

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-417**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY MEMORANDUM

---

NDA: 22-417 (ritonavir [Norvir <sup>®</sup> ] tablets)	Original Submission Date: December 19, 2008
NDA: 20-659 (ritonavir [Norvir <sup>®</sup> ] oral solution)	Resubmission Date: December 11, 2009
Brand Name	Norvir <sup>®</sup>
Generic Name	Ritonavir
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Abbott Laboratories
Formulation; strength(s)	Ritonavir 100 mg oral tablets
Indication	Treatment of HIV-1 infection
Review Type	Class 1 resubmission of 505(b)(1) NDA

---

The applicant, Abbott Laboratories, resubmitted a 505(b)(1) NDA subsequent to a Complete Response (CR) letter that was issued by the Division of Antiviral Products on October 16, 2009. The CR letter was issued because of deficiencies that were identified by the Division of Manufacturing and Product Quality during an inspection of Abbott's manufacturing facility for the ritonavir tablets in Ludwigshafen, Germany.

No new or additional Clinical Pharmacology related information for the ritonavir tablets was included as part of the resubmission. An updated ritonavir tablet prescribing information (label) was submitted by the applicant that included new drug-drug information for ritonavir coadministration with salmeterol or sildenafil (Revatio). This information was previously approved in a supplement for ritonavir capsules and ritonavir oral solution (NDA 20-945 [S-26] and 20-659 [S-47], respectively).

The Office of Clinical Pharmacology (OCP) has reviewed the information in this resubmitted NDA. Approval of the resubmitted application for ritonavir tablets is supported by the information reviewed in the original submission-please see the Clinical Pharmacology review for NDA 22-417 and NDA 20-659 (S-45). The updated ritonavir tablet label is acceptable with minor editorial changes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-20659	SUPPL-45	ABBOTT LABORATORIES PHARMACEUTICAL PRODUCTS DIV	NORVIR (RITONAVIR) ORAL SOLUTION

---

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

---

/s/

---

STANLEY AU  
01/13/2010

KELLIE S REYNOLDS  
01/13/2010

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

---

NDA: 22-417	Submission Date: December 19, 2008
Brand Name	Norvir <sup>®</sup>
Generic Name	Ritonavir
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Sponsor	Abbott Laboratories
Formulation; strength(s)	Ritonavir 100 mg oral tablets
Indication	Treatment of HIV-1 infection
Review Type	505 (b)(1) NDA

---

**Table of Contents**

<b>1</b>	<b>Executive Summary</b> .....	<b>2</b>
1.1	Recommendation .....	2
1.2	Phase IV Commitments .....	3
1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics Findings .....	3
<b>2</b>	<b>Question based review (QBR)</b> .....	<b>11</b>
2.1	General Attributes of the Drug .....	11
2.2	General Clinical Pharmacology .....	13
2.3	Extrinsic Factors .....	15
2.4	General Biopharmaceutics .....	16
2.5	Analytical .....	18
<b>3</b>	<b>Appendices</b> .....	<b>19</b>
3.1	Individual Trial Review-M10-307 .....	19
3.2	Individual Trial Review-M10-235 .....	26
3.3	Review of Published Literature for Protease Inhibitors Coadministered with Pharmacokinetic Boosting Doses of Ritonavir .....	32
3.4	Office of Biostatistics Consult .....	42
3.5	References .....	44

## **1 Executive Summary**

Ritonavir (Norvir), a protease inhibitor, was approved in 1996 for the treatment of HIV-1 infection as both a 100 mg capsule and an 80 mg/mL solution. A brief review of ritonavir's regulatory approval history is located in section 2 (2.1.1).

The current new drug application (NDA) is for a tablet formulation of ritonavir. Two trials conducted with the proposed commercial ritonavir tablet formulation are discussed in this review: a single dose bioequivalence trial conducted under moderate fat conditions and a ritonavir tablet food effect trial.

This review discusses the use of ritonavir tablets at the currently approved adult dosage regimen of 600 mg twice daily for treatment of HIV-1 infection. Use of ritonavir tablets at adult ritonavir dosage regimens of 100 mg once daily to 200 mg twice daily to increase plasma concentrations of coadministered CYP 3A metabolized protease inhibitors through CYP 3A inhibition is also reviewed. Dosage regimens with coadministration of 100 mg once daily to 200 mg twice daily of ritonavir are included in the dosage and administration section of the U.S. prescribing information for the protease inhibitors fosamprenavir, darunavir, atazanavir, tipranavir, and saquinavir that are used in the treatment of HIV-1 infection.

### **1.1 Recommendation**

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA and the information provided supports the approval of the application. This conclusion is based on an examination of clinical trial reports, published or presented information available to the general public, and the FDA approved prescribing information for ritonavir and other protease inhibitors.

The pivotal bioequivalence trial comparing ritonavir tablets to ritonavir capsules was conducted under fed (moderate fat) conditions. A bioequivalence trial comparing the two ritonavir formulations under fasted conditions was not conducted. Therefore, the current draft prescribing information states that ritonavir tablets are to be administered with meals. Administration of ritonavir tablets with light or low fat meals or, for the "worst case scenario", under fasted conditions is a potential safety issue at higher ritonavir exposure with 600 mg twice daily dosing. The following information supports the fact that a potential safety issue exists: a) the predicted ritonavir exposures are as follows- ritonavir tablets (fasted) > ritonavir tablets (fed) > ritonavir capsules (fed) > ritonavir capsules (fasted), and b) in patients who switch from ritonavir capsules to tablets, there is no human pharmacokinetic data currently available regarding the magnitude of the difference in bioavailability for ritonavir tablets compared to ritonavir capsules under fasting conditions. The Division of Antiviral Products discussed the option of a postmarketing commitment or requirement comparing ritonavir tablets to ritonavir capsules under fasted conditions. However, a postmarketing commitment or requirement to evaluate ritonavir tablets compared to ritonavir capsules under fasted conditions is not necessary because the dosage and administration recommendation for ritonavir tablets would not be modified if the trial was conducted.

Modifications to the Dosage and Administration section in the saquinavir, atazanavir, and darunavir prescribing information (label) are not necessary because the three protease inhibitors are coadministered with pharmacokinetic boosting doses of ritonavir capsules under fed conditions.

Two protease inhibitors (fosamprenavir and tipranavir) can be coadministered either under fed or fasted conditions with pharmacokinetic boosting doses of ritonavir capsules. Tipranavir must be coadministered with ritonavir when used in the treatment of HIV-1 infection. A proposal to revise the prescribing information to specify that tipranavir should only be taken with meals when coadministered with ritonavir tablets and strategies for evaluating potential safety issues associated with tipranavir hepatotoxicity with ritonavir tablet coadministration will be discussed with tipranavir's sponsor. Modification of the fosamprenavir prescribing information to restrict dosage and administration to fed conditions when concurrently administered with ritonavir tablets is not necessary. The rationale for these changes is discussed in section 1.3, part C.

## **1.2 Phase IV Commitments**

No Phase IV commitments are necessary for this NDA.

## **1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

This review discusses two clinical purposes for ritonavir: a) the adult dosing of 600 mg twice daily used in the treatment of HIV-1 infection specified in the Dosage and Administration section of the ritonavir (Norvir) prescribing information and b) concurrent administration of ritonavir to increase plasma concentrations of coadministered CYP 3A metabolized protease inhibitors through CYP 3A inhibition. In adults, ritonavir dosage regimens of 100 mg once daily to 200 mg twice daily for pharmacokinetic boosting purposes are specified in the Dosage and Administration section of the following protease inhibitors: fosamprenavir, darunavir, atazanavir, tipranavir, and saquinavir. For the second purpose, the review focuses on the impact of higher bioavailability with ritonavir tablets on the exposure of coadministered protease inhibitors.

Abbott initially submitted four clinical trials as part of the NDA: two trials evaluated the relative bioavailability of experimental ritonavir tablet formulations compared to the soft gel capsules (M10-263 and M06-842), and two trials (a single dose bioequivalence trial conducted under moderate fat conditions [M10-307], and a ritonavir tablet food effect trial [M10-235]) were conducted with the proposed commercial ritonavir tablet formulation. The M10-263 and M06-842 trial reports were not examined as part of this review. No multiple dose ritonavir tablet trials were conducted.

Subsequently, in response to a request from the Division of Antiviral Products (DAVP) to provide information evaluating the impact of increased ritonavir tablet exposure on the pharmacokinetics of coadministered protease inhibitors, information presented at professional meetings and published scientific literature articles was submitted by Abbott. The information contained pharmacokinetic data for coadministered protease

inhibitors with a doubling of the ritonavir dosage regimen. The submitted information enabled the clinical pharmacology reviewer to evaluate the impact of the increased ritonavir tablet  $C_{max}$  (see below) compared to ritonavir capsules on the exposure of coadministered protease inhibitors.

The following issues are discussed in this review:

- The implications of the failed bioequivalence trial conducted under moderate fat conditions comparing ritonavir tablets to ritonavir capsules
  - What is the impact of higher bioavailability with ritonavir tablets on the safety of ritonavir 600 mg twice daily dosing?
  - What is the impact of higher bioavailability with ritonavir tablets on the safety of ritonavir with dosage regimens of 100 mg once daily to 200 mg twice daily under fed or fasted conditions?
  - What is the impact of higher bioavailability with ritonavir tablets on the exposure of coadministered protease inhibitors?
- The implications of increased bioavailability with ritonavir tablets under fasted compared to fed conditions
  - What is the impact on the safety of ritonavir 600 mg twice daily dosing when administered under fasted conditions or with light or low fat meals?
  - What is the impact on the exposures of coadministered protease inhibitors (fosamprenavir and tipranavir) that can be administered under fasted conditions with ritonavir capsules?

#### A) M10-307 and M10-235 clinical trial results

##### **M10-307 trial**

Based on the results of the M10-307 trial, ritonavir tablets are not bioequivalent to ritonavir capsules under moderate fat conditions. The bioequivalence assessment of ritonavir tablets compared to ritonavir capsules is displayed in Table 1 below.

92.8% confidence intervals were calculated because the bioequivalence trial used a group sequential design. Under moderate fat conditions, when a single 100 mg dose of ritonavir tablets or capsules was administered, the lower and upper limits for the 92.8% confidence intervals for  $AUC_{(0-inf)}$  were within 80% to 125%. However, 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%).

The intersubject variability (CV%) values for  $C_{max}$  and  $AUC_{(0-inf)}$  were not calculated by the sponsor. However, based on the submitted pharmacokinetic data, the intersubject variability calculations are as follows- $C_{max}$ : 66% (tablets); 74% (capsules),  $AUC_{(0-inf)}$ : 54% (tablets); 83% (capsules). Minor differences were observed in the intersubject variability for  $C_{max}$ . A lower intersubject variability for  $AUC_{(0-inf)}$  was observed for ritonavir tablets when comparing the two ritonavir formulations.

When the  $C_{max}$  pharmacokinetic data for individual subjects was reviewed, 68% of subjects displayed  $C_{max}$  values that were greater for ritonavir tablets.

**Table 1-Ritonavir bioequivalence assessment (tablets compared to capsules) with single dose administration of ritonavir 100 mg tablets or ritonavir 100 mg capsules**

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	92.8% Confidence Interval
A vs. B	$C_{max}$	0.367	0.290	1.264	1.150 – 1.389
	$AUC_t$	3.154	2.780	1.134	1.068 – 1.205
	$AUC_{\infty}$	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 logarithms.

### **M10-235 trial**

A food effect was observed for ritonavir tablets in the M10-235 trial. The ritonavir tablet food effect comparisons are displayed in Table 2 below. When a single 100 mg dose of ritonavir tablets was administered, high fat and moderate fat meals decreased the bioavailability of the ritonavir tablet when compared to fasted conditions. Under high fat conditions, when compared to fasted conditions, the 90% confidence intervals for  $C_{max}$  and  $AUC_{(0-\infty)}$  were not within 80% to 125%, which indicates the presence of a food effect for ritonavir tablets. The point estimates for  $C_{max}$  and  $AUC_{(0-\infty)}$  under high fat conditions were both decreased by 23%. Similar results were observed for ritonavir tablets under moderate fat conditions when compared to fasted conditions with point estimates for  $C_{max}$  and  $AUC_{(0-\infty)}$  decreased by 22% and 21%, respectively. When high fat meals were directly compared to moderate fat meals, a minimal change in ritonavir tablet bioavailability was observed. The sponsor did not evaluate the effect of low fat or light meals on ritonavir tablet bioavailability compared to fasted conditions.

In contrast to ritonavir tablets, ritonavir capsules demonstrate higher bioavailability under fed conditions. Based on the results from the two trials described above and food effect information from the ritonavir capsule prescribing information, a greater difference in exposure would be predicted for ritonavir tablets relative to ritonavir capsules under fasting conditions. The predicted ritonavir exposures are as follows: ritonavir tablets (fasted) > ritonavir tablets (fed) > ritonavir capsules (fed) > ritonavir capsules (fasted).

The intersubject variability (CV%) values for  $C_{max}$  and  $AUC_{(0-inf)}$  were not calculated by the sponsor. However, based on the submitted pharmacokinetic data, the intersubject variability calculations are as follows- $C_{max}$ : 45% (high fat meals), 55% (moderate fat meals), and 52% (fasting);  $AUC_{(0-inf)}$ : 46% (high fat meals), 51% (moderate fat meals), and 43% (fasting). For ritonavir tablets, minor differences were observed in the intersubject variability under high fat and moderate fat conditions when compared to fasted conditions.

