase the environmental drug substance concentration.

The OPQ review team requested additional information regarding the potential for (b) (4). As per the CMC review of submitted data the risk of (b) (4) is low and under control including when the powder formulation is mixed with a variety of vehicles used to increase palatability such as applesauce or chocolate milk. (b) (4) As per the Sponsor there was a (b) (4) % margin of error. However further review revealed that dosing accuracy could be as low as (b) (4) % of the expected dose. This appeared to be in part dependent on the vehicle used for missing (water vs. chocolate mile). There were no concerns with the manufacturing process.

(b) (4)

The Review Team also requested that the Applicant provide additional information regarding the stability of the reconstituted powder when administered via an NG or enteric feeding tube. After review of the information provided, the product quality review team determined that the studies performed by the Applicant would support the administration of the Norvir oral powder formulation dispersed in water via feeding tube.

For further details, discussion, and conclusions regarding product quality please see the FDA chemistry review by the OPQ Review Team including the drug product reviewer, William McCalmont and the CDRH Device Quality and Performance and Facility compliance reviewers Rong Guo and Crystal Lewis.

Please see section 11 Other Relevant Regulatory Issues regarding OPQ and Chemistry review team recommendations regarding the inspection of an ex US production site of the drug substance and questions regarding drug product integrity.

4. Nonclinical Pharmacology/Toxicology

No additional nonclinical pharmacology/toxicology data was submitted or required in support of the current application. Please refer to original FDA nonclinical pharmacology/toxicology reviews for additional information

5. Clinical Pharmacology and Biopharmaceutics

Clinical Pharmacology:

Apart from the results of the bioavailability studies described below, no additional clinical pharmacology data was submitted or required in support of the current application. Based on the demonstrated bioequivalence of the proposed Norvir Powder for Oral Suspension to the marketed Norvir Oral Solution in Study M11-475, the clinical pharmacology of ritonavir as presented in the New Drug Application (NDA) for Norvir Oral Solution (NDA 020659) can be applied to the proposed Norvir Powder for Oral Suspension. Please refer to original FDA clinical pharmacology reviews for additional information.

Biopharmaceutics

Bioavailability of Norvir Powder for Oral Suspension was assessed in three studies (Studies M11-472, M12-279, and M11-475). Briefly, Study M11-472 (N = 24) was a formulation screening study that compared the relative bioavailability of 3 test regimens of 2 ritonavir powder formulations to the marketed Norvir Oral Solution, Study M12-279 (N = 24) 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, and Study M11-475 (N = 48) 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. The study also evaluated the effect of food and dosing vehicles on the bioavailability of the proposed Norvir Powder for Oral Suspension.

Please refer to the FDA Clinical Pharmacology/Biopharmaceutics review by Dr. Qin Sun for the Agency analyses of the studies submitted to support the bioequivalence of the proposed Norvir Powder for Oral Suspension to the marketed Norvir Oral Solution.

The Agency Clinical Pharmacology Reviewer concluded that:

1. The Norvir Powder formulation is bioequivalent to the oral solution under moderate fat (fed) conditions. NOTE: Norvir is administered with food
2. Following the administration of NORVIR powder formulation, ritonavir exposures are higher (Cmax: ↑ 65%, AUC: ↑30%) under fasted conditions as compared to fed conditions. This is qualitatively consistent with other formulations of NORVIR (tablet Cmax: ↑28%, AUC: ↑28% and oral suspension Cmax: ↑30%, AUC: ↑9% under fasted conditions as compared to fed conditions)

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3. Ritonavir exposures are lower under high fat fed conditions as compared to moderate fat fed conditions (Cmax: ↓17%, AUC: ↓12%). This is not clinically significant.
4. Infant formula, apple sauce, chocolate milk or vanilla-flavored pudding do not have significant effects on the pharmacokinetics of ritonavir when mixed with NORVIR powder formulation and administered under fed conditions. NORVIR powder formulation can be mixed with these vehicles.

6. Clinical Microbiology

No new virology data was provided in support of this submission. Please see the review by Dr. Sung Rhee for an overview of microbiology as it relates to RTV.

