CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-417

MEDICAL REVIEW(S)

ADDENDUM to CLINICAL REVIEW
For
NDA 22-417 (000)

Review of Complete Response document submitted December 11, 2009

Background: NDA 22-417 was originally submitted on December 18, 2008 with a PDUFA goal date of October 19, 2009. The original 2008 NDA submission provided data to support the approval of a new 100 mg film-coated tablet Norvir formulation

Ritonavir (Norvir), an HIV-1 protease inhibitor, was approved in 1996 as 100 mg capsule and oral solution (80 mg/ml) formulations. Due to manufacturing issues, the original 100 mg capsules were discontinued and a new capsule formulation was approved in 1999. Abbott used a melt-extrusion technology to develop the tablet formulation. This formulation represents a major improvement over the currently available capsule formulation because refrigeration storage is no longer a requirement.

No new efficacy data were required for this application. The tablet formulation is not bioequivalent to the currently approved capsule formulation. Under moderate fat conditions bioequivalence was met for AUC; however, the mean C_{max} was increased by approximately 26%. Sufficient safety data were provided to support the increased exposures of the tablet formulation. The safety data submitted included single dose trials with the 100 mg tablets; four previously reviewed multiple dose data in HIV-1 infected patients, previously reviewed QTc and PR prolongation data and pharmacokinetic modeling data.

From a clinical perspective the data in the original NDA submission supported an approval for the new film-coated tablet formulation of Norvir. Based on the analyses provided by Abbott, and confirmed by the Agency it was concluded that the 26- 40% increase in Norvir C_{max} achieved by the new tablet formulation would not likely affect the safety profile of Norvir.

Although an approval action was recommended by the review disciplines, an approval action could not be issued at the time of the PDUFA due date because of deficiencies identified at the Abbott GmbH manufacturing facility in Ludwigshafen, Germany. Therefore a Complete Response Letter was issued for the pending new drug application for Norvir (ritonavir) Tablet, NDA 22-417 on October 16, 2009. The current submission (December 11, 2009) consists of Abbott's response to the complete response letter.

As part of the CR letter the Agency requested the following:

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at

21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

• Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
• Present tabulations of the new safety data combined with the original NDA data.
• Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
• For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Review: No new efficacy of safety data have been submitted for review. There were no additional trials initiated or ongoing when the Complete Response Letter was issued. Additionally, no new clinical trials have been initiated or completed since the issuance of the Complete Response Letter. As a result, there is no new safety information to report to NDA 22-417.

Labeling: On November 23, 2009, the Agency approved a labeling supplement for NDA 20- 659/S-047 and NDA 20-945/S-026 that added new drug interaction information for salmeterol and adds a new contraindication for sildenafil when used for pulmonary arterial hypertension. The agreed upon draft labeling for Norvir Tablets has been updated to incorporate the approved labeling changes from NDA 20-659/S-047 and NDA 20-945/S-026.

Other than these changes, there are no other changes to the agreed upon labeling.

Recommendation: An approval is recommended for NDA 22417/000

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR

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

/s/

M R ALIVISATOS
01/04/2010

KIMBERLY A STRUBLE
01/04/2010

CLINICAL REVIEW

Application Type	22-417 and 20-659
Submission Number	S-000 and S-045
Submission Code	N and PA SLR
Letter Date	December 18, 2008
Stamp Date	December 19, 2008
PDUFA Goal Date	October 19, 2009
Reviewer Name	Regina Alivisatos, MD
Review Completion Date	October 17, 2009
Established Name	Ritonavir (RTV)
(Proposed) Trade Name	Norvir
Therapeutic Class	Antiviral
Applicant	Abbott Laboratories
Priority Designation	S
Formulation	Tablets 100 mg and Solution 80 mg/mL
Dosing Regimen	600 mg BID
Indication	Treatment of HIV-1 Infection
Intended Population	HIV-1 Infected Patients

Table of Contents

Recommendations/Risk Benefit Assessment

This executive summary contains the recommendations and summary of clinical findings for a new 100 mg film coated tablet formulation of NORVIR (Ritonavir; RTV). The tablet formulation under review will replace the 100 mg soft gel capsule (SGC) formulation that is currently approved for use. The new 100 mg tablet formulation did not meet the criteria for bioequivalence with the approved 100 mg SCG formulation under moderate fat conditions because the Cmax achieved with the new tablet formulation is greater than that achieved with the approved SGC formulation (the upper limit for the 92.8% confidence intervals for C_{max} exceeded 125% (point estimate of 26% with an upper limit of approximately 40%). However, the criteria for bioequivalence between the approved 100 mg SGC and the 100 mg tablet formulation were met for the AUC (92.8% CI within 80%- 125%) and therefore no new efficacy data were submitted.

Data in the fasted state were not available; therefore, the label indicates Norvir must be taken with meals because greater increases in exposures are expected in the fasted state.

Safety from four previously reviewed multiple dose pharmacokinetic studies in HIV-1 infected patients were submitted to support the safety of the greater exposures (26 – 40%) achieved with the tablet formulation compared to the marketed SGC formulation at the approved 600 mg dose. In addition the Applicant provided pharmacokinetic modeling to demonstrate that although the exposure (C_{max}) achieved with the tablet at the 600 mg dose is greater than achieved with the approved SGC formulation, this increase is proportional (non-linear) and more in the range of 14%, therefore a lesser and not clinically significant effect on safety would be expected.

The Applicant also provided additional safety support to address the impact of the higher Cmax values potentially achieved with the approved 600 mg dose on QTc and PR interval from the previously reviewed Study M06-809, a thorough QT Phase 1, multiple-dose, open-label, placebo- and active-controlled, randomized study conducted according to a crossover design in 88 healthy volunteers.

NORVIR is primarily used at lower doses (100-200 mg once or twice daily) in combination with other protease inhibitors. Another important assessment of this review was to determine if the higher bioavailability of NORVIR tablet as compared to the approved soft gel capsule formulation will lead to clinically significant changes in the co-administered protease inhibitor concentrations and if the protease inhibitor concentrations are within the range proven safe and effective. The tablet NORVIR formulation is characterized by food dependent dosing as compared to the SGC which can be given without regard to meals. This change in NORVIR administration did not lead to changes in the exposures of the concurrently administered protease inhibitors atanazavir, darunavir, and saquinavir that are labeled to be administered with food. In addition, no changes will be required for the fosamprenavir label which is currently labeled to be administered with or without food. The potential higher AUC and Cmax fosamprenavir values that may be obtained when co-administered with the tablet Norvir formulation are not expected to be of clinical significance.

The potential increases in achievable tipranavir exposures when co-administered with the new tablet Norvir formulation are of potential clinical significance in view of the increased hepatotoxicity associated with higher tipranavir exposures. Administration in the fasted state could also lead to higher tipranavir exposures compared to fed state with ritonavir tablets. Therefore, labeling revisions for tipranavir are needed to ensure the combination of tipranavir and ritonavir is taken with meals. Additionally, for consistency with the tipranavir label, text regarding monitoring patients frequently for evidence of hepatotoxicity is requested. Finally a post-marketing requirement will be requested from the Sponsor of tipranavir to determine the pharmacokinetics of tipranavir when coadministered with the new ritonavir tablets in the fed and fasted state for labeling and also assess if additional labeling with respect to safety monitoring is needed based on the magnitude of increase in tipranavir exposures.

In support of potentially altered exposures of the co-administered protease inhibitors, the Applicant provided literature support of the reduced NORVIR (100- 200 mg doses) doses when administered with these protease inhibitors as well as data from four single dose crossover pharmacokinetic studies in healthy volunteers. The Applicant also referenced eight week safety data from a lopinavir/ritonavir (Kaletra) clinical trial (M05-730) comparing the safety of the Kaletra tablet and SGC formulations. The DAVP agreed to accept the safety data from this study in support of the safety of the Norvir tablet formulation because the manufacturing processes of the Kaletra and Norvir tablet formulations are similar and because the Norvir exposures achieved with the tablet under moderate fat conditions are similar to the Norvir exposures achieved with the approved Kaletra tablet formulation.

Recommendation on Regulatory Action

From a clinical perspective the data in this NDA support approval for the new film-coated tablet formulation of NORVIR. Based on the analyses provided by Abbott, and confirmed by the Agency we concluded the 26- 40% increase in NORVIR C_{max} achieved by the new tablet formulation will not likely affect the safety profile of Norvir.

An approval should also be granted to the prior approval labeling supplement for NORVIR oral solution SLR 20,659/S-045. The goal of this supplement is to incorporate all labeling changes that apply to both formulations. The proposed label is the first in PLR format for NORVIR.

Risk Benefit Assessment

The new tablet formulation provides a significant advantage over the marketed capsule formulation for HIV- 1 infected patients. The primary benefit of the new formulation is that refrigeration is not required for storage. This will enable patients to use a protease inhibitor as part of their anti-retroviral regimen independent of their location or while travelling and thus will likely increase adherence.

Possible risks associated with the new formulation appear minimal. There are no anticipated differences in efficacy as the exposures achieved with the new tablet formulation are greater than

those achieved with the SGC (mean 26% greater C_{max}) and no significant safety issues are expected with the increased Cmax concentrations. Pharmacokinetics in the fasted state were not adequately addressed and will likely lead to even greater increases in Cmax; therefore, NORVIR must be given with food. The label will state that the increase in Cmax may lead to tolerability issues. Additionally, based on the publically available data provided by Abbott, no apparent safety issues of other protease inhibitors when used with the higher bioavailable formulation of NORIVR tablets at 100 mg once daily to 200 mg twice daily were identified. Given that NORVIR tablets must be administered with food, of the protease inhibitors that can currently be administered with or without food when co-administered with NORVIR (fosamprenavir and tipranavir), labeling revisions are necessary only for tipranavir because of the potential increases in achievable tipranavir exposures and increased hepatotoxicity. No changes will be required for the fosamprenavir because the potential higher AUC and Cmax fosamprenavir values that may be obtained when co-administered with the tablet Norvir formulation are not expected to be of clinical significance.

Abbott intends to discontinue distribution of the currently marketed soft gel capsule formation as soon as possible after the approval of the tablet formulation.

1.2.1 Summary of Efficacy

No efficacy data were reviewed for the approval of this NDA. Based on the pharmacokinetic parameters of the film-coated NORVIR tablet formulation as compared to the marketed NORVIR SGC formulation, the tablet formulation is expected to have an efficacy profile similar to the capsule formulation as both the AUC and the C_{max} achieved with this formulation were similar or greater than those achieved with the approved SGC.