**Table 2-Ritonavir food effect comparisons with single dose administration of ritonavir 100 mg tablets**

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
A vs. C (High-Fat vs. Fasting)	C <sub>max</sub>	0.384	0.501	0.766	0.659 – 0.891
	AUC <sub>t</sub>	3.044	3.981	0.765	0.694 – 0.842
	AUC <sub>∞</sub>	3.137	4.049	0.775	0.704 – 0.853
B vs. C (Moderate-Fat vs. Fasting)	C <sub>max</sub>	0.392	0.501	0.782	0.675 – 0.907
	AUC <sub>t</sub>	3.135	3.981	0.788	0.717 – 0.866
	AUC <sub>∞</sub>	3.218	4.049	0.795	0.724 – 0.873
A vs. B (High-Fat vs. Moderate-Fat)	C <sub>max</sub>	0.384	0.392	0.980	0.866 – 1.108
	AUC <sub>t</sub>	3.044	3.135	0.971	0.886 – 1.064
	AUC <sub>∞</sub>	3.137	3.218	0.975	0.890 – 1.068

\* Antilogarithm of the least squares means for logarithms.

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

## B) Assessment of ritonavir tablet bioavailability at 600 mg

### *What is the impact of higher bioavailability with ritonavir tablets on the safety of ritonavir 600 mg twice daily dosing?*

Based on the reviewed information, the predicted magnitude of increase for C<sub>max</sub> at 600 mg twice daily dosing under moderate fat conditions does not present a potential clinically significant safety issue. This conclusion also applies to high fat meals because the decrease in bioavailability was similar under moderate or high fat conditions. However, there are potential tolerability issues which patients should be aware of that are discussed below.

#### Supporting information

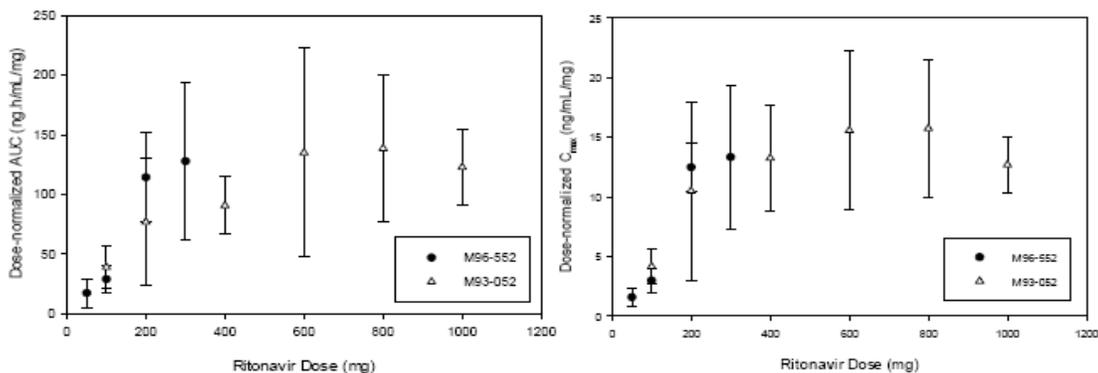
The sponsor did not conduct bioequivalence trials at doses higher than 100 mg, specifically the recommended adult dosage regimen for treatment of HIV-1 infection (600 mg twice daily [BID]) in the current ritonavir prescribing information. Because of the higher C<sub>max</sub> observed with ritonavir tablets compared to ritonavir capsules at 100 mg (point estimate of 26% with an upper limit of approximately 40%) under moderate fat conditions, information was reviewed to determine the predicted magnitude of increase in C<sub>max</sub> with ritonavir dosing at 600 mg. An assessment of the predicted magnitude of increase in C<sub>max</sub> at 600 mg provides critical information in determining whether a potential clinically significant safety issue (e.g. increased gastrointestinal adverse events) exists due to exceeding ritonavir exposure at 600 mg observed with the capsule formulation.

The sponsor's dose normalized AUC and C<sub>max</sub> ritonavir data (using data derived from other ritonavir formulations) indicates that from 50 mg to 200 mg, greater than dose proportional increases in ritonavir exposure are observed while a linearity trend is observed at most of the displayed doses greater than 200 mg (see Table 3 below). However, it is important to note that at all doses, significant intersubject variability for AUC and C<sub>max</sub> existed.

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 degree of gastrointestinal tolerance is an issue with the ritonavir dosage regimen of 600 mg twice daily under moderate or high fat conditions. Therefore, because of the higher expected  $C_{max}$  at 600 mg for ritonavir tablets compared to ritonavir capsules, 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.

**Table 3-Dose normalized ritonavir AUC (left) and  $C_{max}$  (right) pharmacokinetic data from the M93-052 and M96-552 trials**



***What is the impact on the safety of ritonavir 600 mg twice daily dosing when administered under fasted conditions or with light or low fat meals?***

While the ritonavir tablet data indicates that the highest expected ritonavir exposure for the tablet formulation occurs under fasted conditions that partially addresses the safety concerns, the magnitude of increase for AUC or  $C_{max}$  at 600 mg twice daily dosing with ritonavir tablets compared to ritonavir capsules either under fasted conditions or with light or low fat meals is unknown and is a potential clinically significant safety issue. The Division of Antiviral Products discussed the option of a postmarketing commitment or requirement comparing ritonavir tablets to ritonavir capsules under fasted conditions. However, a postmarketing commitment or requirement to evaluate ritonavir tablets compared to ritonavir capsules under fasted conditions is not necessary because the dosage and administration recommendation for ritonavir tablets would not be modified if the trial comparing the two ritonavir formulations was conducted.

Supporting information

Currently, it is recommended that ritonavir capsules 600 mg twice daily should be taken with meals, if possible. As previously indicated, the predicted ritonavir exposures are as

follows: ritonavir tablets (fasted) > ritonavir tablets (fed) > ritonavir capsules (fed) > ritonavir capsules (fasted). With the 600 mg twice daily dosage regimen, in patients either initiating treatment with ritonavir tablets or who are currently taking ritonavir capsules with light or low fat meals and switch to ritonavir tablets, a potential safety issue exists. The potential safety issue is the lack of bioequivalence data comparing ritonavir tablets to ritonavir capsules under conditions where the highest ritonavir exposures are possible: with light or low fat meals or, for the “worst case scenario”, under fasted conditions.

Because of the lack of bioequivalence data on administration of ritonavir tablets compared with ritonavir capsules under fasted conditions or with light or low fat meals and the higher ritonavir tablet bioavailability under fasted conditions, the current draft label for ritonavir tablets states that ritonavir is to be administered with meals (not under fasted conditions). The dosage and administration recommendation would not be revised if a trial comparing the two ritonavir formulations was conducted.

C) Impact of increased ritonavir tablet bioavailability for protease inhibitors coadministered with pharmacokinetic boosting doses of ritonavir

***What is the impact of higher bioavailability with ritonavir tablets on the safety of ritonavir with dosage regimens of 100 mg once daily to 200 mg twice daily under fed or fasted conditions?***

When ritonavir is used to increase the plasma concentrations of coadministered protease inhibitors under fed or fasted conditions, any concentration related safety issues with the increases in ritonavir exposure (AUC and  $C_{max}$ ) observed with ritonavir tablets are covered by the safety profile for the 600 mg twice daily dosage regimen.

***What is the impact of higher bioavailability with ritonavir tablets on the exposure of coadministered protease inhibitors?***

The following conclusions 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 with a doubling (100% increase) of the ritonavir dosage regimen 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 pharmacokinetic boosting doses of ritonavir tablets under fed (moderate or high fat) conditions. The benefit of treatment with tipranavir coadministered with

ritonavir tablets outweigh the risk of tipranavir hepatotoxicity under fed conditions in HIV-1 infected patients who are not coinfecting with Hepatitis B or C or do not have increased alanine transaminase (ALT) or aspartate transaminase (AST) values.

***What is the impact on the exposures of coadministered protease inhibitors (fosamprenavir and tipranavir) that can be administered under fasted conditions with ritonavir capsules?***

- The Dosage and Administration section in the saquinavir, atazanavir, and darunavir prescribing information (label) does not need to be revised because the three protease inhibitors are coadministered with ritonavir capsules under fed conditions.
- Two protease inhibitors (fosamprenavir and tipranavir) can be coadministered either under fed or fasted conditions with pharmacokinetic boosting doses of ritonavir capsules. Tipranavir must be coadministered with ritonavir when used in the treatment of HIV-1 infection. Modification of the tipranavir prescribing information to restrict dosage and administration to fed conditions when concurrently administered with ritonavir and strategies for evaluating potential safety issues with tipranavir hepatotoxicity with ritonavir tablet coadministration will be discussed with tipranavir's sponsor. The fosamprenavir dosage and administration information when concurrently administered with ritonavir will not be modified.

***Supporting information***

Adult ritonavir dosage regimens of 100 mg once daily to 200 mg twice daily are used to increase plasma concentrations of CYP 3A metabolized, coadministered protease inhibitors through CYP 3A inhibition. The U.S. prescribing information for the protease inhibitors fosamprenavir, darunavir, atazanavir, tipranavir, and saquinavir that are used in the treatment of HIV-1 infection include dosage regimens with ritonavir coadministration.

A clinical concern exists that the increase in plasma concentrations of coadministered protease inhibitors will be higher with ritonavir tablets than the increase in concentrations observed with ritonavir capsule coadministration. There is no human pharmacokinetic data currently available evaluating whether the higher  $C_{max}$  observed with ritonavir tablets compared to ritonavir capsules at 100 mg results in greater ritonavir CYP 3A inhibition of the coadministered protease inhibitor's CYP 3A metabolism.

Information was submitted by Abbott that was presented at professional meetings and from published scientific literature articles to address this issue. Additional relevant published information was identified by the clinical pharmacology reviewer. The information was examined by the clinical pharmacology reviewer 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 compared with ritonavir capsules when administered with moderate fat meals.

Detailed information for each of the protease inhibitors when coadministered with ritonavir for pharmacokinetic boosting purposes is located in section 3.

Table 4A displays information provided by Abbott on the impact of a 100% increase in ritonavir dose on the pharmacokinetics of coadministered protease inhibitors (excluding fosamprenavir) and Table 4B displays information on the pharmacokinetics of amprenavir with coadministration of fosamprenavir 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 <sup>+</sup>		
	$C_{max}$ ( $\mu\text{g/mL}$ )	$AUC_{\tau}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$C_{min}$ ( $\mu\text{g/mL}$ )
<b>Atazanavir (Harris M et al.,<sup>1</sup> Figure 2a<sup>^</sup>)</b>			
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
<b>Darunavir (Sekar V et al.,<sup>2</sup> Poster TUPE 0083, Table 1)</b>			
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
<b>Tipranavir (MacGregor TR et al.,<sup>3</sup> Table 2)<sup>&amp;</sup></b>			
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
<b>Saquinavir (Kilby JM et al.,<sup>4</sup> Table 2)</b>			
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.

<sup>^</sup> 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<sup>5</sup>) are presented.

&  $C_{max}$  and AUC are presented in  $\mu\text{M}$  and  $\text{h}\cdot\mu\text{M}$ , respectively.

NA = not available

**Table 4B- $C_{max}$ ,  $t_{max}$ ,  $AUC_{(0-\tau)}$ , and  $C_{min}$  amprenavir pharmacokinetic data with fosamprenavir coadministration with ritonavir**

Regimen	$C_{max}$ ( $\text{mcg/mL}$ )	$T_{max}$ (hours) <sup>*</sup>	$AUC_{24}$ ( $\text{mcg}\cdot\text{hr/mL}$ )	$C_{min}$ ( $\text{mcg/mL}$ )
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).

Two protease inhibitors can be coadministered either under fed or fasted conditions with ritonavir capsules (fosamprenavir and tipranavir). In evaluating the potential for ritonavir to potentially alter the exposure of coadministered protease inhibitors, there are multiple

mechanisms involved that can change tipranavir exposure but fosamprenavir exposure is altered through CYP 3A inhibition only. Tipranavir must be coadministered with ritonavir when used in the treatment of HIV-1 infection. While the benefit of treatment with tipranavir coadministered with ritonavir tablets outweigh the risk of tipranavir hepatotoxicity under fed conditions in HIV-1 infected patients who are not coinfecting with Hepatitis B or C or do not have increased alanine transaminase (ALT) or aspartate transaminase (AST) values, the benefit does not outweigh the risk with ritonavir tablets under fasted conditions. A proposal to revise the prescribing information to specify that tipranavir should only be taken with meals when coadministered with ritonavir tablets and strategies for evaluating potential safety issues with tipranavir hepatotoxicity with ritonavir tablet coadministration will be discussed with tipranavir's sponsor. Modification of the fosamprenavir prescribing information to restrict dosage and administration to fed conditions only when concurrently administered with ritonavir tablets is not necessary because it is not anticipated that increases in ritonavir tablet exposure would result in clinically significant changes in fosamprenavir exposure under fasted conditions. Therefore, no safety issues are expected for fosamprenavir.

## 2 Question based review (QBR)

### 2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Ritonavir (Norvir) was approved in 1996 for treatment of HIV-1 infection as both a 100 mg capsule and an 80 mg/mL solution. The capsule (a semi solid formulation) (b) (4)

Ritonavir's safety and efficacy was established with the 80 mg/mL solution and linked to the 100 mg semi solid capsules through bioequivalence trials.

In November 1997, a New Drug Application (NDA) was submitted by the sponsor, Abbott, for a new ritonavir capsule formulation. The new ritonavir formulation's improvements included enhanced room temperature stability (b) (4)

(b) (4) The new formulation was a soft gelatin capsule that contained a ritonavir solution (b) (4)

During the review process, in July 1998, Abbott reported that ritonavir dissolution testing had failed because of a new ritonavir polymorphic form (Form II) that was less soluble than the existing Form I of ritonavir. The soft gelatin capsule formulation was subsequently modified. The initial NDA for the soft gel capsules was not approved due to incomplete Chemistry, Manufacturing, and Controls (CMC) and missing biopharmaceutics information for the modified soft gelatin capsule formulation. The NDA for the soft gelatin capsules was subsequently resubmitted and approved. The approved soft gelatin capsules were not bioequivalent to the original semi solid capsules and demonstrated higher bioavailability. However, the differences in ritonavir bioavailability were determined not to be clinically significant. In the U.S., soft gelatin

capsules are the currently marketed ritonavir formulation.