7. Clinical/Statistical- Efficacy

No new clinical data was submitted to support the efficacy and safety of the Norvir powder formulation. Evidence of the effectiveness and safety of Norvir was previously assessed and reviewed at the time of the approvals of the respective marketed formulations (solution, SGC, tablets). Specifically, the efficacy of Norvir Oral Solution was supported in NDA 020659 by two studies in adults. Efficacy of Norvir Oral Solution in pediatric HIV-infected patients ages 4 weeks and greater was demonstrated in three studies. Further details can be found in the original Medical Officer Reviews of NDAs 20659 and 22417.

The clinical development program for the powder formulation that assessed safety, tolerability and palatability was comprised of three BA and BE studies performed in healthy adult subjects.

Study M11-472 was the first Phase 1 study assessing the BA, tolerability, and palatability of the new powder formulation. The objective of this study was to compare the BA of a single 100 mg dose of three test regimens of Norvir Oral Powder formulations with that of the reference marketed Norvir Oral Solution (100 mg) under fed conditions.

Study M12-279 was a vehicle qualification Phase 1 study assessing the BA, tolerability, and palatability of the new powder formulation. The objective of this study was to compare the BA of a single 100 mg dose of the Norvir Oral Powder formulation in various vehicles with that of the reference marketed Norvir Oral Solution (100 mg) under fed conditions.

Study M11-475 was conducted to assess the BE of the new Norvir Oral Powder formulation to the marketed Norvir Oral Solution and to evaluate the effect of vehicles and administration with food on the BA of the new formulation.

From a clinical perspective these studies were reviewed only for safety.

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In conclusion, the Applicant has previously provided the substantial evidence of effectiveness required by law [see 21 CFR 314.126(a)(b)] to support approval of the Norvir oral powder formulation because it is bioequivalent to the previously approved Norvir oral solution and therefore the clinical efficacy of Norvir Powder for Oral Suspension can be extrapolated from the demonstrated efficacy from prior Norvir clinical trials.

8. Safety

The safety profile of Norvir has been well established from nonclinical studies and clinical trials of Norvir which led to its initial regulatory approval in 1996, as well as 20 years of postmarketing safety experience. Because of the demonstrated bioequivalence to the currently marketed Norvir Oral Solution, and because the Norvir Powder for Oral Suspension formulation is based on the ritonavir (b) (4) that is used in the manufacture of the approved Norvir Tablet, the clinical safety of Norvir Powder for Oral Suspension can be extrapolated from the safety information from prior Norvir clinical trials and postmarketing experience.

Briefly, the safety profile of Norvir is characterized by the following most frequently reported treatment-emergent adverse events (TEAEs) in patients receiving ritonavir alone or in combination with other ARV agents: gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain, dyspepsia), neurological (including dizziness, paresthesia and oral paresthesia), rash, and fatigue/asthenia.

It should be noted that the adverse event profile in pediatric patients was similar to that seen in adult patients, with gastrointestinal treatment emergent adverse events reported most frequently.

The safety information from the Phase 1 bioequivalence/bioavailability studies of Norvir Powder for Oral Suspension is reviewed below. These studies demonstrated a safety profile for the new formulation consistent with the established safety profile of Norvir.

Study M11-472

Study M11-472 was a single-dose, formulation screening study with a randomized, open-label, 4-period crossover design in 24 healthy adult volunteers that assessed the relative BA of three test regimens of Norvir Oral Powder formulations relative to the marketed Norvir Oral Solution. Subjects were randomly assigned in equal numbers to receive one of four sequences of regimens. A single-dose of Norvir 100 mg was administered with a moderate-fat meal on Study Day 1 of each period as Norvir (b) (4) uncoated powder containing 100 mg of Norvir pre-dispersed 30 minutes prior to administration (Regimen A), Norvir (b) (4) % coated powder containing 100 mg of

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Norvir suspended immediately prior to administration (Regimen B), Norvir (b)(4)% uncoated powder containing 100 mg of Norvir suspended immediately prior to administration (Regimen C), or as the marketed Norvir Oral Solution (Regimen D).