1.2.2 Summary of Safety

No new or unexpected safety signals were identified in the application. The higher NORVIR exposures (C_{max}) produced by the new tablet formulation will not likely alter the well known safety profile of NORVIR when used for the treatment of HIV infection at 600 mg twice daily or when used at reduced doses in combination with other protease inhibitors.. The higher exposures (C_{max}) could lead to a decrease in tolerability (primarily gastrointestinal) and we proposed labeling to convey this issue for those initiating NORVIR or switching from the capsule to tablet formulation.

For the approved 600 mg dose, the safety conclusion is based on the four previously reviewed multiple dose pharmacokinetic studies in HIV-1 infected patients, the review of the thorough QT and PR prolongation study M06-809, and the review of the pharmacokinetic modeling data by the Agency Clinical Pharmacology review team. In addition the safety of the lower doses of Norvir (100-200 mg once or twice daily) and its effect on the co-administered protease inhibitors is based on the review of the safety data from studies of healthy volunteers who received single pharmacokinetic enhancing doses of the tablet or SGC formulations and from the review of safety data from study M05-730 where the safety and tolerability of the marketed Kaletra (LPV/r) tablet formulation were compared with those of the Kaletra SGC when dosed 800/200

mg once daily or 400/100 mg twice daily for eight weeks in combination with nucleoside reverse transcriptase inhibitors in antiretroviral-naïve HIV-1 infected patients. The data from study M05-730 was accepted as supportive of the safety of the NORVIR tablet because the NORVIR exposures achieved with KALETRA at the once or twice daily doses are similar to those achieved with NORVIR alone when administered at the pharmacokinetic enhancing doses.

The safety of the approved 600 mg dose is supported by four previously reviewed multiple dose PK studies in HIV-infected patients who received doses of 400 to 1200 mg total daily of NORVIR. These subjects underwent intensive pharmacokinetic evaluations in order to assess the correlation between pharmacokinetic exposure and adverse events. These studies were Study M93-107 (n = 46), Study M93-112 (n = 48), Study M93-134 (n = 40) and Study M96-604 (N = 6). Given the non linear increase in exposures, as per the Agency Clinical Pharmacology Reviewer, Dr. Stanley Au, the safety profile for the 600 mg dose (SGC or tablet) would not be expected to differ greatly from that of the lower doses (100-200 mg once or twice daily) doses of NORVIR when administered with food. The proposed labeling was modified to address the possible decreased tolerability of the tablet formulation because of the greater C_{max} achieved with the tablet formulation under moderate fat conditions.

The impact of the higher NORVIR C_{max} values (mean 26%) on the QTc and PR intervals was also evaluated using data from the previously reviewed study M06-809, a thorough QT Phase 1, multiple-dose, open-label, placebo- and active-controlled, randomized study conducted according to a crossover design in 88 healthy volunteers. This analysis was previously submitted for Agency review (sNDA 20-659/S043 and (b) (4) and concluded that no significant effect on the QTc interval was observed with NORVIR 400 mg administered twice daily for 2.5 days. There was some evidence for a potential effect of NORVIR on the QTc interval at supratherapeutic concentrations however the evidence was stronger for Kaletra as compared to NORVIR alone. Further there was strong evidence of an effect of Kaletra and NORVIR alone on PR with resultant varying degrees of AV block. Based on these findings, product labeling for both Kaletra and NORVIR were amended to reflect the potential for PR and QTc prolongation to a lesser degree with NORVIR. The new tablet is not likely to alter the NORVIR safety profile with respect to PR or QTc potential.

Overall no new safety signals were identified from the normal volunteer pharmacokinetic single dose crossover studies which were submitted in support of the tablet formulation of NORVIR. No comparative statements regarding relative event frequencies or tolerability between the formulations can be made based on the limited sample size and the limited duration of the studies assessed. The treatment emergent adverse events observed in these trials are similar to the adverse events observed in previous trials of NORVIR in healthy subjects. Treatment emergent adverse events were primarily headache or GI disorders. Similarly the safety review of Study M05-730, a Phase 3, open-label, randomized, multicenter, multicountry study in HIV infected patients designed to assess safety and tolerability of the tablet and SGC formulations of LPV/r (once and twice daily dosing) revealed no new or unexpected adverse events. Reported treatment emergent adverse events were consistent with those previously described in clinical trials with Kaletra. Generally adverse events were reported with similar frequency and character across the tablet and SGC regimens despite the increased NORVIR concentrations achieved with the

approved Kaletra tablet as compared to the Kaletra SGC at NORVIR doses of 100 mg twice daily or 200 mg once daily. There were more reported GI events including diarrhea, nausea, and abdominal distension in patients receiving the tablet. However these differences were not considered clinically significant and did not lead to increased discontinuations or SAEs.

Recommendations for Postmarketing Risk Management Activities

No specific Risk Management Activities were requested from the Applicant.

Recommendations for other Post Marketing Study Commitments

No post-marketing commitments or requirements will be made of Abbott, the sponsor of the Norvir tablet formulation.

Introduction and Regulatory Background

Product Information

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.

Unique however to NORVIR 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. NORVIR is primarily used at these lower doses and rarely or not at all at the 600 mg twice daily approved dose.

Two formulations are currently marketed: a 100 mg soft gelatin capsule (SGC) and an 80 mg/mL oral solution. The tablet formulation under review will replace the SGC.

Tables of Currently Available Treatments for Proposed Indications

Currently there are 32 antiretroviral distinct drug products (ARVs) approved in the US for the treatment of HIV infection, some in multiple formulations and fixed drug combinations. Six classes of antiretroviral agents exist. The classes are based on the mechanism of action in the HIV life cycle: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors (CCR5 co-receptor antagonist), and HIV integrase strand transfer inhibitors.

The PI class is comprised of the following agents: indinavir (Crixivan®), NORVIR (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), atazanavir (Reyataz®), lopinavir/NORVIR fixed dose combination (Kaletra®), fosamprenavir (Lexiva®), tipranavir (Aptivus®) and darunavir (Prezista®).

The Department of Health and Human Services (DHHS) guidelines for use of antiretroviral agents in HIV-1 infected adults and adolescents do not include NORVIR alone as a recommended treatment for HIV-1 infection. NORVIR is only recommended for use at reduced doses in combination with atanazavir, darunavir, fosamprenavir, saquinavir, tipranavir, and lopinavir. A list of approved protease inhibitor antiretroviral agents can be seen below:

Generic Name	**Trade Name**	**Dosing Recommendations**
Protease Inhibitors		
Atanazavir (ATV)	REYATAZ	400 mg Qd TN or with RTV (300/100) in TE
Darunavir (DRV)	PREZISTA	800 DRV/100 RTV QD TN or 600/100 BID TE
Fosamprenavir (FPV)	LEXIVA	1400 BID with or w RTV 100 – 200 mg QD or 700/100 BID
Indinavir	CRIXIVAN	800 mg q 8 hours
Lopinavir/ritonavir (LPV/r)	KALETRA	400/100 BID or 800/200 QD 0r 600/150 with EFV
Nelfinavir (NFV)	VIRACEPT	1250 mg BID or 750 mg TID
NORVIR (RTV)	NORVIR	600 mg q12 or 100- 400 QD in divided doses as PK enhancer
Saquinavir (SQV)	INVIRASE	SQV/RTV 1000/100 BID
Tipranavir (TPV)	APTIVUS	TPV/RTV 500/200 BID

Availability of Proposed Active Ingredient in the United States

NORVIR tablets are not approved in any country. NORVIR soft gel capsules and oral solution formulations are available worldwide for the treatment of HIV infection. The package insert has undergone several revisions since the original 1996 approval in patients with advanced HIV, including the withdrawal of the original NDA 20-680 capsule formulation due to manufacturing issues and the approval of the currently marketed SGC in 1999 under NDA 20-945. The NDA under review and the associated PA SLR for the solution contain new labeling in PLR format. In addition to the above the label has been modified numerous times to incorporate results from numerous drug-drug interaction studies, dosing information in special populations (pediatrics, treatment naïve, hepatic and renal impairment), the addition of Warnings and Precautions for the potential for QT and PR prolongation and numerous revisions of the Post-Marketing Adverse Events section.

Important Safety Issues With Consideration to Related Drugs

Class-related adverse event and laboratory abnormalities and the potential for significant drug-drug interaction potential are common for the approved PIs. NORVIR is the PI with the largest number and greatest magnitude of drug-drug interactions due to its potent inhibition of CYP3A metabolism as a result drug-drug interactions can be clinically significant. These interactions are prominently displayed in the package insert as Contraindications or Warnings. As with other PIs, the NORVIR label includes warnings and precautions for new onset diabetes, hyperglycemia,

increased bleeding episodes in patients with hemophilia, and fat redistribution. In addition NORVIR was recently relabeled to include warnings for possible QT and PR prolongation.

Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA teleconference was held with Abbott on September 23, 2008.

Prior to this meeting the FDA responded to questions from the Applicant regarding the adequacy of the proposed NDA package. Abbott was informed the adequacy of the package to support the safety of the approved 600 mg dose in view of the increased C_{max} could only be determined at the time of review. Also, sufficient data to file an NDA were available to support the safety of the NORVIR when used at reduced doses (100 mg once daily – 200 mg twice daily) with other protease inhibitors; however, the acceptability of this data was determined to be a review issue.

Other Relevant Background Information

Not applicable.

Ethics and Good Clinical Practices

Submission Quality and Integrity

Following internal discussions within the DAVP, an audit of the pivotal BP study site was requested. There were no 483 issues and DSI recommended that the data from M10-307 be accepted for review.

Compliance with Good Clinical Practices

All study protocols were written to conform to accepted ethical standards and were reviewed and approved by Institutional Review Boards overseeing each investigative site prior to enrollment of subjects.

Financial Disclosures

Abbott submitted signed copies of Form FDA 3454 and adequately provided the required information regarding disclosed financial arrangements by the investigators. One investigator disclosed proprietary or financial interests in the product under study. However this investigator was a sub-investigator who performed physical exams only and had no other responsibilities. Based on the disclosure information provided, no significant issues were raised regarding the integrity of the data presented in this NDA.

Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry Manufacturing and Controls

Please refer to Dr. Dorota Matecka's review for details. The tablet formulation was developed using melt-extrusion technology. Norvir (b) (4) film-coated tablets will be available for oral administration in a strength of 100 mg NORVIR with the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, anhydrous dibasic calcium phosphatase, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene 3350, and polysorbate 80. The product is stable to permit storage at room temperature (for climatic zones I/II and zones III/IV) throughout shelf life.

Clinical Microbiology

No new microbiology was provided for review.