Ritonavir is also used to increase the plasma concentrations of CYP 3A metabolized coadministered protease inhibitors through CYP 3A inhibition. The U.S. prescribing information for the protease inhibitors fosamprenavir, darunavir, atazanavir, tipranavir, and saquinavir that are used in the treatment of HIV-1 infection include dosage regimens with ritonavir coadministration.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The ritonavir tablets can be stored without refrigeration. Table 1 below provides information on the active and inactive ingredients for the proposed to be marketed 100 mg ritonavir tablets.

**Table 1-Active and inactive ingredients for the proposed to be marketed 100 mg ritonavir tablets**

Ingredients	Unit Formula (Per Tablet)	Primary Function	Compendia Status	
(b) (4)				
<i>Drug Substance</i>				
Ritonavir	100.0 mg	Active	USP	
<i>Excipients</i>				
Copovidone, (b) (4)	(b) (4)		NF	
Sorbitan monolaurate			NF	
Colloidal silicon dioxide			NF	
(b) (4)				
Sodium stearyl fumarate			NF	
Colloidal silicon dioxide			NF	
Anhydrous dibasic calcium phosphate			USP	
<b>Uncoated Tablet Weight</b>				N/A
(b) (4)				(b) (4)
(b) (4)				USP
<b>Total Tablet Weight</b>	787.4 mg	N/A	N/A	
(b) (4)				
(b) (4)				

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

### Therapeutic indication

The therapeutic indication is the treatment of HIV-1 infection.

### Mechanism of action

Ritonavir's antiviral mechanism of action is to prevent the HIV protease enzyme from processing the gag-pol polyprotein precursor. Subsequently, this blocks the development of mature virus particles.

When used to increase the plasma concentrations of coadministered protease inhibitors that are CYP 3A substrates, ritonavir's mechanism of action is through inhibition of the CYP 3A enzyme system.

#### 2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed new ritonavir formulation is a 100 mg tablet. The dosage regimen is the same as for ritonavir capsules. In adults, for the treatment of HIV-1 infection, the maintenance dosage regimen for ritonavir is 600 mg orally twice daily. The initial dosage regimen is 300 mg orally twice daily, with dose increases of 100 mg twice daily every two to three days.

Use of ritonavir to increase the plasma concentrations of coadministered protease inhibitors that are CYP 3A substrates through inhibition of the CYP 3A enzyme system is not included in the Dosage and Administration section of ritonavir's U.S. prescribing information. Dosage regimens with coadministration of 100 mg once daily to 200 mg twice daily of ritonavir are included in the dosage and administration section of the U.S. prescribing information for the protease inhibitors fosamprenavir, darunavir, atazanavir, tipranavir, and saquinavir that are used in the treatment of HIV-1 infection.

## **2.2 General Clinical Pharmacology**

### 2.2.1 What are the design features of the clinical pharmacology and clinical trials used to support dosing or claims?

A single dose bioequivalence trial comparing ritonavir tablets to ritonavir capsules conducted under moderate fat conditions and a ritonavir tablet food effect trial were conducted using the proposed to be marketed 100 mg ritonavir tablets.

Abbott was requested to provide information to support the conclusion that the increase in  $C_{max}$  observed with ritonavir tablets when compared to ritonavir capsules does not result in clinically significant changes in the exposure of coadministered protease inhibitors. Information from publicly available sources, including presentations from professional meetings, literature articles, and the FDA approved prescribing information were examined by the clinical pharmacology reviewer. Additional information is provided in section 3.

2.2.2 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The efficacy of ritonavir in the treatment of HIV-1 infection has been established in prior ritonavir clinical trials submitted as part of an NDA. The use of ritonavir to increase the plasma concentrations of coadministered protease inhibitors has been established in the clinical trials for coadministered protease inhibitors submitted with the corresponding NDAs. Therefore, there are no efficacy issues that need to be addressed for the ritonavir tablet NDA.

Formal exposure response trials have not been conducted for ritonavir. For the adult ritonavir 600 mg twice daily dosage regimen used in the treatment of HIV-1 infection, the degree of gastrointestinal tolerance is an issue for patients. 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.

For ritonavir dosage regimens that are used to increase the plasma concentrations of coadministered protease inhibitors in the treatment of HIV-1 infection, any concentration related safety issues with the increases in ritonavir exposure (AUC and  $C_{max}$ ) observed with ritonavir tablets are covered by the safety profile for the 600 mg twice daily dosage regimen.

2.2.3 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The single dose bioequivalence trial was conducted using a 100 mg ritonavir dose. No ritonavir tablet trials were conducted evaluating the 600 mg dose in the ritonavir prescribing information.

As discussed in section 1.3, part B, the sponsor provided dose normalized ritonavir AUC and  $C_{max}$  data (using data derived from other ritonavir formulations) which indicates that dose proportionality is not observed from 50 mg to 200 mg, while a linearity trend is observed at most of the displayed doses greater than 200 mg. However, it is important to note that at all doses, significant intersubject variability for AUC and  $C_{max}$  existed.

Based on the dose-concentration relationship, when compared to ritonavir capsules, it is not anticipated that increases in ritonavir exposure (AUC and  $C_{max}$ ) for ritonavir tablets at a single dose of 600 mg would be higher than the increases in exposure observed at a single dose of 100 mg.

## 2.3 Extrinsic Factors

### 2.3.1 Drug-drug interactions

#### 2.3.1.1 What other co-medications are likely to be administered to the target patient population?

### **Use of ritonavir for pharmacokinetic boosting purposes**

The use of ritonavir to increase the plasma concentrations of coadministered protease inhibitors in the treatment of HIV-1 infection is discussed in section 1.3.

### **Drug-drug interactions with concurrent ritonavir coadministration**

Based on the review of the available published literature, the drug-drug interaction information for medications other than concurrently administered protease inhibitors presented in the ritonavir capsule label is expected to apply to the ritonavir tablets.

#### CYP 3A inhibition

A trial by Mathias et al evaluated the effect on midazolam, which is primarily CYP 3A metabolized, when ritonavir, a CYP 3A inhibitor, was coadministered with elvitegravir once daily in healthy subjects for ten days. Ritonavir doses of 20 mg, 50 mg, 100 mg, and 200 mg were evaluated. The authors did not specifically comment on the CYP3A inhibitory potential for elvitegravir, however elvitegravir is not expected to inhibit CYP 3A to a significant degree.

Maximum ritonavir inhibitory effects on midazolam were reported at 100 mg once daily. Therefore, for drug-drug interactions that occur because of ritonavir CYP 3A inhibition, no clinically significant difference in the magnitude of increase in exposure when coadministered with ritonavir tablets compared to ritonavir capsules is anticipated. However, if a drug-drug interaction can occur through multiple mechanisms (e.g. ritonavir CYP 3A inhibition and P-glycoprotein [P-gp] inhibition), the conclusion from this trial that maximum ritonavir inhibitory effects occurs at 100 mg can not be applied in evaluating the potential for ritonavir to alter the exposure of a concurrently administered medication.

#### CYP 2D6 inhibition

Ritonavir also inhibits the CYP 2D6 enzyme system. For drug interactions that occur because of ritonavir CYP 2D6 inhibition, the increase in  $C_{max}$  with ritonavir tablets is not expected to result in a clinically significant difference in the magnitude of increase compared to ritonavir capsules. At 600 mg twice daily dosing, greater ritonavir CYP 2D6 inhibition is expected compared to lower doses used for pharmacokinetic boosting. A published trial (Aarnoutse et al 2005) cited previously published data that reported a 145% increase in desipramine with ritonavir 500 mg twice daily dosing. However, for ritonavir tablets, the magnitude of the ritonavir  $C_{max}$  increase at 600 mg is not expected to

exceed the increase of up to 40% in  $C_{max}$  for a single dose of 100 mg. The increase of approximately 40% in  $C_{max}$  would not be expected to significantly change ritonavir's CYP 2D6 inhibitory effects; therefore the clinical recommendations regarding ritonavir drug-drug interactions with CYP 2D6 substrates are unchanged.

At lower doses used for pharmacokinetic boosting, ritonavir is not a strong CYP 2D6 inhibitor (Aarnoutse et al 2005). A published trial evaluating the effect of ritonavir 100 mg twice daily on a single dose of desipramine, which is primarily a CYP 2D6 substrate, reported that ritonavir increased desipramine geometric mean  $AUC_{(0-\infty)}$  by 26% (Aarnoutse et al 2005).

### Induction

Ritonavir reportedly induces CYP 2C9, 2C19, 2B6, 1A2, 3A and UGT enzymes. Ritonavir does not demonstrate strong CYP 3A induction effects. It appears that at lower doses, ritonavir has less induction effects than at higher doses. While the clinical significance of up to an approximately 40% increase in  $C_{max}$  for ritonavir tablets on ritonavir's induction effects is unknown, the impact should be minimal because statistically significant differences in the overall exposure (AUC) for ritonavir capsules and ritonavir tablets were not observed.

Ritonavir titrated up to 400 mg twice daily was reported to have minimal CYP 3A induction effects on alfentanil at steady state (Kharasch et al 2008). Published information from Abbott derived from modeling results reported that ritonavir induction effects were less at lower ritonavir doses (e.g. 200 mg every 12 hours) compared to higher doses (e.g. 500 mg every 12 hours) [Hsu et al 1997], with reported values of 12% and 45%, respectively.

## **2.4 General Biopharmaceutics**

2.4.1 What is the relative bioavailability for the proposed to-be-marketed tablet formulation relative to the currently approved capsule formulation in the pivotal bioequivalence trial?

Ritonavir tablets are not bioequivalent to ritonavir capsules under moderate fat conditions. Under moderate fat conditions, when a single 100 mg dose of ritonavir tablets or capsules was administered, the lower and upper limits for the 92.8% confidence intervals for  $AUC_{(0-inf)}$  were within 80% to 125%. However, the upper limit for the 92.8% confidence intervals for  $C_{max}$  exceeded 125%. The point estimate for  $C_{max}$  was increased by 26% (92.8% confidence intervals:  $\uparrow 15$ - $\uparrow 39\%$ ), and the point estimate for  $AUC_{(0-inf)}$  was increased by 10% (92.8% confidence intervals:  $\uparrow 4$ - $\uparrow 17\%$ ) for ritonavir tablets relative to ritonavir capsules.

Based on the submitted pharmacokinetic data, the intersubject variability calculations are as follows:  $C_{max}$ : 66% (tablets); 74% (capsules),  $AUC_{(0-inf)}$ : 54% (tablets); 83% (capsules). Minor differences were observed in the intersubject variability for  $C_{max}$ . A

lower intersubject variability for  $AUC_{(0-\infty)}$  was observed for ritonavir tablets when comparing the two ritonavir formulations.

2.4.2 What are the safety or efficacy issues, if any, for the BE trial that failed to meet the 92.8% confidence intervals using equivalence limits of 80-125%?

While the increased  $C_{max}$  under moderate fat conditions is not a safety issue for either 600 mg twice daily or 100 mg once daily to 200 mg twice daily, a greater difference in exposure would be predicted for ritonavir tablets relative to ritonavir capsules under fasting conditions (see question 2.4.4 for ritonavir tablet food effect information). The predicted ritonavir exposures are as follows: ritonavir tablets (fasted) > ritonavir tablets (fed) > ritonavir capsules (fed) > ritonavir capsules (fasted). The higher ritonavir exposure with 600 mg twice daily dosing under fasted conditions is a potential safety issue because of the potential for increased gastrointestinal adverse events such as nausea, vomiting, abdominal pain or diarrhea.

The Division of Antiviral Products discussed the option of a postmarketing commitment or requirement comparing ritonavir tablets to ritonavir capsules under fasted conditions. However, a postmarketing commitment or requirement to evaluate ritonavir tablets compared to ritonavir capsules under fasted conditions is not necessary because the dosage and administration recommendation for ritonavir tablets would not be modified if the trial was conducted.

The current draft ritonavir tablet label states that ritonavir tablets are to be taken with meals. It is recommended that ritonavir capsules 600 mg twice daily should be taken with meals, if possible. In patients either initiating treatment at 600 mg twice daily with ritonavir tablets or who are currently administering ritonavir capsules 600 mg twice daily with light or low fat meals and switch to ritonavir tablets, a potential safety issue exists.

While the ritonavir tablet data indicates that the highest expected ritonavir exposure for the tablet formulation occurs under fasted conditions that partially addresses the safety concerns, the potential safety issue is the lack of bioequivalence data comparing ritonavir tablets to ritonavir capsules under conditions where the highest ritonavir exposures are possible: with light or low fat meals or, for the “worst case scenario”, under fasted conditions.

Potential safety or efficacy issues for protease inhibitors concurrently administered with pharmacokinetic boosting doses of ritonavir tablets are discussed in section 3.3.

2.4.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

See section 1.3, part B for information in regards to the supportive clinical pharmacology information for approval of the to be marketed 100 mg ritonavir tablets. Information supporting the use of protease inhibitors concurrently administered with pharmacokinetic

boosting doses of ritonavir tablets is discussed in section 1.3, part C and section 3.3.

2.4.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A food effect was observed for ritonavir tablets in the M10-235 trial. When a single 100 mg dose of ritonavir tablets was administered, both high fat and moderate fat meals decreased the bioavailability of the ritonavir tablets. The observed decreases in ritonavir tablet bioavailability when administered with moderate and high fat meals were similar.

The sponsor did not evaluate the effect of light or low fat meals on ritonavir tablet bioavailability compared to fasted conditions.

The intersubject variability (CV%) values for  $C_{max}$  and  $AUC_{(0-inf)}$  were not calculated by the sponsor. However, based on the submitted pharmacokinetic data, the intersubject variability calculations are as follows- $C_{max}$ : 45% (high fat meals), 55% (moderate fat meals), and 52% (fasting);  $AUC_{(0-inf)}$ : 46% (high fat meals), 51% (moderate fat meals), and 43% (fasting). For ritonavir tablets, minor differences were observed in the intersubject variability under high fat and moderate fat conditions when compared to fasted conditions.