All 24 enrolled subjects were exposed to at least one dose of a Norvir regimen in the study, with 22 subjects receiving a single-dose of Norvir from each of the three test regimens and the reference. Nine subjects (9/24, 37.5%) reported at least one treatment-emergent adverse event. The proportions of subjects reporting at least one treatment-emergent adverse event (TEAE) summarized by regimen were 5/24 (20.8%) in Regimen A, 2/23 (8.7%) in Regimen B, 1/24 (4.2%) in Regimen C, and 4/23 (17.4%) in Regimen D (reference). The adverse events that were reported by two or more subjects on a given regimen were headache (3 subjects, 12.5%) and abdominal distention in two subjects (8.3%). Two of the three events of headache were assessed by the investigator as not related and probably not related (both on Regimen A). The third adverse event of headache was assessed by the investigator as possibly related (on Regimen D, reference). All remaining adverse events were reported by a maximum of one subject for any given regimen: these events included abdominal pain (lower and upper), flatulence, nausea, vomiting, upper respiratory tract infection, aspartate aminotransferase increased, myalgia, neck pain, dizziness, and rash. Other than one headache event, one event of vomiting was assessed as probably related and one event each of dizziness and rash were assessed as possibly related to study drug.

All of the adverse events were determined by the investigator to be mild in severity. No deaths, serious adverse events or permanent discontinuations of study drug were reported in the study.

No subjects had clinically significant abnormalities of hematology, serum chemistry, or urinalysis values, or ECG.

Study M12-279

Study M12-279 was a single-dose, randomized, open-label, 4-period crossover study conducted to compare the BA of a single (100 mg) dose of the Norvir uncoated powder test formulation in three different vehicles (water, infant formula, and applesauce) with that of the reference marketed Norvir Oral Solution under fed conditions.

Twenty-four healthy adult volunteers were randomly assigned in equal numbers to receive one of four sequences of regimens. A single-dose of Norvir Oral Powder 100 mg was administered with a moderate-fat meal on Study Day 1 of each period in one of the three vehicles per sequence: water (Regimen A) or infant formula (Similac Advance, Abbott) (Regimen B), using 10 mL of one of the liquid vehicles, or applesauce (Regimen C). The last sequence included administration of the commercial marketed Norvir Oral Solution (Regimen D).

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Twenty-three of 24 enrolled subjects (23/24, 95.8%) received a single 100 mg dose of each of the test Regimens A, B, and C and a single 100 mg dose of the reference regimen (Regimen D). One subject discontinued from the study (due to positive drug test) and received only a single 100 mg dose of Norvir Powder for Oral Suspension in infant formula (Regimen B) before being discontinued.

Five (5/24, 20.8%) subjects reported at least one TEAE. The proportions of subjects reporting ≥ 1 TEAE summarized by regimen were 3/23 subjects (13.0%) in Regimen A and 4/23 (17.4%) in Regimen D. Three subjects (12.5%) reported headache. All other TEAEs were reported by one subject each. TEAEs of abdominal pain, nausea, and headache reported after dosing with Regimen A were assessed by the investigator as possibly related to study drug. TEAEs of nausea and headache reported after dosing with Norvir Oral Solution also were assessed by the investigator as possibly related to study drug. All events were assessed as mild and no SAEs were reported. No subject discontinued prematurely due to a TEAE. There were no deaths reported.

No clinically significant values were observed during the study for any hematology, serum chemistry or urinalysis parameter as well as for vital signs and ECGs.

Study M11-475

Study M11-475 was a single-dose, randomized, open-label, 4-period partial-crossover study in 48 HIV-negative adults that was conducted to assess the BE of the Norvir Oral Powder formulation to the reference marketed Norvir Oral Solution under fed conditions and to assess the effect of food and different vehicles on the BA of the Norvir Oral Powder formulation.

Forty-eight HIV-negative adult volunteers were randomly assigned in equal numbers to receive one of eight sequences of regimens. Each subject was to receive four of six regimens (A, B, C, D, E, or F) upon completion of the study.