Preclinical Pharmacology/Toxicology

Please refer to Dr. Pritam Verma's review for further details. The pharmacology/toxicology of NORVIR has been well characterized in previous NDA submissions. No new pharmacology/toxicology information was submitted with this NDA.

The tablet formulation contains the excipient copovidone. Each Norvir tablet contains (b) (4) of copovidone resulting in a total daily dose of (b) (4) of copovidone when a daily Norvir dose of 200 mg (used as a PK enhancer) is prescribed. This amount is less than that in the approved Kaletra tablet formulation (b) (4) When used as a protease inhibitor at the maximum recommended therapeutic dose of Norvir (1200 mg), daily copovidone exposure is (b) (4), a level that is (b) (4) times higher than from the approved Kaletra tablets. The Pharmacology/toxicology review team found that "with the maximum recommended therapeutic dose of Norvir (1200 mg) the daily copovidone exposure (b) (4) has a safety margin of 6 – 16 fold based on NOAELs derived from 26 week rat and 52 week dog studies respectively" and therefore there is a negligible safety risk to patients receiving NORVIR tablets.

Clinical Pharmacology

1.1.1 Mechanism of Action

NORVIR (Norvir®) 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

1.1.2 Pharmacodynamics

The pharmacodynamic effects of NORVIR are well characterized through the conduct of numerous clinical trials where it was used both as a PI and as a PK enhancer in conjunction with lopinavir. No new pharmacodynamic findings for NORVIR are presented in this submission.

1.1.3 Pharmacokinetics

Please refer to Dr. Stanley Au's review for specific details regarding the pharmacokinetics of the tablet formulation as well as an extensive review of the effects of the NORVIR tablet formulation on the concentrations and the safety of the co-administered protease inhibitors.

As per the Agency review of the single dose bioequivalence study M10-307 under moderate fat conditions, the to-be-marketed tablets did not meet the bioequivalence criteria relative to the reference capsule with respect to NORVIR C_{max}. The C_{max} achieved was not within the 80 – 125% CIs necessary to show bioequivalence with a mean increase of C_{max} of 26% (maximum of 40%). Bioequivalence under fasted conditions was not evaluated by the Applicant. The Clinical Pharmacology Review Team advised that the increase in exposure under fasted conditions could be potentially even greater than that seen under fed conditions (up to 55% for AUC and 70% for C_{max}) and therefore the tablet formulation should be administered only with meals. Meal content did not affect NORVIR exposure.

The Applicant's Table of Relative Bioavailability from study M10-037 has been copied below.

R&D/08/1254

Table 1. Relative Bioavailability and 92.8% Confidence Intervals for the Bioequivalence Assessment of Ritonavir from Study M10−307

		Central Value+		Relative Bioavailability	
Regimens Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate†	92.8% Confidence Interval
Ritonavir 100 mg in Healthy Volunteers (Study M10-307)					
A vs. B: (Tablet vs. SGC)	C_{max}	0.367	0.290	1.264	1.150 – 1.389
	AUC_t	3.154	2.780	1.134	1.068 – 1.205
	AUC_∞	3.253	2.949	1.103	1.040 – 1.170

\+ Antilogarithm of the least squares means for logarithms
† Antilogarithm of the difference (test minus reference) of the least squares means for the logarithms

The Agency was also able to confirm the non-linear pharmacokinetics of the NORVIR tablet formulation and therefore that the increase in exposure for the 600 mg dose would be expected to be less than that achieved with the 100 mg dose. The review concluded that the safety profile of the 600 mg twice daily regimen should apply to the reduced doses of ritonavir (100 once daily -

200 mg twice daily) in combination with other protease inhibitors and no additional safety issues should be expected beyond those associated with a potential decrease in tolerability because of the greater exposures (C_{max}). An excerpt from the CP Review is copied below:

"Based on the information provided by Abbott, when comparing ritonavir tablets to ritonavir capsules, it is not anticipated that increases in ritonavir exposure (AUC and C_{max}) at a single dose of 600 mg for ritonavir tablets would be higher than the increases in exposure observed at a single dose of 100 mg for ritonavir tablets. An increase of up to 40% in C_{max} under moderate fat conditions is not anticipated to result in any clinically significant safety issues at 600 mg twice daily dosing."

"However, the 600 mg ritonavir tablet dose is expected to result in higher C_{max} ritonavir exposure when compared to the 600 mg ritonavir capsule dose. The degree of gastrointestinal tolerance is an issue with the ritonavir dosage regimen of 600 mg twice daily under moderate fat conditions. Therefore, in the draft label for ritonavir tablets, a statement has been added indicating that increased gastrointestinal adverse events (e.g. nausea, vomiting, abdominal pain, or diarrhea) could occur in patients who switch from ritonavir capsules to ritonavir tablets. "

During the review, concerns were raised regarding the effect of the increased NORVIR exposures associated with the new tablet formulation and their impact on the exposures of other co-administered protease inhibitors (PIs). As noted above NORVIR exposures are increased for the tablet compared to the capsule when administered under moderate fat conditions. The submission did not adequately address the effect of the fasted state on the PK of the NORVIR tablet formulation compared to the capsule formulation. In the absence of data comparing achievable exposures in the fasted state between the SGC and the tablet formulations, the assumption is that the magnitude of difference in exposures is greatest in the fasted state when comparing ritonavir tablets to ritonavir capsules [ritonavir tablets (fasted) > ritonavir tablets (fed) > ritonavir capsules (fed) > ritonavir capsules (fasted)].

Information was submitted by Abbott from presented abstracts and published scientific literature articles to determine if the increased ritonavir tablet C_{max} compared to ritonavir capsules results in clinically significant changes in the exposure of coadministered protease inhibitors. The information contained pharmacokinetic data for coadministered protease inhibitors with a doubling (100% increase) of the ritonavir dosage regimen. The doubling of the ritonavir dosage regimen covers the expected range of increased C_{max} exposure (point estimate of 26% with an upper limit of approximately 40%) with the ritonavir tablets when administered with moderate fat meals.

The following conclusions from the Clinical Pharmacology review summarize the impact of increased ritonavir tablet bioavailability for the coadministered protease inhibitors fosamprenavir, darunavir, atazanavir, tipranavir, and saquinavir:

- Based on the information provided by Abbott, published or presented information, or from the FDA approved prescribing information, the changes in the exposures of the

concurrently administered protease inhibitors were not clinically significant based on the available pharmacokinetic information for ritonavir and coadministered protease inhibitors.

- The submitted information provides supportive evidence that no dosage adjustments are required when protease inhibitors are coadministered with ritonavir (100 mg once daily – 200 mg twice daily) tablets under fed (moderate or high fat) conditions.

- The Dosage and Administration recommendations in the saquinavir, atazanavir, and darunavir prescribing information (label) do not require revisions because the three protease inhibitors are coadministered with ritonavir capsules under fed conditions.

- For the two protease inhibitors fosamprenavir and tipranavir that can be coadministered with ritonavir capsules either under fed or fasted conditions, no changes will be required for fosamprenavir which is currently labeled to be administered with or without food. The higher AUC and Cmax fosamprenavir values that may be obtained when it is co-administered with the tablet Norvir formulation are not expected to be of clinical significance.

- The potential increases in achievable tipranavir exposures when co-administered with the new tablet Norvir formulation are of potential clinical significance in view of the increased hepatotoxicity associated with higher tipranavir exposures. Administration in the fasted state could also lead to higher tipranavir exposures compared to fed state with ritonavir tablets. Therefore, labeling revisions for tipranavir are needed to ensure the combination of tipranavir and ritonavir is taken with meals. Additionally, for consistency with the tipranavir label, text regarding monitoring patients frequently for evidence of hepatotoxicity is requested. Finally a post-marketing requirement will be requested from the Sponsor of tipranavir to determine the pharmacokinetics of tipranavir when coadministered with the new ritonavir tablets in the fed and fasted state for labeling and also assess if additional labeling with respect to safety monitoring is needed based on the magnitude of increase in tipranavir exposures.

The following tables were provided by the Applicant and copied from the Clinical Pharmacology review Table 4A displays information on the impact of a 100% increase in ritonavir dose on the pharmacokinetics of the coadministered protease inhibitor (excluding fosamprenavir) and Table 4B displays information on the pharmacokinetics of amprenavir with fosamprenavir coadministration with different ritonavir dosage regimens.

Table 4A-C_{max}, $AUC_{(0-\tau)}$, and C_{min} pharmacokinetic data for protease inhibitors coadministered with ritonavir

Coadministered Protease Inhibitor	Geometric Mean+ C_{max} (µg/mL)	AUC_{τ} (µg•h/mL)	C_{min} (µg/mL)
Atazanavir (Harris M et al.,[1] Figure 2a^)			
Atazanavir 300 mg QD + Ritonavir 100 mg QD	2.34	NA	0.59
Atazanavir 300 mg QD + Ritonavir 200 mg QD	2.36	NA	0.68
Darunavir (Sekar V et al,[2] Poster TUPE 0083, Table 1)			
Darunavir 400 mg QD + Ritonavir 100 mg QD	3.13	40.9	0.78
Darunavir 600 mg QD + Ritonavir 200 mg QD	4.63	52.5	1.40
Tipranavir (MacGregor TR et al.,[3] Table 2)&			
Tipranavir 500 mg BID + Ritonavir 100 mg BID	130.1	755	16.3
Tipranavir 500 mg BID + Ritonavir 200 mg BID	129.2	934	26.3
Saquinavir (Kilby JM et al.,[4] Table 2)			
Saquinavir 1200 mg QD + Ritonavir 100 mg QD	6.04	57.5	0.48
Saquinavir 1200 mg QD + Ritonavir 200 mg QD	4.12	33.9	0.28

\+ For atazanavir and darunavir, medians are presented.
^ Data were generated from Figure 2a using Plot Digitizer Version 2.4.1. For the C_{max} data, the mean plasma concentrations at approximately 3 hours post-dose (median T_{max} for atazanavir based on the Reyataz prescribing information[5]) are presented.
& C_{max} and AUC are presented in µM and h•µM, respectively.
NA = not available

The approved dosing regimens for fosamprenavir with or withour food and/or NORVIR can be seen in the following table from the April, 2009 approved Lexiva label:

Table 1-C_{max}, t_{max}, AUC $_{(0-\tau)}$, and C_{min} amprenavir pharmacokinetic data with fosamprenavir coadministration with ritonavir

Regimen	C_{max} (mcg/mL)	T_{max} (hours)*	AUC_{24} (mcg•hr/mL)	C_{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 1,400 mg q.d. plus Ritonavir 100 mg q.d.	7.93 (7.25-8.68)	1.5 (0.75-5.0)	66.4 (61.1-72.1)	0.86 (0.74-1.01)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

*Data shown are median (range).