Because of the lack of bioequivalence data for ritonavir tablets compared with ritonavir capsules under fasted conditions or with light or low fat meals and the higher ritonavir tablet bioavailability under fasted conditions, the current draft label for ritonavir tablets states that ritonavir is to be administered with meals (not under fasted conditions).

Two protease inhibitors (fosamprenavir and tipranavir) can be coadministered either under fed or fasted conditions with pharmacokinetic boosting doses of ritonavir capsules. Tipranavir must be coadministered with ritonavir when used in the treatment of HIV-1 infection. Modification of the tipranavir prescribing information to restrict dosage and administration to fed conditions only when concurrently administered with ritonavir tablets and strategies for evaluating potential safety issues associated with tipranavir hepatotoxicity with ritonavir tablet coadministration will be discussed with tipranavir's sponsor. The fosamprenavir dosage and administration information when concurrently administered with ritonavir will not be modified. The rationale for these recommendations is discussed in section 1.3, part C.

No labeling changes are necessary for the three protease inhibitors (atazanavir, darunavir and saquinavir) coadministered with pharmacokinetic boosting doses of ritonavir capsules under fed conditions.

## 2.5 Analytical

An LC/MS/MS method for ritonavir was validated by   (b) (4)

The lower limit of quantification for the ritonavir method was 1 ng/mL and the upper

limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for ritonavir with the method validation. The ritonavir inter-run accuracy values for the low (3 ng/mL), medium (50 ng/mL), and high (800 ng/mL) QC samples were -4.1%, -5.1%, and -4.0%, respectively. The ritonavir inter-run precision values for the low (3 ng/mL), medium (50 ng/mL), and high (800 ng/mL) QC samples were 5.6%, 2.5% and 3.0%, respectively.

There were no stability issues identified in the ritonavir method validation report.

Please refer to the individual trial reviews (section 3) for information on the bioanalysis of ritonavir plasma samples in the M10-307 and M10-235 trials.

### **3 Appendices**

#### **3.1 Individual Trial Review-M10-307**

##### **1. Title**

Comparison of the Single-Dose Bioavailability of a Ritonavir 100 mg Film-Coated Tablet Relative to a Ritonavir 100 mg Soft Gelatin Capsule in Healthy Adult Subjects

##### **2. Objectives**

The primary objective of this trial was to evaluate the single dose bioavailability of a 100 mg ritonavir tablet compared to a 100 mg ritonavir capsule.

##### **3. Trial Design**

M10-307 was a single dose, open label, crossover trial using a group sequential design conducted in healthy male and female subjects. The trial design differed from a traditional bioequivalence trial in that the protocol was divided into two separate parts: Stage 1 and Stage 2 (see Table 1).

100 subjects were to be enrolled in Stage 1 and if necessary, 60 additional subjects were to be enrolled in Stage 2. If subjects were enrolled in Stage 2, the plan was to include data from both Stage 1 and Stage 2 in the trial's statistical analyses.

The following dosage regimens were administered:

- 1) Regimen A-a single dose of ritonavir 100 mg tablet administered with a moderate fat meal.
- 2) Regimen B-a single dose of ritonavir 100 mg capsule administered with a moderate fat meal.

**Table 1-Dosing sequences for the M10-307 protocol**

Sequence Group	N (Planned)	Stage 1 Regimens		Planned Interim Analysis	Stage 2 Regimens		
		Period 1	Period 2		Period 1	Period 2	
I	50	A	B				
II	50	B	A				
III	30				A	B	
IV	30				B	A	
		≥ 7 days washout between doses				≥ 7 days washout between doses	

An equal number of subjects were enrolled in each trial group in Stage 1 and crossed over. No subjects were enrolled into Stage 2. A minimum of a 7 day washout period separated the dosing between the two dosing regimens. The washout period is appropriate because the ritonavir mean elimination half life is 3 to 5 hours.

The rationale for using a group sequential design was not included in the M10-307 clinical trial report. However, the Clinical Overview information included as part of the NDA submission indicates that a 21% higher point estimate for  $C_{max}$  was observed based on results from the M10-263 trial evaluating an experimental ritonavir tablet formulation compared to the marketed ritonavir capsule. Subsequently, a group sequential design was used for the M10-307 trial because of the potential for a higher  $C_{max}$  with the ritonavir tablets resulting in bioequivalence not being demonstrated for ritonavir tablets compared to ritonavir capsules.

All ritonavir doses were administered in the morning on Day 1 under moderate fat conditions with 240 mL of water. Ritonavir was administered approximately 30 minutes after breakfast was initiated. Information on the specific composition of meals administered on Day 1 in each period is displayed in Table 2.

Conducting the pivotal bioequivalence trial for ritonavir tablets under moderate fat conditions deviates from the recommendation in the FDA guidance document (Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations: March 2003). The guidance document recommends that medications in a single dose bioequivalence trial should be administered under fasting conditions. However, DAVP concurred with conducting the bioequivalence trial under moderate fat conditions because ritonavir is normally administered under fed conditions with 600 mg twice daily dosing to decrease potential gastrointestinal adverse events.

**Table 2-Composition of meals administered on Day 1 in each period**

<b>Meal</b>	<b>Approximate Time</b>	<b>Menu</b>	<b>Meal Composition</b>
Breakfast	0830	4 oz. scrambled eggs, 2 slices wheat toast, 1 medium banana, 4 oz. hash browns, 1 cup 1% milk, 1 pat (5 g.) margarine and ½ oz. jelly	857 Kcal; 31% calories from fat, 56% calories from carbohydrates and 13% calories from protein
Lunch	1315	BBQ Beef Sandwich (3 oz. beef, 1 steak bun—3 oz.), 4 oz. macaroni salad, 3 oz. grapes, 2 oatmeal raisin cookies, 1 cup 1% milk, 12 oz. caffeine-free soda, or water	801-943 Kcal; 25-30% calories from fat, 53-61% calories from carbohydrates and 14-18% calories from protein
Dinner	2000	4 oz. chicken fried steak, 4 oz. mashed potatoes, 3 oz. gravy, 4 oz. green beans, 4 oz. applesauce, 4 oz. vanilla pudding, 1 cup 1% milk, 12 oz. caffeine-free soda, or water	572-728 Kcal; 29-36% calories from fat, 52-63% calories from carbohydrates and 9-14% calories from protein
Snack	2300	1 ½ oz. pretzels, 12 oz. caffeine-free soda	321 Kcal; 4% calories from fat, 90% calories from carbohydrates and 6% calories from protein

#### **4. Rationale for Doses Used in the Trial**

The ritonavir dose evaluated in this study, 100 mg, is the only proposed to be marketed dosage strength for ritonavir tablets.

#### **5. Drugs Used in the Trial**

Ritonavir 100 mg tablets (formulation D0700425) were administered in this study. In addition, ritonavir 100 mg capsules (the currently marketed ritonavir formulation), were administered to subjects as the reference formulation.

#### **6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis**

##### *Sample Collection*

For each period, on Day 1, blood samples were collected for determination of ritonavir concentrations in tubes containing an anticoagulant (EDTA). Blood samples were collected within 10 minutes before dose administration and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30 and 36 hours postdose.

## *Bioanalysis*

Ritonavir concentrations were analyzed using a validated LC/MS/MS method. The samples were analyzed by [REDACTED] <sup>(b) (4)</sup> A Division of Scientific Investigations (DSI) audit of the M10-307 bioanalysis and ritonavir method validation did not identify any critical deficiencies. Therefore, no inspection observations (Form 483) were issued by DSI.

A review of the ritonavir method validation and M10-307 bioanalytical report identified the following issues:

- 1) The validation report did not include the refrigerated (4°C) solution stability data for ritonavir (ABT-538) at the following concentrations: 1 mg/mL, 100 µg/mL, 100 ng/mL and 20 ng/mL. The source cited in the ritonavir method validation report is ORS report 147110 (Protocol M97-720 study binder, Run 11).
- 2) During sample analysis for the M10-307 protocol, samples that were reanalyzed due to the fact that the initial reported concentration were higher than the upper limit of quantification in run #29 were rejected because the acceptance criteria for the dilution QCs were not met. Specific reason(s) or potential reason(s) were not provided explaining why the acceptance criteria for the dilution QCs were not met.
- 3) During sample analysis for the M10-307 protocol, samples 793 to 804 were reanalyzed due to low internal standard response. Information was not provided on the following items:
  - a) Specific reason(s) or potential reason(s) why ritonavir concentrations could not be quantified for these samples.
  - b) Specific reason(s) or potential reason(s) for the low internal standard response.
- 4) During initial analysis of sample numbers 2487 to 2498 (12 samples) in run 24 for the M10-307 protocol, it was reported that a double spiking of internal standard potentially occurred. Consequently, the median of the concentration results from run 24 and run 31 (in run 31, the 12 samples were reanalyzed in duplicate) were reported in the final results. While the doubling of the internal standard resulted in inaccurate and lower than expected ritonavir concentration results for run 24, the ritonavir concentrations were not adjusted when calculating the median concentration from runs 24 and 31. Therefore, there are 12 samples where the actual ritonavir concentrations are higher than the reported ritonavir concentrations.
- 5) In regards to the ritonavir reference standard, the interval retest date was August 21, 2007 and samples were analyzed from March through June 2008 for the M10-235 and M10-307 protocols. However, no information was provided on whether the ritonavir reference standard was recertified before August 21, 2007.
- 6) If the ritonavir reference standard was not recertified, Abbott needs to provide

information on how it was verified that there are no stability or purity issues with the ritonavir reference standard used in analyzing samples for the M10-235 and M10-307 protocols.

7) For the ritonavir method validation, Abbott needs to clarify if the experiments were conducted before the interval retest date for the ritonavir reference standard (no certificate of analysis [COA] was provided with the ritonavir method validation report).

8) If there is no certificate of analysis for the internal standard (b) (4) Abbott needs to provide information on how it was verified that there are no stability or purity issues with the (b) (4) reference standard used in analyzing samples for the M10-235 and M10-307 protocols or for the ritonavir method validation.

In discussions with the DSI auditor, the auditor stated that the stock solution stability was acceptable and that samples 793 to 804 were reanalyzed because of a pipetting error for the internal standard with the initial analysis. The auditor did not have any additional information on the cause(s) of the failure of dilution quality control samples (QCs).

The issues identified in items #5 through #8 were sent to the sponsor for follow up. The follow up responses from Abbott were acceptable. Abbott indicated that the reference standard was recertified prior to analysis of samples for the M10-235 and M10-307 trials. The ritonavir method validation was conducted after the reference standard was recertified. The internal standard was evaluated during method validation and bioanalysis to verify that there were no issues with the material used.

There were no deficiencies that the clinical pharmacology reviewer believes would affect the validity of the bioequivalence trial results.

The lower limit of quantification for the ritonavir method was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for ritonavir with the M10-307 sample analysis. For the M10-307 sample analysis, the ritonavir inter-run accuracy values for the low (3 ng/mL), medium (50 ng/mL), and high (800 ng/mL) QC samples were -0.3%, 1.2%, and -1.25%, respectively. The ritonavir inter-run precision values for the low (3 ng/mL), medium (50 ng/mL), and high (800 ng/mL) QC samples were 6.9%, 6.2% and 6.7%, respectively.

### *Pharmacokinetic Assessments*

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including the following parameters:  $C_{max}$ ,  $t_{max}$ , the elimination half life ( $t_{1/2}$ ),  $AUC_{(0-t)}$ , and  $AUC_{(0-inf)}$ .

Scheduled sampling times were used to calculate pharmacokinetic parameters for subjects, with the exception of the subjects displayed in Table 3 that did not have actual sampling times that were either within 10% of the scheduled blood sampling time for samples collected from 0 to 5 hours or within 30 minutes of the scheduled blood

sampling time for samples collected from 6 to 36 hours. For these subjects, actual sampling times were used in calculating pharmacokinetic parameters.

**Table 3-Subjects with actual sampling times used in calculating pharmacokinetic parameters**

Subject Number	Period	Planned Time (h)	Actual Time (h)	Difference
1005	1	36.0	36.8	48 minutes late
1006	1	0.5	0.55	3 minutes late
1008	1	0.5	0.55	3 minutes late
1011	1	36.0	36.5	30 minutes late
1032	1	1.0	1.1	6 minutes late
1033	1	1.0	1.1	6 minutes late
1034	1	1.0	1.1	6 minutes late
1035	1	1.0	1.1	6 minutes late
1035	1	2.0	2.32	19 minutes late
1036	1	1.0	1.1	6 minutes late
1037	1	1.0	1.1	6 minutes late
1038	1	1.0	1.1	6 minutes late
1040	1	1.0	1.1	6 minutes late
1042	1	1.0	1.1	6 minutes late
1045	1	1.0	1.1	6 minutes late
1050	1	0.5	0.55	3 minutes late
1050	1	1.0	1.13	8 minutes late
1051	2	0.5	0.6	6 minutes late
1065	1	30.0	34.0	240 minutes late
1079	1	0.5	0.58	5 minutes late
1085	2	0.5	0.55	3 minutes late

### *Statistical Analysis*

Using ANOVA, the antilogarithm of the logarithmic least squares means were calculated and 92.8% confidence intervals for ritonavir were derived based on the antilogarithm of the difference of the pharmacokinetic parameter's logarithmic least squares means for the test and reference arms. A bioequivalence test was performed evaluating the relative bioavailability of the ritonavir tablets (test arm) compared to ritonavir capsules (reference arm).

Bioequivalence was demonstrated if the 92.8% confidence intervals for  $C_{max}$  and AUC were within 80% to 125%. 92.8% confidence intervals were used instead of the traditional 90% confidence intervals because the bioequivalence trial used a group sequential design that allows for the possibility of multiple data analysis iterations. The use of 92.8% confidence intervals does not alter the conclusions of the bioequivalence trial. A consult submitted to the Office of Biostatistics requesting feedback on the appropriateness of using a group sequential design for a pivotal bioequivalence trial indicated that while 93.6% confidence intervals were more appropriate because of the one sided futility criteria in Stage 1, there was no change in the bioequivalence conclusions for AUC or  $C_{max}$  (the Office of Biostatistics consult is located in Appendix 3.4).