Eight subjects (8/48, 16.7%) reported at least one TEAE. Two of 48 subjects (4.2%) reported TEAEs after dosing with the Norvir Oral Solution (Regimen A) and Norvir Powder for Oral Suspension in water (Regimen B), both under moderate-fat conditions. During the dosing periods of powder mixed in water – high-fat condition (Regimen C), powder mixed in water – fasting condition (Regimen D), and Norvir Powder for Oral Suspension mixed in chocolate milk – moderate fat condition (Regimen E), one of 24 subjects (4.2%) reported TEAEs. Two of 24 subjects (8.3%) reported TEAEs after dosing with Norvir Powder for Oral Suspension mixed in vanilla pudding – moderate fat condition (Regimen F).

Four subjects reported headache, 2 after dosing with Norvir Powder for Oral Suspension mixed in vanilla pudding – moderate fat condition (Regimen F) and one each after dosing with the Norvir Oral Solution – moderate fat condition (Regimen A)

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and Norvir Powder for Oral Suspension in water – moderate fat condition (Regimen B).

All other TEAEs were reported by one subject each. Seven subjects reported only adverse events that were assessed by the investigator as having no reasonable possibility of relationship to study drug, while one subject reported events of headache and nausea that were assessed as having a reasonable possibility of relationship. All TEAEs were assessed as mild.

One SAE of "induced abortion" was reported in a 21-year-old subject who underwent an elective abortion in the post-treatment period. This event was evaluated by the investigator as having no reasonable possibility of relationship to the study drug. No deaths or discontinuations due to adverse events occurred during the study.

No clinically significant or potentially clinically significant values were observed after dosing for any hematology or chemistry parameter.

Mild changes to blood pressure and temperature that were not clinically significant occurred with various regimens. No clinically significant abnormalities were observed during the study for any ECG value.

Safety Assessment of Norvir Powder for Oral Suspension Product Presentation

Specific to this submission was the assessment of safety relative to the removal from the drug product of excipients that are toxic to certain pediatric subgroups, the design of suitable child-resistant packaging for single-use administration that increased drug product stability, (b) (4) .

Excipients:

Norvir Powder for Oral Suspension does not contain the alcohol or propylene glycol that is found in the Norvir Oral Solution ((b) (4) % [v/v] of alcohol or (b) (4) mg alcohol per mL and (b) (4) % [v/v] of propylene glycol or (b) (4) mg propylene glycol per mL). Therefore the risk of toxicities attributed to the high concentrations of alcohol and propylene glycol in the Norvir Oral Solution such as the potential for lactic acidosis, acute renal failure, CNS depression and respiratory complications, heart block, heart failure, and cardiomyopathy should be reduced with use of Norvir Powder for Oral Suspension.

Comment: From a clinical standpoint, the development of the powder formulation provides a major safety advantage relative to the use of RTV in young children. For further details on the effects of these agents in this population, Please see the Medical Officer Review of Norvir labeling supplements for NDAs 20945/S-35, 22417/S-8 and NDA 20659/S-57 dated November, 2012.

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Packaging:

Norvir Powder for Oral Suspension is packaged in single-use foil laminate packets containing 100 mg of drug product and is prepared for administration by the patient or caregiver by mixing with liquids and/or soft foods. The 100 mg dose of Norvir was selected as the presentation based on the current and anticipated future dosing needs for pediatric patients.

The packets provide an excellent moisture barrier, and the powder remains intact. As per the Applicant, the product has a packaged shelf life of 36 months under global climatic storage conditions (30°C). Finally the packets are child-resistant (but accessible to the elderly).

NOTE: Defer to FDA Chemistry Review Team to confirm the validity of Sponsor's statement regarding stability. From a clinical standpoint the prolonged shelf life is a major benefit worldwide.

Dose Preparation of Clinically Acceptable Dose Range

The methods of administration/instructions for use (IFU) in the US prescribing information (USPI) were developed by the Applicant initially in two formative usability studies. After review by the Agency, the Division of Medication Error Prevention and Analysis (DMEPA) and Patient Labeling Review Teams worked with the Applicant to develop a third comprehensive formative study that included three rounds of a usability studies and knowledge task studies, each comprising several steps of development, revision, and testing based on feedback from health care providers (HCPs) and caregivers. The final human factors (HF) validation study focused on the abilities of untrained caregivers (n = 18) as well as medical professionals (n = 18) to follow the directions in the IFU in preparing doses (b) (4) [redacted]. The study also assessed the participants' ability to find and understand critical task information and other key information in the IFU. There were a large number of failures throughout the processes as well as in the comprehension phase in both groups with the greater number occurring in the untrained caregiver group. (b) (4) [redacted] Further, as per the Applicant, the human factors validation study demonstrated that the majority of the attempts to prepare doses (also known as trials) were within the acceptance criteria of ± 15%, despite the presence of a number of errors. (b) (4) [redacted]