For detailed prescribing information for each of the co-administered protease inhibitors please see Appendix 2. Also included in Appendix 2 are the references used to reach the conclusions of this review. Please note that all the information used is publically available and included published literature as well as pharmacokinetic information of each protease inhibitor that is included in current labeling.

This review will not discuss further the three protease inhibitors (saquinavir, darunavir, and atanazavir,) because no clinically significant changes in their achievable exposures are expected. As a result we do not have any safety concerns. For further details, Please see the Clinical Pharmacology review by Dr. Stanley Au.

In addition, no changes will be required for the fosamprenavir label which is currently labeled to be administered with or without food. The potential higher AUC and Cmax fosamprenavir values that may be obtained when co-administered with the tablet Norvir formulation are not expected

to be of clinical significance. As per the Clinical Pharmacology review (refer to Applicant Table 1 above):

"When fosamprenavir 1,400 mg coadministered with ritonavir 100 mg once daily was compared with fosamprenavir 1,400 mg coadministered with ritonavir 200 mg once daily, the $AUC_{(0-24h)}$ and C_{max} were higher by approximately 5% and lower by approximately 10%, respectively with a doubling of ritonavir doses from 100 mg to 200 mg. Fosamprenavir C_{min} is higher by approximately 70% with the doubling of ritonavir doses.

No pharmacokinetic information was provided by Abbott evaluating the doubling of ritonavir doses from 100 mg to 200 mg when coadministered with fosamprenavir 700 mg twice daily. However, maximum ritonavir CYP 3A inhibitory effects on midazolam were reported to occur at 100 mg once daily (Mathias et al 2008). Therefore, it is not anticipated with fosamprenavir 700 mg coadministered with ritonavir 100 mg twice daily that an increase in ritonavir exposure would significantly increase the fosamprenavir $AUC_{(0-12h)}$ and C_{max}. "

For the protease inhibitors tipranavir that can be coadministered either under fed or fasted conditions with ritonavir capsules further details around the rationale for requiring labeling changes and a post-marketing requirement from the sponsor of that drug are as follows:

As per the June, 2009 label, the approved tipranavir dose in adult is 500 mg with 200 mg of NORVIR twice daily with or without food.

Information evaluating the doubling of ritonavir doses (400 mg twice daily) in combination with tipranavir at the recommended dosage of 500 mg twice daily is not available. As per current labeling, 200 mg of ritonavir coadministered with tipranavir provide ritonavir concentrations similar to 100 mg of ritonavir coadministered with protease inhibitors other than tipranavir. When tipranavir 500 mg was coadministered with ritonavir 100 mg twice daily and compared with tipranavir 500 mg coadministered with ritonavir 200 mg twice daily, the tipranavir C_{max} values for both regimens were similar. The $AUC_{(0-12h)}$ was higher by approximately 25% and C_{min} was higher by approximately 60% with the doubling of ritonavir doses from 100 to 200 mg twice daily).

As per the Clinical Pharmacology review, "Maximum ritonavir CYP 3A inhibitory effects were reported at 100 mg once daily (Mathias et al 2008). However, this conclusion does not apply to tipranavir because tipranavir is a P-gp substrate and ritonavir does have P-gp inhibitory and induction effects (Kharasch et al 2008). Subsequently, changes in tipranavir exposure when coadministered with 200 mg of ritonavir tablets due to mechanisms other than CYP 3A inhibition are possible. However, at steady state, ritonavir P-gp induction may attenuate P-gp inhibitory effects (Kharasch et al 2008)."

From discussions with the Agency Clinical Pharmacology Review team it was concluded that the clinical significance of the increased tipranavir exposures associated with the co-administration of tipranavir 500 mg with the new Norvir tablets is unknown and may be a potential safety issue given the potential for increased hepatotoxicity with minimal increases in tipranavir exposure.

This potential will need to be adequately addressed via a post-marketing requirement for the Sponsor of tipranavir to assess the effects of the Norvir tablet formulation on the concentrations of tipranavir with and without food and to re-label accordingly. Further the Norvir label will be revised to reflect the Agency concerns for possible increased hepatotoxicity and the need for close monitoring of patients receiving both Norvir and tipranavir.

Sources of Clinical Data for Safety Evaluation

Tables of Clinical Studies

Type of Study	Study ID	Objectives	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	M06-842a	Compare BA of 3 compressed tablets and 1 extrudate tablet with the marketed SGC	Partial crossover	4 tablet formulations and 1 capsule formulation, each 100 mg, oral	32	Healthy subjects	Single dose
BA	M10-235	Assess the effect of food on BA	Crossover	100 mg tablet, oral	27	Healthy subjects	Single dose
BE	M10-263a	Compare BA of tablet with marketed SGC	Crossover	Tablet, 100 mg, oral SGC, 100 mg, oral	24	Healthy subjects	Single dose
BE	M10-307	Compare BA of tablet with marketed SGC	Crossover	Tablet, 100 mg, oral SGC, 100 mg, oral	93	Healthy subjects	Single dose

Review Strategy

No new efficacy data are provided in this NDA. In support of the safety of the approved 600 mg twice daily dose previously reviewed data from four clinical studies in 140 HIV-1 infected patients who received various multiple-doses (400 to 1200 mg total daily dose) of NORVIR are summarized, (M93-107 (n = 46), Study M93-112 (n = 48), Study M93-134 (n = 40) and Study M96-604 (N = 6).

The impact of the higher NORVIR C_{max} values (14 to 26%) on the QTc and PR intervals was also evaluated using data from Study M06-809, a thorough QT Phase 1, multiple-dose, open-label, placebo- and active-controlled, randomized study conducted according to a crossover design in 88 healthy volunteers. This analysis was previously submitted for review (sNDA 20-659/S043 and (b) (4)) and the conclusions are summarized in section 7.

In addition four pharmacokinetic single dose studies were reviewed for the safety of the 100 – 200 mg BID doses that are used in conjunction with other protease inhibitors. JMP Statistical Discovery software was used to independently evaluate the safety data. Eight week safety data from the LPV/r (study M05-730) was also summarized. This study compared the safety and tolerability of the marketed LPV/r tablet formulation with those for the LPV/r SGC when dosed 800/200 mg once daily or 400/100 mg twice daily for eight weeks in combination with nucleoside reverse transcriptase inhibitors in antiretroviral-naïve HIV-1 infected patients. The

eight and 48 week safety data from this study were reviewed in detail during the review of sNDA 21-906/s017.

Discussion of Individual Studies

For detailed reviews of the BE studies and the necessity of the pharmacokinetic modeling and the logistic regression analysis to assess for the association between AEs in HIV-infected subjects and exposures please see Dr. Stanley Au's review.

For a detailed review of the LPV/r study (M05-730), please see the MOR of sNDA 21-906/S017.

For a detailed review of the thorough QT study M06-809, please the MOR of sNDA20-659/S043 and (b) (4)).

Review of Efficacy

Efficacy Summary

No efficacy data were included in this application. The new tablet formulation results in higher exposures compared to the capsule formulation; therefore, the tablet formulation is expected to have an efficacy profile similar to the capsule formulation.

Indication

No new indication is sought with this NDA.

Review of Safety

Safety Summary

Methods

1.1.4 Clinical Studies Used to Evaluate Safety

See Section 5.2.

Safety Findings:

7.2.1 Previously reviewed HIV infected Patient studies

Based on the prediction that the higher NORVIR concentrations achieved with the tablet will be between 14% and 26% greater than those achieved with the SGC, the Applicant provided an analysis of the potential impact of the higher C_{max} (14 to 26%) on the safety profile of the 600 mg dose utilizing historical data from 4 NORVIR clinical trials in HIV-1 infected subjects.

The safety data from these studies were previously submitted to the Agency and reviewed in support of other applications or as final study reports.

One hundred forty (140) subjects were included in the analyses. NORVIR doses ranged from 400 – 1200 mg total daily dose and were administered either twice daily or every six or eight hours. These studies were Study M93-107 (n = 46), Study M93-112 (n = 48), Study M93-134 (n = 40) and Study M96-604 (N = 6). In these studies, the NORVIR encapsulated liquid (Formulation A, Studies M93-107, M93-112 and M93-134) and the semi-solid capsule (SSC, Formulation L, Study M96-604) formulations were administered to study subjects.

Abbott provided an analysis of NORVIR exposures (AUC and C_{max}) relative to the reported adverse events in order to assess if there was a relationship between them. Initally Abbott identified 29 Treatment Emergent Adverse Events (TEAEs) that occurred in at least five subjects or 3% of the total population.

Table 4. Ritonavir Adverse Events Reported by 5 or More Subjects in the Combined Data Set for Studies M93−107, M93−112, M93−134 and M96−604

Adverse Event COSTART Term	Number of Subjects with Adverse Event (Total N = 140)	Number of Subjects with Adverse Event in BID Regimen (N = 100)	Number of Subjects with Adverse Event in Q6H and Q8H Regimens (N = 40)
Diarrhea	55	31	24
Headache	24	10	14
Nausea	22	11	11
Circumoral Paresthesia	20	13	7
Asthesia	18	12	6
Pharyngitis	16	8	8
Rash	16	8	8
Abdominal Pain	14	9	5
Fever	13	9	4
Dyspepsia	12	4	8
Oral Moniliasis	12	6	6
Leukoplakia of Mouth	11	8	3
Taste Perversion	11	5	6
Vomiting	11	4	7
Cough Increased	9	4	5
Herpes Simplex	8	6	2
Rhinitis	8	3	5
Flu Syndrome	7	6	1
Peripheral Paresthesia	7	4	3
Abnormal Stools	6	5	1
Bronchitis	6	5	1
Dizziness	6	3	3
Pruritus	6	5	1
Dyspnea	5	1	4
Hepatomegaly	5	2	3
Lymphadenopathy	5	2	3
Mouth Ulcer	5	2	3
Paresthesia	5	4	1
Vasodilation	5	3	2

Table Note: Adverse events are listed in the order of prevalence.

The logistic regression model used by Abbott to evaluate the association of each adverse event with NORVIR exposure (C_{max} and AUC) controlled for effects of dose, age and weight. (M93-134). The analyses were performed separately for the twice daily (200 mg, 300 mg, 400 mg, 500 mg and 600 mg) regimens and for the combination of the every six and eight hour regimens (200 mg and 300 mg).