## 7.1 Pharmacokinetic and Statistical Results

93 subjects enrolled in the trial, and 84 subjects (47 males and 37 females) completed both arms of the trial. Eight subjects withdrew or were withdrawn prior to Period 2 dosing (subjects 1004, 1013, 1022, 1024, 1026, 1046, 1068, and 1092). One subject (subject 1012) withdrew from the study after Period 2 dosing. All nine subjects were excluded from the statistical analyses.

The ritonavir pharmacokinetic results for ritonavir tablets and ritonavir capsules are displayed in Table 4 and the bioequivalence assessment is displayed in Table 5.

**Table 4-Ritonavir pharmacokinetic parameters under moderate fat conditions with single dose administration of ritonavir 100 mg tablets or ritonavir 100 mg capsules**

Pharmacokinetic Parameters (units)	Regimen A: Test Tablet <sup>f</sup> (N = 84)	Regimen B: Reference SGC <sup>f</sup> (N = 84)
T <sub>max</sub> (h)	4.4 ± 1.2 <sup>§</sup>	6.0 ± 4.0
C <sub>max</sub> (µg/mL)	0.44 ± 0.29 <sup>§</sup>	0.35 ± 0.26
AUC <sub>t</sub> (µg•h/mL)	3.6 ± 2.0 <sup>§</sup>	3.3 ± 2.6
AUC <sub>∞</sub> (µg•h/mL)	3.7 ± 2.0 <sup>§</sup>	3.5 ± 2.9*
λ <sub>z</sub> (1/h)	0.114 ± 0.022 <sup>§</sup>	0.108 ± 0.025*
t <sub>1/2</sub> <sup>e</sup> (h)	6.10 ± 1.18 <sup>§</sup>	6.45 ± 1.52*

<sup>f</sup> Ritonavir was administered as a 100 mg dose.

<sup>§</sup> Statistically significantly different from reference regimen (Regimen B, ANOVA, p < 0.05).

\* N = 83: the λ<sub>z</sub> value of Subject 1050 could not be determined; therefore, AUC<sub>∞</sub> and t<sub>1/2</sub> were not estimated.

<sup>e</sup> Harmonic mean ± pseudo-standard deviation; evaluations of t<sub>1/2</sub> were based on statistical tests for λ<sub>z</sub>.

**Table 5-Ritonavir bioequivalence assessment (tablets compared to capsules) with single dose administration of ritonavir 100 mg tablets or ritonavir 100 mg capsules**

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>*</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	92.8% Confidence Interval
A vs. B	C <sub>max</sub>	0.367	0.290	1.264	1.150 – 1.389
	AUC <sub>t</sub>	3.154	2.780	1.134	1.068 – 1.205
	AUC <sub>∞</sub>	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 logarithms.

### Discussion of results

The results for the pivotal bioequivalence trial indicate that ritonavir tablets are not bioequivalent to ritonavir capsules under moderate fat conditions. The lower and upper limits for the 92.8% confidence intervals for AUC<sub>(0-inf)</sub> were within 80% to 125%. However, the upper limit for the 92.8% confidence intervals for C<sub>max</sub> exceeded 125%.

Under moderate fat conditions, when a single 100 mg ritonavir dose was administered, the point estimate for C<sub>max</sub> was increased by 26% (92.8% confidence intervals: ↑15-

↑39%), and the point estimate for  $AUC_{(0-inf)}$  was increased by 10% (92.8% confidence intervals: ↑4-↑17%) for ritonavir tablets relative to ritonavir capsules.

No information is available comparing ritonavir tablets to ritonavir capsules under fasting conditions.

## 7.2 Safety Analysis

Adverse events reported by three or more subjects included 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%]). There were no deaths or serious adverse events reported.

The percentage of subjects reporting an adverse event was comparable between the ritonavir tablet and ritonavir capsule: (Regimen A [21.3%], and Regimen B [23.6%]).

## 8. Conclusions

Ritonavir tablets are not bioequivalent to ritonavir capsules under moderate fat conditions, based on the pharmacokinetic results and statistical analysis from protocol M10-307. The lower and upper limits for the 92.8% confidence intervals for  $AUC_{(0-inf)}$  were within 80% to 125%. However, the upper limit for the 92.8% confidence intervals for  $C_{max}$  exceeded 125%. For  $C_{max}$ , the point estimate was 26% with an upper limit of approximately 40%. An increase of up to 40% in  $C_{max}$  under moderate fat conditions is not anticipated to result in any clinically significant safety issues.

### 3.2 Individual Trial Review-M10-235

#### 1. Title

Assessment of the Effect of Food on Ritonavir Bioavailability Following Administration of a Single Ritonavir 100 mg Film-Coated Tablet Dose in Healthy Adult Subjects

#### 2. Objectives

The primary objective of this trial was to evaluate the effect of food on the bioavailability of a 100 mg ritonavir tablet formulation. The effect of high fat and moderate fat meals compared to fasting conditions as well as high fat compared to moderate fat meals was evaluated.

#### 3. Trial Design

M10-235 was a single dose, open label, crossover trial conducted in healthy male and female subjects. Subjects were initially randomized to one of three trial regimens and then crossed over to the other two regimens (see Table 1):

- 1) Regimen A-a single dose of ritonavir 100 mg administered after a high fat meal.
- 2) Regimen B-a single dose of ritonavir 100 mg administered after a moderate fat meal.
- 3) Regimen C-a single dose of ritonavir 100 mg administered under fasting conditions.

**Table 1-Dosing sequences for the M10-235 protocol**

Sequence Group	Subject Numbers	Regimens		
		Period 1	Period 2	Period 3
I	503, 506, 509, 511, 513, 517, 521, 524, 527	A	B	C
II	502, 504, 507, 510, 515, 516, 519, 523, 525	B	C	A
III	501, 505, 508, 512, 514, 518, 520, 522, 526	C	A	B

An equal number of subjects were enrolled in each trial group. A 7 day washout period separated the dosing between the trial regimens. The washout period is appropriate because the ritonavir mean elimination half life is 3 to 5 hours.

All ritonavir doses were taken with 240 mL of water. Under fasting conditions, ritonavir was administered after fasting for ten hours. Under fed conditions, ritonavir was administered approximately 30 minutes after breakfast was initiated. Information on the specific composition of meals administered on Day 1 in each period is displayed in Table 2.

**Table 2-Composition of meals administered on Day 1 in each period**

Meal	Approximate Time	Menu	Meal Composition
Breakfast – Regimen A (high-fat)	0815	2 slices toasted wheat bread with 5 g margarine each, 2 fried eggs, 2 strips bacon, 4 oz. hash brown potatoes, 1 cup whole milk	907 Kcal; 52% calories from fat, 33% calories from carbohydrates and 15% calories from protein
Breakfast – Regimen B (moderate-fat)	0815	4 oz. scrambled eggs, 2 slices wheat toast with 1 pat (5 g) margarine and ½ oz. jelly, 1 medium banana, 4 oz. hash browns, 1 cup 1% milk	857 Kcal; 31% calories from fat, 56% calories from carbohydrates and 13% calories from protein
Lunch	1300	BBQ beef sandwich (3 oz. beef, 1 steak bun—3 oz.), 4 oz. macaroni salad, 3 oz. grapes, 2 oatmeal raisin cookies, beverage (1 cup 1% milk or caffeine-free soda or water)	801 – 943 Kcal; 25 – 30% calories from fat, 53 – 61% calories from carbohydrates and 14 – 18% calories from protein
Dinner	1900	4 oz. chicken fried steak, 4 oz. mashed potatoes, 3 oz. gravy, 4 oz. green beans, 4 oz. applesauce, 4 oz. vanilla pudding, beverage (1 cup 1% milk or caffeine-free soda or water)	572 – 728 Kcal; 29 – 36% calories from fat, 52 – 63% calories from carbohydrates and 9 – 14% calories from protein
Snack	2245	1 ½ oz. pretzels, 12 oz. caffeine-free soda	321 Kcal; 4% calories from fat, 90% calories from carbohydrates and 6% calories from protein

#### 4. Rationale for Doses Used in the Trial

The ritonavir dose evaluated in this study, 100 mg, is the only proposed to be marketed dosage strength for ritonavir tablets.

#### 5. Drugs Used in the Trial

Ritonavir 100 mg tablets (formulation D0700425) were administered in this study.

#### 6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

##### *Sample Collection*

For each period, on Day 1, blood samples were collected for determination of ritonavir concentrations in tubes containing an anticoagulant (EDTA). Blood samples were collected within 10 minutes before dose administration and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30 and 36 hours postdose.

##### *Bioanalysis*

Ritonavir concentrations were analyzed using a validated LC/MS/MS method. The samples were analyzed by (b) (4)

The following issue from the M10-235 sample analysis was identified by the clinical pharmacology reviewer, however, because this issue did not alter the trial's conclusions, a follow up comment was not sent to the sponsor:

1) During sample analysis for the M10-235 protocol, run 12 was rejected due to QCs failing to meet acceptance criteria. The bioanalytical laboratory did not provide a reason(s) or potential reason(s) explaining why the acceptance criteria for the QCs were not met.

A review of the ritonavir method validation and M10-235 bioanalytical report did not indicate any deficiencies that the clinical pharmacology reviewer believes would affect the validity of the food effect trial results. An issue identified with the ritonavir reference standard and (b) (4) (internal standard) is discussed in the trial review for M10-307.

The lower limit of quantification for the ritonavir method was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for ritonavir with the M10-235 sample analysis. For the M10-235 sample analysis, the ritonavir inter-run accuracy values for the low (3 ng/mL), medium (50 ng/mL), and high (800 ng/mL) QC samples were 7.7%, 6%, and 3.5%, respectively. The ritonavir inter-run precision values for the low (3 ng/mL), medium (50 ng/mL), and high (800 ng/mL) QC samples were 6.9%, 7.1% and 5.4%, respectively.

## Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including the following parameters:  $C_{\max}$ ,  $t_{\max}$ , the elimination half life ( $t_{1/2}$ ),  $AUC_{(0-t)}$ , and  $AUC_{(0-\infty)}$ .

Scheduled sampling times were used to calculate pharmacokinetic parameters for subjects, with the exception of the subjects displayed in Table 3 that did not have actual sampling times that were within 10% of the scheduled blood sampling time. For these subjects, actual sampling times were used in calculating pharmacokinetic parameters.

**Table 3-Subjects with actual sampling times used in calculating pharmacokinetic parameters**

Subject Number	Period	Planned Time (h)	Actual Time (h)	Difference
501	1	1.0	1.10	6 minutes late
517	1	0.5	0.57	4 minutes late
521	2	0.5	0.55	3 minutes late

## Statistical Analysis

Using a linear mixed effects model, the antilogarithm of the logarithmic least squares means were calculated and 90% confidence intervals for ritonavir were derived based on the antilogarithm of the difference of the pharmacokinetic parameter's logarithmic least squares means for the test and reference arms. Only subjects with pharmacokinetic data from a minimum of two periods were included in the statistical analysis.

The following bioequivalence tests were performed:

- 1) High fat (test arm) compared to fasting (reference arm)
- 2) Moderate fat (test arm) compared to fasting (reference arm)
- 3) High fat (test arm) compared to moderate fat (reference arm)

The absence of a food effect for ritonavir tablets for comparisons #1 and #2 was demonstrated if the 90% confidence intervals for  $C_{\max}$  and AUC were within 80% to 125%. For #3, if the 90% confidence intervals for  $C_{\max}$  and AUC were within 80% to 125%, the type of meal administered (either high or moderate fat) did not impact ritonavir tablet bioavailability.

## 7. Results

### 7.1 Pharmacokinetic and Statistical Results

27 subjects enrolled in the trial, and pharmacokinetic data from 27 subjects were included in the statistical analyses. 25 subjects (12 males and 13 females) completed all three trial regimens. Two subjects were discontinued from the trial: a) subject 515 was

discontinued prior to Period 3 dosing because of a positive urine amphetamine test result, and b) subject 527 was withdrawn prior to Period 3 dosing because mild hematuria that occurred during Period 2 progressed to severe hematuria by Period 3 (in Period 2, ritonavir blood samples for subject 527 were not collected after the 36 hour time point).

The ritonavir pharmacokinetic results are displayed in Table 4 and the results of food effect comparisons are displayed in Table 5.

**Table 4-Ritonavir pharmacokinetic parameters under high fat, moderate fat or fasted conditions with single dose administration of ritonavir 100 mg tablets**

Pharmacokinetic Parameters (units)	Regimens <sup>‡</sup>		
	Regimen A: High-Fat Breakfast (N = 26)	Regimen B: Moderate-Fat Breakfast (N = 27)	Regimen C: Fasting (N = 26)
T <sub>max</sub> (h)	4.8 ± 1.1*	4.3 ± 1.2*	3.2 ± 1.2
C <sub>max</sub> (µg/mL)	0.44 ± 0.20*	0.47 ± 0.26*	0.60 ± 0.31
AUC <sub>t</sub> (µg•h/mL)	3.6 ± 1.6*	3.8 ± 1.9*	4.6 ± 2.0
AUC <sub>∞</sub> (µg•h/mL)	3.7 ± 1.7*	3.9 ± 2.0*	4.7 ± 2.0
λ <sub>z</sub> <sup>†</sup> (1/h)	0.12 ± 0.025	0.12 ± 0.021	0.13 ± 0.023
t <sub>½</sub> <sup>‡,ϕ</sup> (h)	6.0 ± 1.3	5.8 ± 1.0	5.5 ± 1.0

‡ All three regimens were administered as a single 100-mg tablet.

\* Statistically significantly different from reference regimen (Regimen C, linear mixed effects analyses, p < 0.05).