The DMEPA Review Team concluded that the overall (b) (4) [redacted] The DMEPA Review concluded that the "Human Factors validation study results showed multiple failures across multiple critical tasks and across the two user groups. These results and associated

root cause analyses indicate that the user interface does not support safe and effective use [redacted] (b) (4) ."

In addition to suggesting numerous changes to the IFU, the DMEPA Team also concluded that a new HF study was necessary in order to assess the outcome when the new instructions were used. They requested that this study be performed within the current review cycle. In addition, the submission of a new HF study would constitute a major amendment and would extend the current cycle by three months. However, when this information was communicated to the Applicant, the Applicant indicated that (in their view) further modifications to the IFU would be unlikely to yield substantial improvement on the results already observed (according to the Sponsor, 4 studies have already been conducted with the last 2 showing similar results).

Specifically, in a communication dated April 24, 2017, the Applicant proposed that the DAVP instead consider an approval of the NDA by the current PDFUA approval date of June 7th, [redacted] (b) (4) based on the following: 1) the anticipated improved safety of the oral powder formulation compared to the oral solution due to the removal of the alcohol and propylene glycol excipients; 2) the greater stability of the powder and; 3) the absence of human-factors-based concerns with administration of doses [redacted] (b) (4)

The Applicant's proposal was acceptable to the Review Team.

For a detailed review and discussion of the adequacy of the submitted human factors assessment, please see the DMEPA, OPDP, and Patient Labeling Review Team consults.

Palatability

Palatability can be an issue with any medication administered to pediatric subjects and administering a pediatric medication with food or drink in order to mask the unpleasant flavor of the drug is common practice. Ritonavir has an inherent intense bitterness that persists following administration (up to 30 minutes). The palatability of the powder formulation was assessed in adults during drug development by the Applicant. Specifically, a 2-part palatability assessment was conducted using an expert adult taste panel to further evaluate the taste characteristics of ritonavir under various conditions (Study HF-NOR-2013-D-01). In Part One, it was determined that the dominant taste characteristic of ritonavir as suspended Norvir powder was the intensely bitter taste that lingered for a prolonged period. These results were

consistent with the palatability findings of Studies M11-472, M12-279, and M11-475 discussed in the Clinical Pharmacology review. These results suggest that coating of the Norvir powder granules or modification of the vehicle would not completely mitigate the intense bitterness.

In Part Two (Study HF-NOR-2013-D-02), a number of administration vehicles were assessed including a variety of soft foods (vanilla pudding, applesauce) and liquids (water, infant formula, chocolate milk) that differ in composition (e.g., fat and sugar content). All were demonstrated to be suitable as vehicles although the palatability scores improved with foods and liquids that were high in fat and sugar content (peanut butter, hazelnut chocolate spread, black currant fruit drink concentrate, golden syrup, and chocolate syrup). These vehicles were most effective in decreasing the bitterness and burnt aftertaste. As per the Applicant, compared with the currently marketed Norvir Oral Solution, Norvir Powder for Oral Suspension in chocolate milk in Study M11-475 had better overall palatability. Additionally, Norvir Powder for Oral Suspension in chocolate milk had statistically significantly better overall impression of palatability and taste compared with Norvir Powder for Oral Suspension in water. The overall impression of palatability, taste, aftertaste, and smell of Norvir Powder for Oral Suspension in vanilla pudding was also improved compared with Norvir Powder for Oral Suspension in water.