In the Applicant's analysis for the twice daily regimens, three adverse events (increase in bronchitis (0.3% to 0.8-1.8%), decrease in oral leukoplakia (2% to 0.7%) and increase in pruritus (2.2% to 3.5-5%)) were significantly associated with a 14 – 26% increase in C_{max}. There is general agreement with Abbott's analysis that the correlation between these AEs is consistent with the effects of either severe underlying immunodeficiency observed in subjects with HIV when these studies were performed (1990s). In addition the reported adverse events and the frequency of reporting were consistent with the well known safety profile of NORVIR.

The available data support the conclusion that the possible increase in the NORVIR Cmax achieved with the tablet formulation of 14- 26% is not likely to affect the overall safety profile of NORVIR although there may be some initial tolerability issue for which labeling has been proposed.

7.2.2: Pharmacokinetic modeling

The Applicant performed a linear regression analysis of dose-normalized NORVIR C_{max} versus NORVIR dose to estimate the potential increase in NORVIR C_{max} at a 600 mg dose of the to-be-marketed tablet relative to the SGC. For details of this analysis please see Dr. Stanley Au's review. This analysis indicated that the mean percent increase in NORVIR C_{max} after administration of a 600 mg dose of NORVIR tablets compared to SGC is likely to be approximately 14% but would be no more than the mean 26% increase in C_{max} observed at the 100 mg dose. The Agency review concurred that given the non-linear pharmacokinetics of RTV, the increase in C_{max} at the 600 mg dose is expected to lower than that seen with the 100 mg dose and therefore there should be minimal effects on the safety profile of NORVIR.

7.2.3: Study M06-809 (effect on QT and PR)

Study M06-809 was reviewed as part of the April 25, 2008 SLR Kaletra NDAs 21-906/S-014 and 21-251/S-023 and Norvir NDAs NDA 20-659/S-042 and 20-945/S-022 submissions. Please refer to the MOR for details.

Briefly, Study M06-809 was a phase 1 study of the potential for QTc and PR interval prolongation in patients receiving LPV/r or NORVIR alone. The study was a multiple-dose, open-label, placebo and active controlled, randomized study conducted according to a crossover design for LPV/r and NORVIR. Adult males and females, in general good health were included. For the NORVIR portion of the study, 48 subjects were randomized in equal numbers to receive placebo or NORVIR 400 mg twice daily in two periods. The dose of NORVIR that was selected for this study was chosen because this dose was expected to provide pharmacokinetic exposure similar to the approved clinical dosing regimen for NORVIR (600 mg twice daily) at steady state while limiting the number of study discontinuations due to adverse events and confounding effects on QT assessment. The NORVIR concentrations achieved at steady state were approximately double those achieved in Phase 1 studies of the 600 mg twice daily dose.

The Agency review concluded that no significant effect on the QTc interval was observed with Norvir 400 mg administered twice daily for 2.5 days. There was some evidence for a potential

effect of NORVIR on the QTc interval at supratherapeutic concentrations however the evidence was stronger for LPV/r as compared to NORVIR alone. Further there was strong evidence of an effect of LPV/r and RTV alone on PR with resultant varying degrees of AV block.

Based on these findings, product labeling for both LPV/r and NORVIR were amended to reflect the potential for PR and QTc prolongation to a lesser degree with NORVIR.

Comment: The NORVIR exposures in this study were approximately double those observed at steady state with the labeled doses of NORVIR. The exposures and the safety from this study support the safety of the tablet formulation and the resultant increased exposures achieved with either the lower Norvir doses(100- 200 mg) that are co-administered with other protease inhibitors or the approved 600 mg dose.

7.2.4 Healthy Volunteer Studies

Data from four single dose pharmacokinetic studies in healthy volunteers were submitted (see table of clinical studies) for review. Each study was reviewed separately and the relevant reviews can be found in Appendix 1. In addition, the data from three of the four studies were combined into an integrated safety summary. Study M06-842 (N = 32) was not included in this summary as it was a partial crossover study of four different tablet formulations and the SGC. Not all the formulations tested in this study were bioequivalent and thus the results of that study are mentioned separately in order to avoid dilution of the safety data. The three studies M10-263, M10-307, and M10-235 included in the summary include safety data from 144 subjects who enrolled and received NORVIR marketed soft gel capsules (SGCs), the prototype tablet formulation, or the to-be-marketed tablet formulation.

The safety analyses included all subjects from four normal volunteer studies (M06-842, M10-263, M10-307, and M10-235) who received at least one dose of study medication. The safety database for the tablet formulation includes 176 subjects (144 healthy adult subjects from three studies as well as an additional 32 subjects from the crossover (M06-842) study).

The safety data for the 144 subjects who enrolled and received at least one dose of NORVIR tablet (N = 140) or NORVIR SGC (N = 111) under fed conditions in the three completed studies were analyzed together. As noted previously the data from study M06-842 were not included in this combined analysis because only two of the four tablet formulations used in that study were bioequivalent. The 144 subjects included in the integrated analysis included 130 who completed the studies and fourteen who discontinued prematurely; three subjects discontinued prematurely due to the occurrence of one or more adverse events.

Since crossover designs were used in all of the pharmacokinetic studies, subjects were counted in more than one treatment category according to each treatment received in the study. Under fed conditions, 107 subjects received a dose of both the NORVIR tablet and NORVIR SGC. Of the 144 subjects who received at least one dose of either the NORVIR tablet or NORVIR SGC, 114 subjects received one dose of NORVIR tablet, 26 subjects received two doses of NORVIR tablets (under moderate- and high-fat conditions in Study M10-235), and 111 subjects received

one dose of the NORVIR SGC. In Study M10-235, 25 subjects received three doses of the NORVIR tablet under moderate-fat, high-fat, and fasting conditions.

Adverse event and laboratory data were collected for each patient at the protocol defined study visits. AEs and laboratory abnormalities were graded according to a modified ACTG toxicity grading scheme. Investigators assigned a severity grade and relationship to study drug. SAEs were collected in accordance with regulations and include those events which resulted in death, life-threatening situation, hospitalization (or prolonged), persistent or significant disability, congenital anomaly or other medically important event. Treatment Emergent Adverse Events (TEAEs) and HIV-1 related adverse events were coded using MedDRA version 9. The AEs were grouped by system organ class (SOC).

Safety Findings from the Healthy Volunteer Studies:

No deaths were reported in the four studies provided for review. One subject (Subject 308 in Study M10-263) experienced 2 serious adverse events. Neither event was considered related to study drug administration. These events were an initial episode of "acute confusional state" in the afternoon after receiving single-dose NORVIR tablet 100 mg on Study Day 1 of Period 2. The subject was discontinued from the study the following day (Study Day 2) after consultation with a psychiatrist. The subject was referred to the emergency room and then hospitalized for further evaluation. The subject was subsequently transferred to an in-patient psychiatric unit and later discharged. A second adverse event of acute psychosis and catatonia was reported in the same subject 27 days after the last dose of study drug. The subject was treated at an in-patient psychiatric hospital and discharged.

Comment: The Reviewer agreed with the investigator's determination of unrelatedness. A chart review of this subject confirmed that the subject had a history of similar psychiatric episodes that was elicited at a later timepoint.

No other SAEs were reported from the remaining subjects from all four studies.

Overall fourteen subjects prematurely discontinued from the three PK crossover studies. None of the 32 subjects from the crossover (M06-842) study discontinued. Of the fourteen subjects who prematurely discontinued, three discontinued due to adverse events. The adverse events leading to discontinuation included one event each of asymptomatic hematuria (considered related), acute confusional state (not related), and fever (not related). The remaining reasons for premature discontinuation included positive drug screen (2), personal reasons (6), withdrew consent (2), and venipuncture site pain (1).

Subject 527, M10-235: asymptomatic hematuria in one subject (Subject 527) led to premature discontinuation from the study and was determined by the investigator to be possibly related to study drug. This event occurred on study day 2 of period 2 (Regimen B). The subject had previously received Regimen A. The event was completely resolved on a follow-up visit 8 days after discontinuation. The same subject developed a second AE, elevated bilirubin 7 days after the last single dose. This event was also determined by the investigator to be possibly related to study drug. The increased bilirubin was considered to be resolved on Study Day 19, 11 days after last treatment. This event was also judged by the investigator as possibly related to study drug.

Subject 1013/Study M10-307) was discontinued from the study (prior to dosing in Period 2) due to illness (fever). This adverse event leading to study discontinuation was judged by the investigator as not related to study drug
Subject 308, M10-263: acute confusional state (see SAEs)

Generally similar percentages of subjects treated with the tablet or the SGC reported a treatment emergent AE (32/140 (22.9%) tablet versus 24/111 (21.6%) SGC). The most commonly reported treatment emergent adverse events of subjects receiving the NORVIR tablet were headache (14/140, 10%) and nausea (5/140, 3.6%). The most common adverse events reported in the SGC recipients were headache (9/111, 8.1%), dizziness (5/111, 4.5%), and nausea (5/111, 4.5%) (see table). Similarly headache was the most frequently reported event (3/32, 9.3%) in the 5 arm M06-842 study with all headache events reported from subjects on the BE arms (A tablet, C tablet and E SGC, one each).

Adverse Events Studies M10-263, M10-307, and M10-235

	RTV Tablet 100 mg N = 140	**RTC SGC 100 mg N = 111**
Lymph Node Pain	0	1 (0.9%)
Lymphadenopathy	0	1 (0.9%)
Upper Abdominal Pain	1 (0.7%)	2 (1.8%)
Constipation	0	1 (0.9%)
Diarrhea	3 (2.1%)	2 (1.8%)
Nausea	5 (3.6%)	5 (4.5%)
Teeth Sensitivity	1 (0.7%)	0
Stomach Discomfort	2 (1.4%)	0
Vomiting	2 (1.4%)	2 (1.8%)
Fatigue	2 (1.4%)	3 (2.7%)
Feeling Abnormal	1 (0.7%)	0
Feeling Hot	3 (2.1%)	1 (0.9%)
Pain	1 (0.7%)	0
Pyrexia	1 (0.7%)	0
Venipuncture Site Pain	1 (0.7%)	0
UTI	0	1 (0.9%)
Increased Bilirubin	1 (0.7%)	0
Anorexia	1 (0.7%)	0
Muscle Spasms	1 (0.7%)	0
Musculoskeletal Pain	1 (0.7%)	0
Dizziness	3 (2.1%)	5 (4.5%)
Dysarthria	1 (0.7%)	0
Headache	14 (10%)	9 (8.1%)
Paresthesia	1 (0.7%)	0
Sinus Headache	0	1 (0.9%)
Somnolence	1 (0.7%)	0
Syncope	0	1 (0.9%)
Acute Psychosis	1 (0.7%)	0
Catatonia	1 (0.7%)	0
Confusional State	1 (0.7%)	0
Hematuria	1 (0.7%)	0
Nasal Congestion	1 (0.7%)	2 (1.8%)
Pharyngolaryngeal Pain	1 (0.7%)	1 (0.9%)
Rhinorrhea	1 (0.7%)	1 (0.9%)

Sinus Congestion	0	1 (0.9%)
Hyperhidrosis	1 (0.7%)	0
Pallor	0	1 (0.9%)

There were no apparent differences among the regimens under fed conditions (NORVIR tablet and SGC) with respect to safety in any of the studies and no apparent differences in safety between the fed and fasted regimens in Study M10-235, despite the increased exposures observed with fasting.