† Parameter was not tested statistically.

ϕ Harmonic mean ± pseudo-SD.

**Table 5-Ritonavir food effect comparisons with single dose administration of ritonavir 100 mg tablets**

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
A vs. C (High-Fat vs. Fasting)	C <sub>max</sub>	0.384	0.501	0.766	0.659 – 0.891
	AUC <sub>t</sub>	3.044	3.981	0.765	0.694 – 0.842
	AUC <sub>∞</sub>	3.137	4.049	0.775	0.704 – 0.853
B vs. C (Moderate-Fat vs. Fasting)	C <sub>max</sub>	0.392	0.501	0.782	0.675 – 0.907
	AUC <sub>t</sub>	3.135	3.981	0.788	0.717 – 0.866
	AUC <sub>∞</sub>	3.218	4.049	0.795	0.724 – 0.873
A vs. B (High-Fat vs. Moderate-Fat)	C <sub>max</sub>	0.384	0.392	0.980	0.866 – 1.108
	AUC <sub>t</sub>	3.044	3.135	0.971	0.886 – 1.064
	AUC <sub>∞</sub>	3.137	3.218	0.975	0.890 – 1.068

\* Antilogarithm of the least squares means for logarithms.

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

## Discussion of results

A food effect was observed for ritonavir tablets. When a single 100 mg dose of ritonavir was administered, food decreased the bioavailability of the ritonavir tablets. Under high fat conditions, a 23% decrease in the point estimate for  $AUC_{(0-\infty)}$  (90% confidence intervals:  $\downarrow 30\%$ - $\downarrow 15\%$ ), and a 23% decrease in point estimate for  $C_{max}$  (90% confidence intervals:  $\downarrow 34\%$ - $\downarrow 11\%$ ) was observed relative to fasting conditions. Under moderate fat conditions, a 21% decrease in the point estimate for  $AUC_{(0-\infty)}$  (90% confidence intervals:  $\downarrow 28\%$ - $\downarrow 13\%$ ), and a 22% decrease in the point estimate for  $C_{max}$  (90% confidence intervals:  $\downarrow 33\%$ - $\downarrow 9\%$ ) was observed relative to fasting conditions.

The observed decreases in ritonavir tablet bioavailability when administered with moderate or high fat meals were similar. When high fat was directly compared to moderate fat meals, the 90% confidence intervals for both  $C_{max}$  and  $AUC_{(0-\infty)}$  were within 80% to 125%. The sponsor did not evaluate the effect of low fat or light meals on ritonavir tablet bioavailability compared to fasted conditions.

In contrast to ritonavir tablets, the ritonavir capsules currently marketed in the U.S. demonstrated higher bioavailability under fed conditions. Ritonavir bioavailability (measured using AUC), with a soft gelatin capsule was 13% higher when administered with a meal (615 Kcal; 14.5% fat, 9% protein, and 76% carbohydrate) compared to dosing under fasted conditions.

### *7.2 Safety Analysis*

Headache was the most common adverse event reported (8 subjects, 29.6%). There were no deaths or serious adverse events reported. The percentage of subjects reporting an adverse event was comparable between the different regimens: (Regimen A [15.4%], Regimen B [18.5%], and Regimen C [19.2%]).

## **8. Conclusions**

A food effect is observed for ritonavir tablets based on the pharmacokinetic results and statistical analyses from protocol M10-235. When a single 100 mg dose of ritonavir tablets was administered, food decreased the bioavailability of the ritonavir tablets under fat conditions. Similar decreases in ritonavir bioavailability were observed for ritonavir tablets under moderate fat conditions when compared to fasted conditions. When high fat meals were directly compared to moderate fat meals, a minimal change in ritonavir tablet bioavailability was observed. The effect of low fat or light meals on ritonavir tablet bioavailability compared to fasted conditions is unknown.

In contrast to ritonavir tablets, ritonavir capsules demonstrated higher bioavailability under fed conditions. The current draft prescribing information (label) for ritonavir tablets states that ritonavir tablets are to be taken with meals. The rationale for this recommendation is based on the following considerations: a) ritonavir tablet bioavailability is higher under fasted conditions, and b) there is no human bioequivalence

data currently available regarding the magnitude of the difference in bioavailability for ritonavir tablets compared to ritonavir capsules under fasting conditions.

### **3.3 Review of Published Literature for Protease Inhibitors Coadministered with Pharmacokinetic Boosting Doses of Ritonavir**

Table 1 below summarizes the dosage and administration information for the five protease inhibitors that are currently approved for coadministration with pharmacokinetic boosting doses of ritonavir. This section also provides a summary of the information submitted by Abbott with 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 compared to ritonavir capsules when administered with moderate fat meals. This conclusion also applies to high fat meals because the decrease in bioavailability was similar under moderate or high fat conditions.

**Table 1-Protease inhibitors dosage regimens with concurrent administration of pharmacokinetic boosting doses of ritonavir\***

<p><b>1) Fosamprenavir</b></p> <p>Fosamprenavir tablets may be taken with or without food</p> <p><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</p> <p><u>Protease inhibitor experienced adults:</u>  Fosamprenavir 700 mg twice daily plus ritonavir 100 mg twice daily</p>
<p><b>2) Darunavir</b></p> <p>Darunavir tablets should be taken with food</p> <p><u>Treatment naive adult patients:</u>  800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food</p> <p><u>Treatment experienced adult patients:</u> 600 mg (one 600 mg tablet or two 300 mg tablets) taken with ritonavir 100 mg twice daily and with food</p>
<p><b>3) Atazanavir</b></p> <p>Atazanavir capsules should be taken with food</p> <p><u>Treatment naive patients:</u> 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.</p> <p><u>Treatment experienced patients:</u> Atazanavir 300 mg with ritonavir 100 mg once daily with food</p>
<p><b>4) Tipranavir</b></p> <p>Tipranavir capsules can be administered with and without food</p> <p><u>Treatment experienced patients:</u>  Adults: 500 mg tipranavir, co-administered with 200 mg ritonavir, twice daily with or without food</p>
<p><b>5) Saquinavir</b></p> <p>Administer saquinavir with ritonavir within 2 hours after meals</p> <p>1000 mg twice daily with ritonavir 100 mg twice daily</p>

\*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).

The information examined by the clinical pharmacology reviewer supports the conclusion that no dose adjustment for fosamprenavir is required with ritonavir tablet coadministration even though an increased  $C_{max}$  is observed with ritonavir tablets when compared to ritonavir capsules under moderate fat conditions.

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.

Based on the information in Table 1, a doubling of fosamprenavir exposure ( $AUC_{[0-24h]}$  and  $C_{max}$ ) was not observed with a doubling of ritonavir doses from 100 mg to 200 mg when coadministered with fosamprenavir 1400 mg once daily. Higher  $AUC_{(0-24h)}$  and  $C_{max}$  values were observed, however the change was minimal. The  $C_{min}$  was higher but this is not expected to result in any efficacy or safety concerns. Therefore, the increased  $C_{max}$  observed with ritonavir tablets is not expected to result in clinically significant changes in amprenavir exposure that would be a potential safety issue.

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  $C_{max}$ .

Currently, fosamprenavir can be coadministered with pharmacokinetic boosting doses of ritonavir capsules under fed or fasted conditions. In evaluating the potential for ritonavir

to potentially alter the exposure of coadministered protease inhibitors, fosamprenavir exposure is altered through CYP 3A inhibition only. Modification of the fosamprenavir prescribing information to restrict dosage and administration to fed conditions only when concurrently administered with ritonavir tablets is not necessary because it is not anticipated that increases in ritonavir tablet exposure would result in clinically significant changes in fosamprenavir exposure under fasted conditions.

## 2) Darunavir

Reference: Sekar V, Spinosa-Guzman S, Lefebvre E, Hoetelmans R. Clinical pharmacology of TMC114-a new HIV protease inhibitor. 16<sup>th</sup> International AIDS Conference, 2006

The information examined by the clinical pharmacology reviewer supports the conclusion that no dose adjustment for darunavir is required with ritonavir tablet coadministration even though an increased  $C_{max}$  is observed with ritonavir tablets when compared to ritonavir capsules under moderate fat conditions.

There was no darunavir pharmacokinetic information provided by Abbott evaluating the doubling of ritonavir doses from 100 mg to 200 mg at the same darunavir dose (e.g. 600 mg or 800 mg).

The information submitted by Abbott was a Phase I, parallel group trial in healthy subjects (TMC114-C112). Pharmacokinetic data after 14 days of treatment was provided for five dosage regimens in which darunavir was coadministered with ritonavir (darunavir/ritonavir): a) 200 mg/100 mg once daily, b) 400 mg/100 mg once daily, c) 600 mg/100 mg once daily (Day 1), 300 mg/100 mg twice daily (Days 2 through 14), d) 600 mg/200 mg once daily, and e) 1200 mg/200 mg once daily. All regimens were administered under fed conditions. For each trial arm, the number of subjects with available pharmacokinetic data was less than 10.

When darunavir 400 mg was coadministered with ritonavir 100 mg once daily was compared with darunavir 600 mg coadministered with ritonavir 200 mg once daily, the  $AUC_{(0-24h)}$  and  $C_{max}$  values were higher by approximately 30% and 50%, respectively with a 50% higher darunavir dose and doubling (100% increase) of ritonavir doses. Darunavir  $C_{min}$  was higher by approximately 80% with the doubling of ritonavir doses.

A doubling of darunavir exposure ( $AUC_{[0-24h]}$  and  $C_{max}$ ) was not observed with a doubling of ritonavir doses from 100 mg to 200 mg and a 50% higher darunavir dose from 400 mg to 600 mg. The higher darunavir exposure was no greater than the 50% higher darunavir dose and can potentially be attributed to a 50% higher darunavir dose with minimal or no additional ritonavir CYP 3A inhibition with a doubling of ritonavir doses from 100 mg to 200 mg. Therefore, the increased  $C_{max}$  observed with ritonavir tablets is not expected to result in clinically significant changes in darunavir exposure that would be a potential safety issue. The higher  $C_{min}$  is not expected to result in any efficacy or safety concerns.

### 3) Atazanavir

#### References:

1) 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. 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment, 2005

2) O'Mara E, Mummaneni V, Bifano M, Randall D, Uderman H, KnoxL, Gerald M. Pilot Study of the Interaction Between BMS-232632 and Ritonavir. Conference on Retroviruses and Opportunistic Infections, 2001

The information examined by the clinical pharmacology reviewer provide supportive data that no dose adjustment for atazanavir is required with ritonavir tablet coadministration even though an increased  $C_{max}$  is observed with ritonavir tablets when compared to ritonavir capsules under moderate fat conditions.

In the trial conducted by Harris et al, blood samples were collected from HIV infected subjects who were on antiretroviral treatment for a minimum of two weeks. Blood samples were collected at 30 minutes, 1, 2, and 3 hours postdose. If subjects had subtherapeutic atazanavir concentrations (the subtherapeutic threshold was not defined by the authors), the atazanavir regimen could be changed to either atazanavir 300 mg coadministered with 200 mg ritonavir once daily or atazanavir 400 mg coadministered with 200 mg ritonavir once daily.

Twenty eight pairwise comparisons were available evaluating atazanavir 300 mg coadministered with 100 mg ritonavir once daily compared to atazanavir 300 mg coadministered with 200 mg ritonavir once daily. In Table 3A (located in section 1.3), Abbott displays actual atazanavir pharmacokinetic values for atazanavir 300 mg coadministered with 100 mg ritonavir once daily and atazanavir 300 mg coadministered with 200 mg ritonavir once daily. However, the information provided was derived by Abbott using Plot Digitizer software (version 2.4.1) from Figure 1 below (Harris et al 2005). The 3 hour concentration data was used to derive  $C_{max}$  values and presumably the predose concentration data was used to derive  $C_{min}$  values.

**Figure 1-Atazanavir plasma concentration time profiles for atazanavir 300 mg coadministered with 100 mg of ritonavir once daily or atazanavir 300 mg coadministered with 200 mg of ritonavir once daily**

(b) (4)



Harris et al collected atazanavir blood samples up until 3 hours post dose, which is the median  $t_{max}$  value for HIV-1 infected subjects receiving atazanavir 300 mg coadministered with ritonavir 100 mg once daily. The profiles for both regimens (atazanavir 300 mg coadministered with ritonavir 100 mg once daily compared with atazanavir 300 mg coadministered with ritonavir 200 mg once daily in Figure 1) are similar. Of note, for atazanavir 300 mg coadministered with ritonavir 100 mg once daily, the geometric mean 3 hour concentration of approximately 2340 ng/mL is approximately 50% lower than the geometric mean  $C_{max}$  value of 4422 ng/mL for HIV infected subjects in the atazanavir label. Therefore, it is unclear if the 3 hour atazanavir concentration reflects the  $C_{max}$  value.

To determine whether an accurate estimate of the  $C_{max}$  value is critical, atazanavir pharmacokinetic profiles from a second trial conducted by Bristol Myers Squibb (O'Mara et al 2001) were evaluated (Figure 2). In this trial, 32 healthy subjects were assigned to one of four trial arms (8 subjects per arm). The following regimes were administered:

Trial arm A-Atazanavir 200 mg once daily for six days, followed by coadministration with ritonavir 100 mg once daily for ten days.

Trial arm B-Atazanavir 200 mg once daily for six days, followed by coadministration with ritonavir 200 mg once daily for ten days.

Trial arm C- Atazanavir 400 mg once daily for six days, followed by coadministration with ritonavir 100 mg once daily for ten days.

Trial arm D- Atazanavir 400 mg once daily for six days, followed by coadministration with ritonavir 200 mg once daily for ten days.