In summary, a number of administration vehicles were assessed including a variety of soft foods (vanilla pudding, applesauce) and liquids (water, infant formula, chocolate milk). All were suitable as vehicles although the palatability scores varied with best effect with high fat and sugar content chasers (soft and liquid foods that can be eaten immediately after dosing such as peanut butter, hazelnut chocolate spread, black currant fruit drink concentrate, golden syrup, and chocolate syrup). These were shown to reduce the intensity and duration of the bitter aftertaste.

In conclusion, based on studies in healthy adults, palatability can be improved if the drug is administered with chasers, which may help with issues of compliance in the target pediatric population.

Overall Conclusion of Safety

In conclusion, the three BA/BE studies included in the submission demonstrated the safety and tolerability of single-doses of the different formulations of Norvir Oral Powder. The safety results were consistent with the known safety profile of Norvir. Headache and gastrointestinal events were the most frequently reported TEAEs in these studies. No deaths were reported; one unrelated SAE of induced abortion was reported. No clinically significant values in clinically laboratory evaluations or ECGs were observed. None of the data presented for review was from a foreign source. No new safety issues that could cause concern post approval were identified.

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Specific to the Norvir powder formulation (b) (4)

For patients prescribed an exact 100 mg or 200 mg dose, an entire packet can be administered by sprinkling on a soft food (applesauce or vanilla pudding) or suspended in a liquid vehicle (water, infant formula, chocolate milk) wherein the whole volume of the mixture is to be consumed.

(b) (4)

(b) (4)

However the HF study submitted in support of the application was determined by the DMEPA review team to be a failed study (b) (4)

(b) (4)

(b) (4)

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

10. Pediatrics

AbbVie submitted an initial pediatric study plan (iPSP) to FDA on 25 October 2013 (IND 43718, eCTD Sequence 0615), and subsequently met with the FDA on 06 December 2013. AbbVie provided an overview of the Norvir Oral Powder development program and addressed the Agency's questions about the iPSP. On 24 December 2013, FDA indicated agreement with AbbVie's proposed iPSP and on 01 April 2014 FDA officially confirmed its agreement with the agreed iPSP. Specifically, FDA acknowledged AbbVie's plans to waive studies in patients less than 1 month of age because safety and efficacy studies of the RTV powder formulation would be impossible or highly impractical. In addition, FDA agreed with AbbVie's intent not to conduct new clinical studies (including PK studies) in pediatric populations greater than 1 month and less than 18 years of age because the Norvir Oral Powder formation was found to be bioequivalent to the approved Norvir Oral Solution.

11. Other Relevant Regulatory Issues

The sponsor noted that the BA/BE studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

The study protocols and amendment(s) were reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

The Applicant examined financial disclosure information from all clinical investigators for the clinical studies M11-475 and M12-279 and completed FDA Form 3454 for Financial Certification. There are no investigators who participated in these studies who have financial interests or arrangements with AbbVie that require financial disclosure. Study M11-472 was conducted at the AbbVie Phase 1 unit by AbbVie personnel, North Chicago, IL. No financial disclosure information was required for Study M11-472.

The Clinical Pharmacology review team requested clinical and analytical site inspections for study M11-475. These inspections are conducted by the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS). In their review dated February 13, 2017, OSIS recommended

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accepting data without an on-site inspection because the facility was recently inspected.

In the absence of clinical efficacy data, no additional clinical site inspections were deemed necessary for this NDA by the Clinical Review Team/Division.

During the review period an ex-US drug substance production site was issued a warning letter. Therefore product integrity issues relative to all products produced at that facility were called into question including the Norvir powder formulation under review. At the time this review was completed discussions were underway regarding the issuance of a complete response for the NDA because of these production issues.

12. Labeling

At the time this review was completed, formal labeling discussions had not yet been completed with the Applicant. Recommendations regarding labeling had been made by some of the review disciplines as follows:

CMC: 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". The drug product specification table and other relevant sections of the USPI were updated accordingly.

DMEPA: Based on their review of the HF validation study the DMEPA team made a number of recommendations to modify the IFU section of the USPI in order to address the failures observed during the study. Specific recommendations were made to address issues of (b)(4) as well as revisions to improve users' ability to locate key information that will help them safely and effectively utilize the IFU to prepare prescribed doses of Norvir. (b)(4) nly recommendations to better facilitate the preparation and administration of doses of 100 and 200 mg will be incorporated into the final label.