Laboratory Abnormalities:

Only one subject experienced a laboratory abnormality that met the Abbott criteria for "very high" or "very low" (similar to Grade 3 and 4 events per DAIDS Toxicity Grading Scheme). That subject prematurely discontinued the study because of a clinically significant urinalysis result (too numerous to count red blood cells). These abnormalities later resolved. An adverse event of moderate elevated bilirubin was also reported for this same subject. No other clinically significant values were observed during the three studies for any hematology, serum chemistry, or urinalysis parameters.

Overall no new safety signals were identified from the normal volunteer pharmacokinetic single dose crossover studies. No comparative statements regarding relative event frequencies between the formulations can be made based on the limited sample size and assessed and the limited duration of the studies. The treatment emergent adverse events observed in these studies are similar to the adverse events observed in previous trials of NORVIR in healthy subjects although GI events were not the most frequently reported events possibly because only a single dose was administered.

7.2.5: Eight week safety data from the LPV/RTV Study M05-730 (summary)
NOTE: Please review of sNDA 21-906/S017 for details on all discontinuations, deaths, and SAEs.

Study M05-730 was a Phase 3, open-label, randomized, multicenter, multicountry clinical trial designed to designed to assess safety and tolerability of the tablet and SGC formulations of LPV/r through eight weeks of treatment (once and twice daily dosing) and then to demonstrate the safety, tolerability, pharmacokinetics, and antiviral activity of the LPV/r tablet formulation when dosed once daily vs. twice daily in combination with NRTIs in the treatment of antiretroviral-naïve, HIV-1 infected patients. This study was previously reviewed.

Reported treatment emergent adverse events (TEAEs) were consistent with those previously described in clinical trials with LPV/r. No new TEAEs were reported. Generally adverse events were reported with similar frequency and character across the tablet and SGC regimens despite the increased NORVIR concentrations achieved with the approved LPV/r tablet as compared to the LPV/r SGC at NORVIR doses of 100 mg twice daily or 200 mg once daily. There appeared to be more GI adverse events including diarrhea, nausea and abdominal distension in patients receiving the tablet. These differences did not lead to increased discontinuations or SAEs.

Comment: The adverse events associated with lopinavir versus those associated with NORVIR cannot easily be differentiated. However there was no difference between the treatment arms with regards to clinically significant adverse events.

Additional Clinical Issues

Dosing Regimen and Administration

No changes to the currently approved dosing regimens are sought with this application. The effects of the new tablet formulation and the need to administer with food are discussed in section 2.5. Based on the analyses provided by Abbott, and confirmed by the Agency we concluded the 26- 40% increase in NORVIR C_{max} achieved by the new tablet formulation will not likely affect the safety profile of ritonavir.

Drug-Drug Interactions

No drug-drug interaction studies were submitted with this NDA. See discussion in section 4.4.3

Special Populations

Not applicable to this application

Pediatrics

The Applicant submitted a request for a full waiver of the pediatric study requirement for the 100 mg Norvir (NORVIR film-coated tablets), a new dosage form of NORVIR that is intended to replace the currently marketed soft gel capsule. Norvir (RTV) has been studied and approved for use in pediatric patients > 1 month of age. The appropriate dose of RTV for pediatric patients is based on body surface area and, therefore, accurate measurement and administration of the dose is most appropriately accomplished using Norvir oral solution. The film-coated tablets under review do not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and are unlikely to be used in a substantial number of pediatric patients.

For neonates from birth to 1 month of age, studies are impossible or highly impracticable due to the small numbers of HIV-infected patients in this age group within the United States. HIV studies would need to be performed in other countries and these studies are challenging. Therefore a full waiver should be granted.

Advisory Committee Meeting

Not applicable

Literature Review

All references provided by the Applicant is support of this application including the effect of the 100 —200 mg doses of NORVIR on the concentrations of co-administered protease inhibitors can be found in Appendix 2.

Overall Assessment

Conclusions

For efficacy conclusions see section 6.1.6

Safety: See Section 1.2.1

Recommendation on Regulatory Action

An approval action is recommended.

Recommendation on Postmarketing Actions

1.1.5 Risk Management Activity

Not applicable

1.1.6 Required Phase 4 Commitments

See section 1.4

1.1.7 Other Phase 4 Requests

Not applicable

1.1.8 Pediatrics

See section 7.6

Labeling Review

NOTE: For finalized labeling please see approved label.

The issue of the inclusion of clinically relevant labeling in the DOSAGE and ADMINISTRATION section (2) for the use of NORVIR at reduced doses with other approved protease inhibitors was extensively discussed during the course of the review as current labeling reflects this use only in the Drug-Drug Interactions (7) section.

At the DAVP's request, the Applicant proposed the following modifications in an updated labeling submission in 02/09:

- Revise the recently-approved dose modification statement in Dosage and Administration and also include the specific names of the FDA-approved protease inhibitors approved for co-administration with a reduced dose of RTV and remind prescribers to refer to the other protease inhibitor's prescribing information throughout the Norvir labeling (i.e., Dosage and Administration, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Special Populations, and Information for Patients).

The Applicant's proposals were generally acceptable although the Agency made a number of changes to the proposed wording. At the time of completion of this review labeling negotiations were not complete. In addition this submission represents the first PLR conversion for NORVIR and therefore numerous changes have been proposed to all sections of the label. Relevant to this submission the following changes were proposed to the Applicant in a FAX dated August 5, 2009:

(b) (4)

(B) 1 page of propsed labeling has been withheld in full immediately following this page as B4 CCI/TS

(b) (4)

In addition numerous changes were also proposed for the Highlights and the Information for Patients sections. Extensive revisions were also proposed to the Medication Guide as per DDMAC.

Comments to Applicant

No comments to the applicant were required at the conclusion of this review.

Appendices

Appendix 1: Review of Individual Studies:

1.1 M06-842: Assessment of the Single-Dose Bioavailability of NORVIR Tablet and Extrudate Tablet Formulations Relative to the Soft Gelatin Capsule in Healthy Adult Subjects

Phase 1, single-dose, non-fasting, open-label study was conducted according to a four-period, randomized, partial-crossover design. Subjects were randomly assigned in equal numbers to receive one of 5 regimens (Regimen A: a single dose of one D0600207 NORVIR 100 mg film-coated tablet, Formulation 15, B: a single dose of one D0600208 NORVIR 100 mg film-coated

tablet, Formulation 18, C: a single dose of one D0600209 NORVIR 100 mg film-coated tablet, Formulation 20, D: a single dose of one D0600213 NORVIR 100 mg film-coated tablet, Formulation E-15, and E: a single dose of one NORVIR 100 mg capsule, marketed Norvir SGC).

Subjects were dosed 30 minutes after starting a moderate-fat meal on Study Day 1 of each period. A washout interval of at least 7 days separated the doses of the consecutive study periods. The objective of this study was to compare the single-dose bioavailability of three NORVIR tablets and one NORVIR extrudate tablet with that of the marketed reference NORVIR soft gelatin capsule (SGC) formulation under non-fasting conditions. The safety and tolerability of the tablets and extrudate tablet was also assessed. Only regimens A and C were considered BE to regimen E (the approved SGC).

Thirty-two healthy adult male and female subjects ages 18 – 55 in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory tests enrolled in the study and were assessed for safety. The mean age was 40.7 years (ranging from 20 to 53 years), the mean weight was 77.4 kg (ranging from 53 to 97 kg) and the mean height was 176.6 cm (ranging from 163 to 190 cm).

There were no deaths, discontinuations or SAEs reported. All reported TEAEs were rated as mild or moderate in severity. One AE was considered treatment related (abnormal faeces) sequence 15/Regimen A. The most frequently reported AE was headache reported by one subject receiving the BE regimens A, C and E. Only musculoskeletal pain was reported in more than one subject. All other events were reported in one subject each. Two episodes of headache, the skin laceration and the limb injury were considered moderate.

An overview of reported AEs by treatment sequence as generated in jmp can be seen in the following table.

	Regimen A N = 24	Regimen B N = 24	Regimen C N = 24	Regimen D N = 24	Regimen E N = 31	Total N = 32
ALL Subjects with AE	4 (17%)	1 (4%)	3 (13%)	0	4 (13%)	9 (28%)
ABNORMAL FAECES	1 (4%)					1 (3%)
DIZZINESS			1 (4%)			1 (3%)
HAEMATOMA					1 (3%)	1 (3%)
HAEMORRHOIDAL HAEMORRHAGE		1 (4%)				1 (3%)
HEADACHE	1 (4%)		1 (4%)		1 (3%)	3 (9%)
LIMB INJURY	1 (4%)					1 (3%)
MUSC/SKEL PAIN			1 (4%)		1 (3%)	2 (6%)
NASOPHARYNGITIS			1 (4%)			1 (3%)
NECK PAIN			1 (4%)			1 (3%)
RASH MAC/PAP			1 (4%)			1 (3%)
SCIATICA	1 (4%)					1 (3%)
SKIN LACERATION					1 (3%)	1 (3%)

Conclusion: In study M06-842, two of the four tablet regimens tested (A and C) were considered BE to the SGC (Regimen E). This is evidenced by the pattern of TEAEs with most events occurring in subjects on one of the 3 BE regimens. Study regimens were well tolerated. No deaths or other serious adverse events were reported in this study. No subject discontinued from

the study. The most frequently reported event was headache. There were no apparent differences among the regimens with regard to safety.

1.2 Study M10-235: Assessment of the Effect of Food on NORVIR Bioavailability Following Administration of a Single NORVIR 100 mg Film-Coated Tablet Dose in Healthy Adult Subjects

Phase 1, single-dose, open-label study conducted according to a three-period, randomized crossover design. Subjects were randomly assigned on study Day 1 of each period in equal numbers to receive one of three sequences of:

- Regimen A (a single NORVIR 100-mg tablet administered following a high-fat breakfast),
- Regimen B (a single NORVIR 100-mg tablet administered following a moderate-fat breakfast)
- Regimen C (a single NORVIR 100-mg tablet administered under fasting condition)

A washout interval of 7 days separated the doses of the three study periods.