**Figure 2-Atazanavir plasma concentration time profiles for atazanavir 200 mg or 400 mg administered once daily by itself or coadministered with either 100 mg or 200 mg of ritonavir once daily**

(b) (4)

In Figure 2, the atazanavir plasma concentration profiles for atazanavir 200 mg coadministered with ritonavir 100 mg once daily compared to atazanavir 200 mg coadministered with ritonavir 200 mg once daily displayed a clear separation prior to  $t_{max}$ . In contrast, the atazanavir plasma concentration profiles for atazanavir 400 mg coadministered with ritonavir 100 mg once daily compared to atazanavir 400 mg

coadministered with ritonavir 200 mg once daily prior to  $t_{max}$  were virtually superimposable.

Therefore, even if the plasma concentration profiles in Figure 1 do not provide an accurate estimate of the  $C_{max}$  value, the trends identified in Figure 1 support the fact that minimal changes in atazanavir exposure are expected with once daily dosing at 300 mg when doubling the dose of ritonavir from 100 mg to 200 mg. Subsequently, the increased  $C_{max}$  observed with ritonavir tablets is not expected to cause clinically significant changes in atazanavir exposure at 300 mg that would be a potential safety issue.

#### 4) Tipranavir

Reference: MacGregor TR, Sabo JP, Norris SH, Johnson P, Galitz L, McCallister S. Pharmacokinetic characterization of different dose combinations of coadministered tipranavir and ritonavir in healthy volunteers, HIV Clin Trials 2004; 5(6): 371-382

In HIV-1 infected patients where the benefits of tipranavir coadministration with ritonavir outweigh the risks, the information provided supports the conclusion that no dose adjustment for tipranavir is required with ritonavir tablet coadministration even though an increased  $C_{max}$  is observed with ritonavir tablets when compared to ritonavir capsules under moderate fat conditions. This conclusion does not apply to dosing of tipranavir concurrently with ritonavir tablets under fasted conditions.

There was no pharmacokinetic information provided by Abbott evaluating the doubling of ritonavir doses at the recommended dosage regimen for tipranavir coadministered with ritonavir: 500 mg of tipranavir with 200 mg of ritonavir twice daily for treatment experienced patients in the tipranavir label. The tipranavir label states that 200 mg of ritonavir coadministered with tipranavir provide ritonavir concentrations similar to 100 mg of ritonavir coadministered with protease inhibitors other than tipranavir. 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).

The information submitted by Abbott was a Phase I, parallel group, trial in healthy subjects. Tipranavir was administered by itself for 11 days with dosage regimens ranging from 250 mg to 1250 mg twice daily. After Day 11, tipranavir with coadministration of 100 mg to 200 mg twice daily of ritonavir was added for 21 days. For each trial arm, the number of subjects with available pharmacokinetic data was less than 15. Trial medications were administered at least one hour after a light meal or at least one hour before or 2.5 hours after a normal meal.

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.

While tipranavir exposures were increased, a doubling of tipranavir exposure with a doubling of ritonavir doses from 100 mg to 200 mg when coadministered with 500 mg of tipranavir was not observed. No change was observed in tipranavir  $C_{max}$  and the higher  $AUC_{(0-12h)}$  of approximately 25% is a potential safety issue in HIV-1 infected patients coinfecting with Hepatitis B or C or in HIV-1 infected patients with increased alanine transaminase (ALT) or aspartate transaminase (AST) values. The higher  $C_{min}$  is not expected to result in any efficacy or safety concerns.

In evaluating the potential for ritonavir to potentially alter the exposure of coadministered protease inhibitors, there are multiple mechanisms involved that can change tipranavir exposure. Therefore, ritonavir effects on tipranavir exposure are difficult to predict.

Based on the information submitted by Abbott with coadministration of tipranavir 500 mg with either 100 mg or 200 mg of ritonavir, and the mechanisms through which ritonavir can alter tipranavir exposure, an increased ritonavir tablet  $C_{max}$  at a 200 mg ritonavir tablet dose is not expected to result in a clinically significant change in tipranavir exposure that would be a potential safety issue outweighing the benefits of treatment under moderate fat conditions with the exception of the HIV-1 infected patient subpopulations indicated above.

Tipranavir must be coadministered with ritonavir when used in the treatment of HIV-1 infection. Currently, tipranavir can be coadministered with pharmacokinetic boosting doses of ritonavir capsules under fed or fasted conditions. The benefit of treatment with tipranavir coadministered with ritonavir tablets outweigh the risk of tipranavir hepatotoxicity under fed conditions in HIV-1 infected patients who are not coinfecting with Hepatitis B or C or do not have increased alanine transaminase (ALT) or aspartate transaminase (AST) values, however, the benefit does not outweigh the risk with ritonavir tablets under fasted conditions. A proposal to revise the prescribing information to specify that tipranavir should only be taken with meals when coadministered with ritonavir tablets and strategies for evaluating potential safety issues with tipranavir hepatotoxicity with ritonavir tablet coadministration will be discussed with tipranavir's sponsor.

## 5) Saquinavir

1) Reference: 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

The information examined by the clinical pharmacology reviewer provides conflicting

information as to whether a dose adjustment for saquinavir (a CYP 3A and P-gp substrate) is required with ritonavir coadministration due to the increased  $C_{max}$  observed with ritonavir tablets when compared to ritonavir capsules under moderate fat conditions. The reviewed information indicates that saquinavir exposure may be decreased with an increase in the ritonavir dosage regimen. However, potential decreases in saquinavir exposure are not expected to result in saquinavir exposure that is lower than at saquinavir 1200 mg administered three times a day without ritonavir coadministration. Clinical efficacy for saquinavir was established with saquinavir 1200 mg administered three times a day.

There was no pharmacokinetic information provided by Abbott evaluating a doubling of ritonavir doses from 100 mg to 200 mg when coadministered with saquinavir (Invirase) 1000 mg twice daily.

The information submitted by Abbott was a parallel group trial in healthy subjects. The following dosage regimens were administered: a) saquinavir 1200 mg administered three times a day, b) 1200 mg saquinavir coadministered with 100 mg of ritonavir once daily, c) 1600 mg saquinavir coadministered with 100 mg of ritonavir once daily, d) 1800 mg saquinavir coadministered with 100 mg of ritonavir once daily, and e) 1200 mg saquinavir coadministered with 200 mg of ritonavir once daily. For each trial arm, the number of subjects with available pharmacokinetic data was 10 or less.

It is important to note that the pharmacokinetic data provided used the soft gelatin capsule formulation of saquinavir (Fortovase) that is no longer marketed in the United States. Saquinavir hard gelatin capsules and tablets (Invirase) are currently marketed in the United States. As indicated in Table 1 below, at equivalent saquinavir doses of 1000 mg coadministered with ritonavir 100 mg twice daily,  $AUC_{(0-24h)}$  and  $C_{min}$  values for the soft gelatin capsule saquinavir formulation were approximately 30% and 20% higher compared to Invirase.

When 1200 mg saquinavir coadministered with 100 mg ritonavir once daily was compared with 1200 mg saquinavir coadministered with 200 mg ritonavir once daily,  $AUC_{(0-24h)}$ ,  $C_{max}$ , and  $C_{min}$  geometric mean values were lower by approximately 40%, 30%, and 40%, respectively with a doubling of ritonavir doses.

In contrast to other protease inhibitors coadministered with ritonavir, when 1200 mg of saquinavir was coadministered with 100 mg of ritonavir once daily compared to 1200 mg of saquinavir coadministered with 200 mg ritonavir once daily, lower saquinavir exposure was observed with a doubling (100%) of ritonavir doses for both  $AUC_{(0-24h)}$  and  $C_{max}$ . Saquinavir bioavailability does not appear to be a potential cause for the observed lower exposure. Approximately dose proportional higher saquinavir  $AUC_{(0-24h)}$  and  $C_{max}$  were observed with saquinavir 1200 mg to 1600 mg once daily coadministered with 100 mg ritonavir once daily, indicating that higher saquinavir exposures are achievable at doses higher than 1200 mg. The reason for the observed decreases in saquinavir exposure is unknown.

A follow up question from DAVP to Abbott requested information demonstrating that the new ritonavir tablets do not cause a clinically significant change in the pharmacokinetics of saquinavir. The information submitted by Abbott did not directly address the issue of decreased saquinavir exposure with increased ritonavir doses.

2) a) Reference: Kilby JM, Hill A, Buss N. The effect of ritonavir on saquinavir plasma concentration is independent of ritonavir dosage: combined analysis of pharmacokinetic data from 97 subjects, HIV Med, 2002; Apr;3(2):97-104

b) Reference: Buss N, Snell P, Bock J, Hsu A, Jorga K. Saquinavir and ritonavir pharmacokinetics following combined ritonavir and saquinavir (soft gelatin capsules) administration. Br J Clin Pharmacol. 2001 Sep;52(3):255-64.

The published information discussed below supports the fact that no dose adjustment for saquinavir is required with ritonavir tablet coadministration even though an increased  $C_{max}$  is observed with ritonavir tablets when compared to ritonavir capsules under moderate fat conditions.

To further investigate the effect of increased ritonavir doses when coadministered with saquinavir, the clinical pharmacology reviewer evaluated a second paper by Kilby et al (2002). In this paper, a regression analysis was conducted using selected pharmacokinetic data from two trials: a) the trial discussed above (Kilby et al 2000) and b) a parallel group trial in healthy subjects (Buss et al 2001). In the Buss et al trial, twice daily dosage regimens were administered consisting of saquinavir soft gel capsule doses ranging from 400 mg to 800 mg coadministered with ritonavir doses ranging from 200 mg to 400 for 14 days. Additionally, saquinavir 800 mg twice daily or ritonavir 400 mg twice daily were dosed in two separate arms. All medications were administered with meals.

With the exception of the ritonavir 400 mg twice daily dosage regimen, all the dosage regimens cited above from both trials were included in the regression analysis. Using multivariate regression analysis, geometric mean saquinavir  $C_{min}$  or  $C_{max}$  was evaluated as the dependent variable and saquinavir and ritonavir doses were evaluated as the independent variable. The results of the regression analysis are displayed in Table 2 below. A statistically significant relationship was not observed between ritonavir dose and saquinavir  $C_{min}$  and  $C_{max}$  values.

**Table 1-Pharmacokinetic parameters for saquinavir or saquinavir coadministered with ritonavir**

Dosing Regimen	N	AUC <sub>τ</sub> (ng·h/mL)	AUC <sub>24h</sub> (ng·h/mL)	C <sub>min</sub> (ng/mL)
INVIRASE 600 mg tid (arithmetic mean, %CV)	10	866 (62)	2598	79
Saquinavir soft gel capsules 1200 mg tid (arithmetic mean)	31	7249	21747	216
INVIRASE 400 mg bid + ritonavir 400 mg bid (arithmetic mean ± SD)	7	16000 ± 8000	32000	480 ± 360
INVIRASE 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	14607 (10218-20882)	29214	371 (245-561)
Saquinavir soft gel capsules 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	19085 (13943-26124)	38170	433 (301-622)

τ is the dosing interval (ie, 8h if tid and 12h if bid)

**Table 2-Regression analysis evaluating the effect of saquinavir or ritonavir doses on the pharmacokinetics of saquinavir**

Parameter	Estimate	95% CI	P-value
$C_{min} r^2$ (adj.) = 0.7976			
Intercept	1.18953	(0.8885, 1.4905)	< 0.0001
SQV dosage*	0.04611	(0.0195, 0.0727)	0.0010
Any RTV†	1.37359	(1.0881, 1.6591)	< 0.0001
RTV dosage‡	0.04799	(- 0.0499, 0.1479)	0.3393
$C_{max} r^2$ (adj.) = 0.6451			
Intercept	2.57934	(2.3351, 2.8236)	< 0.0001
SQV dosage*	0.02923	(0.0076, 0.0508)	0.0093
Any RTV†	0.74008	(0.5084, 0.9718)	< 0.0001
RTV dosage‡	0.03163	(- 0.0478, 0.1111)	0.4373

adj., adjusted; SQV-SGC, saquinavir-soft gel capsule; RTV, ritonavir. \*Twice-daily dose of saquinavir (hundreds of mg). †0 if no ritonavir, 1 if some ritonavir. ‡Twice-daily dose of ritonavir (hundreds of mg).

### 3.4 Office of Biostatistics Consult

Donald J. Schuirmann

*Please evaluate the appropriateness of using a group sequential design and 92.8% confidence intervals in the pivotal bioequivalence trial (M10-307) for NDA 22-417 (ritonavir tablets).*

#### A) Overall assessment

The calculated 93.6% confidence intervals (corresponding to a nominal level of significance of 0.032) are as follows:

C<sub>max</sub>            1.146, 1.393  
AUC<sub>(0-t)</sub>        1.066, 1.207

AUC<sub>(0-inf)</sub> 1.039, 1.171

1) The sponsor (Abbott) specified a one-sided futility criterion-they would stop for futility if the stage 1 results for the test product (ritonavir tablets) were too high, but they would not stop for futility if the stage 1 results for the test product (ritonavir tablets) were too low.

2) Because of this one-sided futility criterion, the chance of concluding equivalence (at either stage 1 or stage 2) when, in fact, the true ratio of geometric means (Test/Reference) was 0.80 was too high-around 0.054-0.055.

3) In order for the overall Type I error rate to be controlled at 0.05 regardless of whether the true ratio of geometric means was 1.25 or was 0.80, Abbott needed to use a nominal level of significance of about 0.032 (e.g. 93.6% confidence intervals) instead of the nominal level of 0.036 (92.8% confidence intervals) that was used in the M10-307 trial.

4) If Abbott had used a nominal level of 0.032, their outcome would have been the same-passing at the first stage for AUC<sub>(0-t)</sub> and AUC<sub>(0-inf)</sub>, failing at the first stage for C<sub>max</sub>-as it was with their 92.8% confidence intervals. Therefore, we can accept their conclusions in regards to the bioequivalence assessment for ritonavir tablets compared to ritonavir capsules.

5) The sponsor used a group sequential design with a futility criterion. There is nothing "exotic" about such a design, and if it is done validly, it is acceptable for a bioequivalence trial. However, using a one-sided futility criterion, Abbott's choice of significance level - 0.036-(implemented using 92.8% confidence intervals) did not protect them from falsely concluding equivalence if the bioavailability of the test product (ritonavir tablets) was too low, as stated above. However, if a valid level of significance (e.g. 0.032) with calculation of 93.6% confidence intervals is used, the bioequivalence outcome is the same.