Further details regarding finalized labeling can be found in the approved USPI.

13. Recommendations/Risk-Benefit Assessment

Recommended Regulatory Action

An approval of the NORVIR Powder for Oral Suspension at doses of 100 mg (and increments of 100 mg) in combination with other antiretroviral agents for the treatment of pediatric HIV-1 infection is recommended. (b) (4)

Risk Benefit Assessment

The recommendation for the approval of the Norvir powder formulation at doses of 100 (and increments of 100 mg) in pediatric patients is directly supported by the substantial evidence of effectiveness previously provided by the Applicant and as required by law [see 21 CFR 314.126(a)(b)] because it is bioequivalent to the previously approved Norvir oral solution and therefore the clinical efficacy of Norvir Powder for Oral Suspension can be extrapolated from the demonstrated efficacy from prior Norvir clinical trials. Specifically, evidence of the effectiveness and safety of Norvir was previously assessed and reviewed at the time of the approvals of the respective marketed formulations (solution, SGC, tablets). Efficacy of Norvir Oral Solution in pediatric HIV-infected patients ages 4 weeks and greater was demonstrated in three studies.

Because of the demonstrated bioequivalence to the currently marketed Norvir Oral Solution, and because the Norvir Powder for Oral Suspension formulation is based on the ritonavir (b) (4) that is used in the manufacture of the approved Norvir Tablet, the clinical safety of Norvir Powder for Oral Suspension can be extrapolated from the safety information from prior Norvir clinical trials and 20 years of postmarketing experience.

In addition to the previously reviewed evidence of efficacy and safety, the recommendation for approval is made because of the substantial benefits associated with this product. Norvir Powder for Oral Suspension does not contain the alcohol or propylene glycol that is found in the Norvir Oral Solution ((b) (4) % [v/v] of alcohol or (b) (4) mg alcohol per mL and (b) (4) % [v/v] of propylene glycol or (b) (4) mg propylene glycol per mL). Therefore the risk of toxicities attributed to the high concentrations of alcohol and propylene glycol in the Norvir Oral Solution such as the potential for lactic acidosis, acute renal failure, CNS depression and respiratory complications, heart block, heart failure, and cardiomyopathy should be reduced with use of Norvir Powder for Oral Suspension.

Recommendations of Postmarketing Requirements and Commitments

This product has Orphan Drug designation and therefore no additional pediatric development can be required of the Applicant via a PREA PMR. (b) (4)

(b) (4)

14. Recommended Comments to the Applicant

At the time this review was submitted, recommendations related to manufacturing issues were pending.

DRAFT

Appendix 1:

Table 1
Overall Distribution of Norvir Oral Solution Usage by Age in the US from January to December 2013

Age Group	Patients a		Ritonavir Dose Needed b	
	Number	Percent	PI Being Boosted	RTV Dose
≥ 13 years	309	89.6%	Darunavir Atazanavir Fosamprenavir Tipranavir c	100 mg 100 mg 100 mg 200 mg c
4 weeks – 12 years	36	10.4%	Darunavir Atazanavir Fosamprenavir Tipranavir c	32 to 100 mg 80 mg or 100 mg 29 to 100 mg 60 to 200 mg c
Total	345	100%		

a. Number and percentage of patients in each age group is based the distribution from US health care claims data from Source Healthcare Analytics, January 2013 through December 2013 (data on file at AbbVie).

b. Based on the current approved USPI dosages of Norvir and average weight/age for children per CDC Clinical

Growth Charts http://www.cdc.gov/growthcharts/clinical_charts.htm

c. Not recommended per the DHHS guideline

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Table 2
Proportion of Norvir Oral Solution Usage among Overall Norvir Usage in the US from January to December 2013

Formulation Group	Number of Patients a
Number of unique patients using Norvir – any formulation	(b) (4)
Number of unique patients using Norvir Oral Solution	
Percent Norvir Oral Solution usage	

a. Number and percentage of patients in each group is based the distribution from US health care claims data from

Source Healthcare Analytics, January 2013 through December 2013 (data on file at AbbVie).

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/s/

M R ALIVISATOS
05/09/2017

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