The objective was to compare the effect of food on NORVIR bioavailability following a single 100 mg dose of a NORVIR tablet. The safety and tolerability of the NORVIR tablet was also assessed.

Twenty-seven healthy adult male and female subjects ages 19 – 55 were enrolled. All enrolled subjects were evaluated for safety and PK. The mean age was 30.3 years (ranging from 20 to 55 years), the mean weight was 72.0 kg (ranging from 53 to 97 kg) and the mean height was 171.4 cm (ranging from 155 to 188 cm).

Twenty-six (26/27) subjects received a single 100 mg dose of NORVIR as each of Regimen A and Regimen C, and 27 subjects received a single 100 mg dose of NORVIR as Regimen B. NOTE: 25 subjects received all three single dose regimens.

Two subjects were discontinued from the study and received the following doses of NORVIR:

- Subject 515 received a single 100 mg dose of NORVIR in each of Periods 1 and 2 (Regimens B and C, respectively). The subject was discontinued from the study prior to dosing in Period 3 (Regimen A) due to a positive urine drug screen.
- Subject 527 received a single 100 mg dose of NORVIR in each of Periods 1 and 2 (Regimens A and B, respectively). The subject was discontinued from the study prior to dosing in Period 3 (Regimen C) due to hematuria.

Safety: Safety was evaluated based on assessments of adverse events, physical examinations, vital signs and laboratory tests.

Twelve of 27 subjects (44.4%) reported at least one treatment-emergent adverse event. Headache was the most frequently reported adverse event. The number of reported treatment-emergent adverse events were similar across the regimens although subjects receiving Regimen C (fasting regimen) had the greatest proportion of AEs reported (Regimen A (4/26, 15.4%), Regimen B (5/27, 18.5%) and Regimen C (5/26, 19.2%).

	Regimen A N = 26	Regimen B N = 27	Regimen C N = 26	All N = 27

Subjects with Any TEAE	4 (15.4%)	5 (18.5%)	5 (19.2%)	12 (44.4%)
Nausea	0	0	1 (3.8%)	1 (3.7%)
Teeth Sensitivity	0	1 (3.7%)	1 (3.8%)	1 (3.7%)
Vomiting	0	0	1 (3.8%)	1 (3.7%)
Fatigue	0	1 (3.7%)	0	1 (3.7%)
Increased Bilirubin	0	1 (3.7%)	0	1 (3.7%)
Musculoskeletal Pain	0	1 (3.7%)	0	1 (3.7%)
Dizziness	0	0	1 (3.8%)	1 (3.7%)
Headache	4 (15.4%)	1 (3.7%)	4 (15.4%)	8 (29.6%)
Hematuria	0	1 (3.7%)	0	1 (3.7%)

Most adverse events were assessed by the investigator as possibly related to study drug and mild in severity. The reported GI events of nausea and vomiting as well as musculoskeletal pain, dizziness and two episodes of headache were considered not related. Only the event of hematuria was considered severe and related. The events of nausea, vomiting and musculoskeletal pain were considered moderate and not related. The event of increased bilirubin was considered moderate and related. All other events were reported as mild.

There were no deaths or other serious adverse events were reported. One AE, asymptomatic hematuria in one subject (Subject 527), led to premature discontinuation from the study and was determined by the investigator to be possibly related to study drug. This event occurred on study day two of period two (Regimen B). The subject had previously received Regimen A. The event was completely resolved on a follow-up visit eight days after discontinuation. The same subject developed a second AE, elevated bilirubin seven days after the last single dose. This event was also determined by the investigator to be possibly related to study drug. The increased bilirubin was considered to be resolved on Study Day 19, 11 days after last treatment. This event was also judged by the investigator as possibly related to study drug. No further information was provided.

No clinically significant values were observed during the study for any hematology or serum chemistry parameters, except the elevated bilirubin values observed in Subject 527. Three urinalysis values, all in the same subject, met Abbott criteria for Very High (including urinary RBCs that were too numerous to count (TNTC) on Study Days 7 and 8). The subject's base line value on Study Day 1 was 10 – 15 RBCs.

In conclusion the NORVIR single dose 100 mg regimens tested was well tolerated by healthy volunteer subjects. One subject reported two adverse events (asymptomatic hematuria and elevated bilirubin) determined by the investigator to be possibly related to study drug. There were no other clinically significant vital signs or laboratory measurements observed during the course of the study. No differences were seen among regimens for their adverse event profiles. There were no apparent differences among the regimens with respect to safety. The reported AE profile is consistent with that previously described for NORVIR at a 100 mg dose.

1.3 Study M10-263: A Comparison of the Single Dose Bioavailability of an Experimental NORVIR Tablet Formulation Relative to the NORVIR Soft Gelatin Capsule in Healthy Adult Subjects

Phase 1, single-dose, open-label study conducted according to a two-period, randomized crossover design. Subjects were randomly assigned under non-fasting conditions in the AM of study day 1 of each period in equal numbers to receive one of two sequences of

- Regimen A (one 100 mg NORVIR tablet, Formulation D0700376, test)
- Regimen B (one 100 mg NORVIR marketed SGC, reference)

A washout interval of at least seven days separated the doses of the two study periods. The objective of this study was to compare the bioavailability of a single (100 mg) dose of a test tablet of NORVIR with that of a reference NORVIR soft gelatin capsule (SGC, 100 mg) under non-fasting conditions. The safety and tolerability of the tablet and SGC were also assessed via assessments of adverse events, physical examinations, vital signs, ECGs, and laboratory tests.

Twenty four healthy adult male and females subjects entered the study and were evaluated for safety. Twenty two subjects were dosed in both periods and 21 completed the study. The mean age was 38.4 years (ranging from 23 to 55 years), the mean weight was 69.8 kg (ranging from 53 to 89 kg) and the mean height was 166.6 cm (ranging from 145 to 182 cm).

Twenty-four (24/24) subjects received a single 100 mg dose of NORVIR as the test tablet (Regimen A) and 22 subjects received a single 100 mg dose of NORVIR as the reference SGC (Regimen B).
Three subjects were discontinued from the study and received the following doses of NORVIR:

- Subject 304 received a single 100 mg dose of the NORVIR tablet in Period 1. The subject withdrew from the study prior to dosing in Period 2 due to withdrawal of consent and loss to follow-up.
- Subject 308 received a single 100 mg dose of the NORVIR SGC in Period 1 and a single 100 mg dose of the NORVIR tablet in Period 2. The subject withdrew from the study due to a serious adverse event during Period 2.
- Subject 309 received a single 100 mg dose of the NORVIR tablet in Period 1. The subject withdrew from the study prior to dosing in Period 2 due to withdrawal of consent.

No deaths were reported in this study. One subject (Subject 308) reported a serious adverse event (acute confusional state) that led to premature discontinuation from the study on Study Day 2 of Period 2 and was determined by the investigator to be probably not related to study drug. The same subject reported the serious AEs of and psychosis/catatonia 27 days after the study that were determined by the investigator to be not related to study drug. Review of the case report revealed probable pre-existing psychiatric disorder.

Five (5/24, 20.8%) subjects reported at least one treatment-emergent adverse event. Only one of these 5 subjects reported only 1 event.

	Regimen A N = 24	Regimen B N = 22	All N = 24
All subjects with AE	4 (16.7%)	3 (13.6%)	5 (20.8%)
Nausea	2 (8.3%)	1 (4.5%)	2 (8.3%)
Fatigue	1 (4.2%)	2 (9.1%)	2 (8.3%)
Feeling abnormal	1 (4.2%)	0	1 (4.2%)
Feeling Hot	1 (4.2%)	0	1 (4.2%)
Dizziness	1 (4.2%)	0	1 (4.2%)
Dysarthria	1 (4.2%)	0	1 (4.2%)
Headache	2 (8.3%)	1 (4.5%)	2 (8.3%)
Somnolence	1 (4.2%)	0	1 (4.2%)
Acute Psychosis	1 (4.2%)	0	1 (4.2%)
Catatonia	1 (4.2%)	0	1 (4.2%)
Confusional State	1 (4.2%)	0	1 (4.2%)

No adverse event was reported by more than two subjects. Adverse events reported by two subjects in any regimen were fatigue (2/24, 8.3%), nausea (2/24, 8.3%) and headache (2/24, 8.3%). All remaining adverse events were reported in any regimen by one subject each. The frequency and nature of the adverse events were similar between regimens. The majority of adverse events were assessed by the investigator as possibly or probably related to study drug and mild in severity.

Results of other safety analyses, including individual subject changes, changes over time and individually clinically significant values for vital signs, ECG and laboratory measurements, and were unremarkable for each treatment group.

Safety conclusions: Both the tablet and SGC single dose regimens tested were generally well tolerated. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study. There were no apparent differences between the regimens with regard to safety.

1.4 Study M10-307: Comparison of the Single-Dose Bioavailability of a NORVIR 100 mg Film-Coated Tablet Relative to a NORVIR 100 mg Soft Gelatin Capsule in Healthy Adult Subjects

Phase 1, single-dose, non-fasting, open-label study conducted according to a two-period, randomized, two-stage, group-sequential, crossover design. Subjects were randomly assigned in equal numbers to receive under non-fasting conditions in the morning on Study Day 1 of each period one of two sequences of:

- Regimen A (one 100 mg NORVIR tablet, test)
- Regimen B (one 100 mg NORVIR marketed SGC, reference)

A washout interval of at least seven days separated the doses of the two study periods.

The objective of this study was to compare the single-dose bioavailability of a NORVIR 100 mg tablet with that of a NORVIR 100 mg soft gelatin capsule (SGC) under non-fasting conditions. The safety and tolerability of the tablet and SGC was also assessed

Ninety three healthy adult male and female NV subjects were enrolled and 85 participated in both study periods. All subjects enrolled were included in the safety analyses.

For the 93 subjects who participated in the study, the mean age was 29.2 years (ranging from 19 to 55 years), the mean weight was 74.5 kg (ranging from 45 to 106 kg) and the mean height was 172.7 cm (ranging from 150 to 196 cm).

Eighty-five (85/93) subjects received both a single 100 mg dose of NORVIR as the test Regimen A and a single 100 mg dose of NORVIR as the reference Regimen B.

Nine subjects were discontinued from the study and received the following doses of NORVIR:

- Subjects 1004, 1026, and 1046 received a single 100 mg dose of NORVIR (Regimen A) in Period 1. The subjects withdrew from the study prior to dosing in Period 2 for personal reasons.
- Subjects 1024 and 1068 received a single 100 mg dose of NORVIR (Regimen B) in Period 1. The subjects withdrew from the study prior to dosing in Period 2 for personal reasons.
- Subject 1012 received a single 100 mg dose of Regimen A in Period 1 and a single 100 mg dose of Regimen B in Period 2. The subject withdrew from the study after completing PK sampling at hour 5 (Period 2) for personal reasons.
- Subject 1013 received a single 100 mg dose of NORVIR (Regimen A) in Period 1. The subject was discontinued from the study prior to dosing in Period 2 due to illness.
- Subject 1022 received a single 100 mg dose of NORVIR (Regimen B) in Period 1. The subject was discontinued from the study prior to dosing in Period 2 due to difficult venipunctures.
- Subject 1092 received a single 100 mg dose of NORVIR (Regimen B) in Period 1. The subject was discontinued from the study prior to dosing in Period 2 due to positive test results for amphetamines.

The number and percentage of subjects reporting adverse events were tabulated by regimen. Laboratory test values and vital signs measurements that were Very High or Very Low, according to predefined criteria, were identified.

In the Applicant's analysis, 35/93 (37.6%) subjects reported at least one treatment-emergent adverse event. Adverse events reported by three or more subjects were headache (15 subjects, 16.1%), dizziness (seven subjects, 7.5%), nausea (six subjects, 6.5%), diarrhea (four subjects, 4.3%), vomiting (four subjects, 4.3%), feeling hot (three subjects, 3.2%), nasal congestion (three subjects, 3.2%), and upper abdominal pain (three subjects, 3.2%). All remaining adverse events were reported by a maximum of 2.2% of subjects (two subjects).

	Regimen A N = 89	**Regimen B N = 89**	**All N = 93**
Total subjects with AE	19 (21.2%)	21 (23.6%)	35 (37.6%)
Lymph Node Pain	0	1 (1.1%)	1 (1.1%)
Lymphadenopathy	0	1 (1.1%)	1 (1.1%)
Upper Abdominal Pain	1 (1.1%)	2 (2.2%)	3 (3.2%)
Constipation	0	1 (1.1%)	1 (1.1%)

Diarrhea	3 (3.4%)	2 (2.2%)	4 (4.3%)
Nausea	3 (3.4%)	4 (4.5%)	6 (6.5%)
Stomach Discomfort	2 (2.2%)	0	2 (2.2%)
Vomiting	2 (2.2%)	2 (2.2%)	4 (4.3%)
Fatigue	0	1 (1.1%)	1 (1.1%)
Feeling Hot	2 (2.2%)	1 (1.1%)	3 (3.2%)
Pain	1 (1.1%)	0	1 (1.1%)
Pyrexia	1 (1.1%)	0	1 (1.1%)
Venipuncture site Pain	1 (1.1%)	0	1 (1.1%)
UTI	0	1 (1.1%)	1 (1.1%)
Anorexia	1 (1.1%)	0	1 (1.1%)
Muscle Spasms	1 (1.1%)	0	1 (1.1%)
Dizziness	2 (2.2%)	5 (5.6%)	7 (7.5%)
Headache	7 (7.9%)	8 (9%)	15 (16.1%)
Paresthesia	1 (1.1%)	0	1 (1.1%)
Sinus Headache	0	1 (1.1%)	1 (1.1%)
Syncope	0	1 (1.1%)	1 (1.1%)
Nasal Congestion	1 (1.1%)	2 (2.2%)	3 (3.2%)
Pharyngolaryngeal Pain	1 (1.1%)	1 (1.1%)	2 (2.2%)
Rhinorrhea	1 (1.1%)	1 (1.1%)	2 (2.2%)
Sinus Congestion	0	1 (1.1%)	1 (1.1%)
Hyperhidrosis	1 (1.1%)	0	1 (1.1%)
Pallor	0	1 (1.1%)	1 (1.1%)

In the FDA analysis, the total number of subjects assessed by unique subject ID with an AE was 38. Due to the difference in the denominator, there were differences between the analyses of total number of reports for each AE. However the general conclusions were similar. Headache was the most commonly reported AE (25 reports) followed by diarrhea vomiting, nausea, and dizziness.

Of the reported events none were categorized as severe, five on each arm were assessed as moderate and the remainder were of mild severity. All reports of diarrhea were related to RTV as were 15 reports of headache.

No deaths or other serious adverse events were reported in this study. One subject (Subject 1013) was discontinued from the study (prior to dosing in Period 2) due to illness (fever). This adverse event leading to study discontinuation was judged by the investigator as not related to study drug. There were no other adverse events that led to premature discontinuation from the study. The majority of the treatment-emergent adverse events were assessed by the investigator as possibly related to the study drug and mild in severity. No differences between formulations in adverse event profiles were observed. No differences were seen among regimens for their adverse event profiles. There were no apparent differences among the regimens with respect to safety.

Appendix 2:

Table 1-Protease inhibitors dosage regimens with concurrent administration of reduced doses of ritonavir*

1) Fosamprenavir
Fosamprenavir tablets may be taken with or without food
<u>Therapy naive adults</u>:

Fosamprenavir 1,400 mg twice daily (without ritonavir) Fosamprenavir 1,400 mg once daily plus ritonavir 200 mg once daily Fosamprenavir 1,400 mg once daily plus ritonavir 100 mg once daily Fosamprenavir 700 mg twice daily plus 100 mg ritonavir twice daily Protease inhibitor experienced adults: Fosamprenavir 700 mg twice daily plus ritonavir 100 mg twice daily
2) Darunavir Darunavir tablets should be taken with food Treatment naive adult patients: 800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food Treatment experienced adult patients: 600 mg (one 600 mg tablet or two 300 mg tablets) taken with ritonavir 100 mg twice daily and with food
3) Atazanavir Atazanavir capsules should be taken with food Treatment naive patients: Atazanavir 300 mg with ritonavir 100 mg once daily with food or atazanavir 400 mg once daily with food. When coadministered with tenofovir, the recommended dose is atazanavir 300 mg with ritonavir 100 mg. Treatment experienced patients: Atazanavir 300 mg with ritonavir 100 mg once daily with food
4) Tipranavir Tipranavir capsules can be administered with and without food Treatment experienced patients: Adults: 500 mg tipranavir, co-administered with 200 mg ritonavir, twice daily with or without food
5) Saquinavir Administer within 2 hours after meals 1000 mg twice daily with ritonavir 100 mg twice daily

*Information in Table 1 is extracted from the Dosage and Administration section of the U.S. prescribing information

1) Fosamprenavir

Reference: Lexiva (fosamprenavir) prescribing information, April 2009

Table 1-C_{max}, t_{max}, AUC $_{(0-\tau)}$, and C_{min} amprenavir pharmacokinetic data with fosamprenavir coadministration with ritonavir

Regimen	C_{max} (mcg/mL)	T_{max} (hours)*	AUC_{24} (mcg•hr/mL)	C_{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 1,400 mg q.d. plus Ritonavir 100 mg q.d.	7.93 (7.25-8.68)	1.5 (0.75-5.0)	66.4 (61.1-72.1)	0.86 (0.74-1.01)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

*Data shown are median (range).

Literature references provided by the Applicant to support the concomitant use of NORVIR tablet with each Co-administered PI at 100- 200 mg doses.

1)) Sekar V, Spinosa-Guzman S, Lefebvre E, Hoetelmans R. Clinical pharmacology of TMC114- a new HIV protease inhibitor. 16th International AIDS Conference, 2006
2) Harris M, Alexander C, Bonner S, Joy R, Guillemi S, Phillips E, Langridge S, Harrigan R, Montaner J. Effect on Atazanavir (ATV) and Ritonavir (rtv) Plasma Levels of Increasing ATV/rtv Daily Dosing from 300/100 mg to 300/200 mg and 400/200 mg. 3rd IAS Conference on HIV Pathogenesis and Treatment, 2005
3) O'Mara E, Mummaneni V, Bifano M, Randall D, Uderman H, KnoxL , Geraldes M. Pilot Study of the Interaction between BMS-232632 and Ritonavir. Conference on Retroviruses and Opportunistic Infections, 2001
4) MacGregor TR, Sabo JP, Norris SH, Johnson P, Galitz L, McCallister S. PK characterization of different dose combinations of coadministered tipranavir and ritonavir in healthy volunteers, HIV Clin Trials 2004; 5(6): 371-382
5) Kilby JM, Sfakianos G, Gizzi N, Siemon-Hryczyk P, Ehrensing E, OO C, Buss N, Saag MS. Safety and pharmacokinetics of once daily regimens of soft gel capsule saquinavir plus minidose ritonavir in HIV negative adults, Antimicrobial Agents and Chemotherapy, 2000; 2672-2678

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR

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

/s/

M R ALIVISATOS
09/29/2009

KIMBERLY A STRUBLE
09/29/2009

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-417 **Applicant: Abbott** **Stamp Date: December 19, 2008**

Drug Name: NORVIR (Ritonavir) **NDA/BLA Type: N**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			Yes, an ISS including SD PK studies, PK modeling and referenced MD and clinical study reports in HIV patients was submitted
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	Efficacy data not included because efficacy approval is based on bioequivalence between new tablet and approved SGC formulations.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	x			Yes the applicant has submitted exposure data to determine

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: Study Title: Sample Size: Arms: Location in submission: M53 section				dose. See attached table
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			x	See item 10
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	See item 10
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	See item 10
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	See item 10
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			Yes referenced previously reviewed definitive QTc study M06-809
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			Yes. Norvir SGC formulation already approved. NDA based on similar exposures as documented in SD

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					PK studies
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			PK exposure endpoints
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

Type of Study	Study ID	Objectives	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	M06-842a	Compare BA of 3 compressed tablets and 1 extrudate tablet with the marketed SGC	Partial crossover	4 tablet formulations and 1 capsule formulation, each 100 mg, oral	32	Healthy subjects	Single dose
BA	M10-235	Assess the effect of food on BA	Crossover	100 mg tablet, oral	27	Healthy subjects	Single dose
BE	M10-263a	Compare BA of tablet with marketed SGC	Crossover	Tablet, 100 mg, oral SGC, 100 mg, oral	24	Healthy subjects	Single dose
BE	M10-307	Compare BA of tablet with marketed SGC	Crossover	Tablet, 100 mg, oral SGC, 100 mg, oral	93	Healthy subjects	Single dose

---

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

/s/

Kimberly Struble
1/29/2009 11:14:10 AM