## **B) Background**

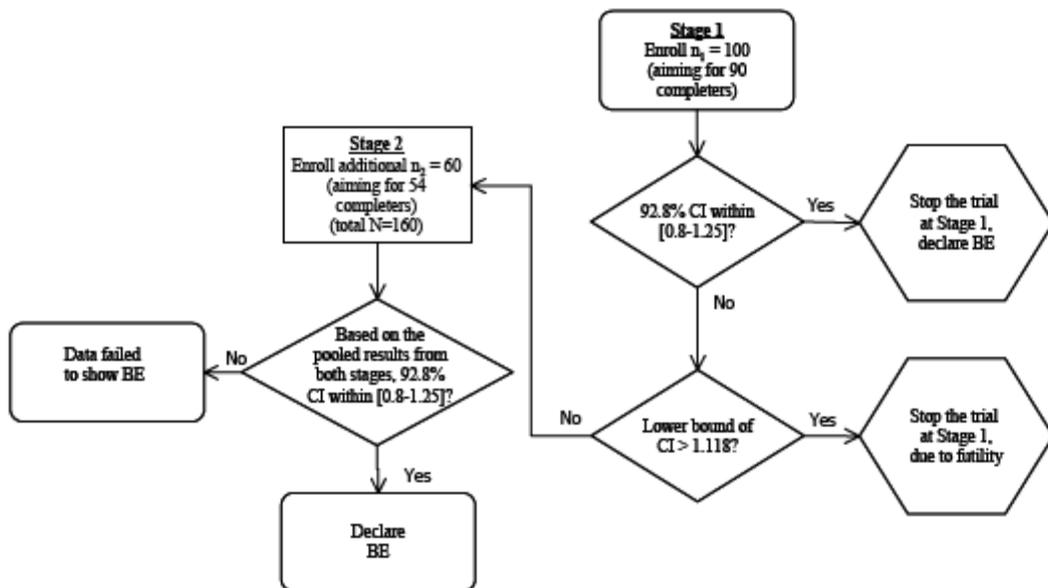
A 21% higher point estimate for C<sub>max</sub> was observed based on results from the M10-263 trial evaluating an experimental ritonavir tablet formulation compared to the marketed ritonavir capsule.

Based on the potential for a higher C<sub>max</sub> with the ritonavir tablets resulting in bioequivalence not being demonstrated for ritonavir tablets compared to ritonavir capsules, a group sequential design was selected for the pivotal bioequivalence trial. The group sequential design (see Figure 1) consisted of two stages (Stages 1 and 2) in the bioequivalence trial comparing ritonavir tablets to ritonavir capsules (M10-307 trial).

In order to maintain the overall Type I error rate at 0.05, a more conservative level of significance was required at individual stage. In selecting 92.8% confidence intervals (instead of the usual 90% confidence intervals), Abbott decided to use a level of

significance of 0.036 at each stage ( $1-2*0.036 = 0.928$ ).

**Figure 1-M10-307 two stage group sequential design**



### 3.5 References

- 1) Aarnoutse RE, Kleinnijenhuis J, Koopmans PP, Touw DJ, Wieling J, Hekster YA, Burger DM. Effect of low-dose ritonavir (100 mg twice daily) on the activity of cytochrome P450 2D6 in healthy volunteers. *Clin Pharmacol Ther.* 2005 Dec;78(6):664-74.
- 2) Hsu A, Granneman GR, Witt G, Locke C, Denissen J, Molla A, Valdes J, Smith J, Erdman K, Lyons N, Niu P, Decourt JP, Fourtillan JB, Girault J, Leonard JM. Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother.* 1997 May;41(5):898-905.
- 3) Kharasch ED, Bedynek PS, Walker A, Whittington D, Hoffer C. Mechanism of Ritonavir Changes in Methadone Pharmacokinetics and Pharmacodynamics: II. Ritonavir Effects on CYP3A and P-Glycoprotein Activities. *Clin Pharmacol Ther.* 2008 Oct; 84(4):506-12.
- 4) Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther.* 2009 Jan; 85(1):64-70.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20659	SUPPL-45	ABBOTT LABORATORIES PHARMACEUTICAL PRODUCTS DIV	NORVIR (RITONAVIR) ORAL SOLUTION
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
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/

STANLEY AU  
09/23/2009

KELLIE S REYNOLDS  
09/23/2009

## CLINICAL PHARMACOLOGY TEAM LEADER MEMORANDUM

<b>Date</b>	September 17, 2009
<b>Review Author</b>	Kellie Reynolds, Pharm.D
<b>NDA#</b>	22-417
<b>Drug Name</b>	Ritonavir (Norvir®)
<b>Dosage forms / Strength</b>	100 mg tablets
<b>Indication</b>	Treatment of HIV-1 infection
<b>Dosing Regimen</b>	600 mg twice daily (adults)
<b>Cross Reference</b>	NDA 20-659; SLR-045 (Norvir oral solution)
<b>Applicant</b>	Abbott Laboratories
<b>Date of Submission</b>	December 19, 2008
<b>PDUFA Goal Date</b>	October
<b>Review type</b>	505(b)(1); Standard Review; New formulation
<b>Recommended</b>	Approval

### Introduction:

This new drug application is for a 100 mg tablet formulation of ritonavir (Norvir). Ritonavir 100 mg capsules and 80 mg/mL oral solution were approved in 1996 for the treatment of HIV-1 infection. A new capsule formulation was approved in 1999 and the original capsules were discontinued.

The storage conditions for the tablets provide an advantage over the approved ritonavir capsules. The recommended storage conditions for the capsules are stated in the label: *Store soft gelatin capsules in the refrigerator between 36-46°F (2-8°C) until dispensed. Refrigeration of NORVIR soft gelatin capsules by the patient is recommended, but not required if used within 30 days and stored below 77°F (25°C).* The requirement to store the capsules in the refrigerator if the capsules are not used within 30 days leads to difficulties for some patients. The tablet formulation can be stored at room temperature (store at 68° to 77°F, with excursions permitted to 59° to 86°F).

### Background: Use of ritonavir in HIV therapy

Ritonavir is an HIV protease inhibitor. The approved dose of ritonavir is 600 mg twice daily, in combination with other antiretroviral drugs, for treatment of HIV infection in adult patients. This dose of ritonavir is the only adult dose included in the Norvir label. However, ritonavir is not used often at the 600 mg twice daily dose.

The majority of ritonavir use is as a pharmacokinetic enhancer (also referred to as pharmacokinetic boosting). Ritonavir is used as a pharmacokinetic enhancer because it is a strong CYP3A inhibitor. Most of the other approved HIV protease inhibitors are CYP3A substrates. Ritonavir (100-200 mg once or twice per day) is coadministered with other HIV protease inhibitors (PIs) to increase their concentrations. Use of ritonavir as an enhancer is an essential part of the approved dosing regimens for other PIs, for their indicated use. Some of the other PIs are fully dependent on ritonavir for their use (they do not have an approved dosing regimen that does not include ritonavir).

### Current application

Two clinical trials were reviewed for this NDA. (See details in Clinical Pharmacology review by Stanley Au, Pharm.D.)

1. A fed bioequivalence study compared ritonavir exposure following single 100 mg dose administration of the new ritonavir tablet to exposure following administration of the approved capsule. Doses were administered following a moderate fat meal. Results indicate ritonavir

AUC was similar following administration of both formulations, but the tablets provided higher ritonavir C<sub>max</sub> (C<sub>max</sub> increased, on average, by 26%).

2. A food effect study evaluated ritonavir concentrations following administration of 100 mg ritonavir tablets under three different conditions: fasted, following a moderate fat meal (857 kcal; 30 g fat), and following a high fat meal (907 kcal; 52 g fat). Administration of ritonavir tablets with food decreased plasma ritonavir concentrations. On average, ritonavir AUC and C<sub>max</sub> were 21 to 23% lower following administration with food, with similar effects of moderate and high fat meals.

In contrast to ritonavir tablets, administration with food increases bioavailability of ritonavir capsules. Based on the results from the two ritonavir tablet trials and previous food effect information for the ritonavir capsules, a greater difference in exposure is predicted for ritonavir tablets relative to ritonavir capsules under fasting conditions than under fed conditions. The predicted order of ritonavir exposures are as follows: ritonavir tablets (fasted) > ritonavir tablets (fed) > ritonavir capsules (fed) > ritonavir capsules (fasted).

### **Review questions**

Based on the lack of bioequivalence between the ritonavir tablet and the approved ritonavir capsule, there are two review questions. The review team considered the observed food effect when they addressed the questions.

1. How does the higher ritonavir C<sub>max</sub> observed following administration of the tablet compared to the capsule affect safety and efficacy of ritonavir administered 600 mg twice daily for the treatment of HIV?

2. When other protease inhibitors are administered with the new ritonavir tablet (doses of 100 to 200 mg once or twice daily), will the PI concentrations be within the range proven safe and effective? (Clinical trials for the other PIs were conducted using the PI co-administered with ritonavir capsules.)

### **Discussion of question 1**

As indicated in Dr. Stanley Au's review, the predicted magnitude of increase in C<sub>max</sub> at 600 mg twice daily dosing under moderate fat or high fat conditions does not present a clinically significant safety issue. However, patients may experience more gastrointestinal intolerance with the tablet than the capsule, because of the higher ritonavir concentrations.

Ritonavir concentrations are higher when the tablet is administered under fasted conditions compared to fed conditions. Ritonavir concentrations following administration of ritonavir tablets 600 mg twice daily under fasted conditions may exceed the concentrations in subjects who participated in the ritonavir safety and efficacy studies. Thus, the ritonavir label will instruct patients to take ritonavir tablets with a meal.

### **Discussion of question 2**

To address question 2, the review team asked the applicant to provide information that describes the impact of higher ritonavir exposure on the pharmacokinetics of coadministered protease inhibitors. Abbott submitted information from presented abstracts and published scientific literature articles. In addition to the information Abbott submitted, the review team referred to approved product labels for the protease inhibitors. The review team evaluated the drug labels and the information submitted by Abbott to determine the impact of doubling the ritonavir dose on protease inhibitor concentrations. Although switching from the ritonavir capsule to the ritonavir tablet does not double the ritonavir concentrations, the review team took a conservative "worst case" approach because of variability in ritonavir concentrations and the different food effects for the two formulations.

The review considered the conclusions of an article by Mathias et al (*Clinical Pharmacology and Therapeutics*, 2009 Jan; 85(1):64-70), which indicates dose-related CYP3A inhibition by ritonavir in the dose range of 20 to 100 mg ritonavir, with no further CYP3A inhibition by 200 mg ritonavir. The article suggests the increase in ritonavir concentrations following administration of the tablet will not alter the effective concentrations of coadministered protease inhibitors. However, the review considered each individual protease inhibitor because ritonavir may alter protease inhibitor concentrations by mechanisms other than CYP3A inhibition.

The dosage and administration sections for the following protease inhibitors include coadministration with ritonavir: darunavir, tipranavir, saquinavir, atazanavir, and fosamprenavir. The remainder of this review describes considerations and conclusions for each protease inhibitor. See Dr. Stanley Au's clinical pharmacology review for more details.

Darunavir: (approved regimens: 600 mg darunavir/100 mg ritonavir twice daily; 800 mg darunavir/100 mg ritonavir once daily; administered under fed conditions)

When darunavir 600 mg/ritonavir 200 mg once daily was compared with darunavir 400 mg/ritonavir 100 mg once daily, the darunavir AUC and  $C_{max}$  values were higher by approximately 30% and 50%. Thus, the increase in darunavir concentrations was similar to the increase in darunavir dose, with no additional effect by the increase in ritonavir dose. (Reference: Sekar V, et al; 16<sup>th</sup> International AIDS Conference, 2006)

Administration of the new ritonavir tablet with darunavir does not present safety or efficacy concerns.

Tipranavir: (approved regimen: 500 mg tipranavir/200 mg ritonavir twice daily; administered under fed or fasted conditions)

There are no pharmacokinetic data for tipranavir following administration with ritonavir doses greater than 200 mg. When tipranavir 500 mg/ritonavir 200 mg was compared to tipranavir 500 mg/ritonavir 100 mg twice daily, the tipranavir  $C_{max}$  values for both regimens were similar. The AUC was approximately 25% higher and  $C_{min}$  was approximately 60% higher with the higher ritonavir dose. (Reference: MacGregor TR, et al; HIV Clin Trials 2004; 5(6): 371-382)

It is difficult to interpret tipranavir concentrations across regimens because tipranavir concentrations are highly variable. The results of the comparison are in contrast to the conclusion of Mathias, et al that ritonavir 100 mg provides maximum CYP3A inhibition. Two considerations assist the interpretation of the tipranavir/ritonavir information. (1) Interactions between tipranavir and ritonavir are complex-- tipranavir is a CYP3A substrate and inducer and a P-gp substrate and inducer; and ritonavir is a CYP3A substrate, inhibitor and inducer and a P-gp inhibitor and inducer. Thus, CYP3A alone does not explain the interaction between ritonavir and tipranavir. (2) Ritonavir concentrations following administration of 200 mg with tipranavir are similar to ritonavir concentrations following administration of 100 mg with most other protease inhibitors. Thus, tipranavir plus ritonavir 100 mg may not provide maximum CYP3A inhibition.

The review team is concerned about potential increases in tipranavir concentrations because clinical hepatitis and hepatic decompensation have been reported in patients on tipranavir/ritonavir therapy. The high variability in tipranavir concentrations, the lack of increase in tipranavir  $C_{max}$ , and the 25% increase in tipranavir AUC when ritonavir dose doubled from 100 mg to 200 mg suggest that higher ritonavir concentrations when the tablet is administered will not significantly increase tipranavir concentrations. Thus, ritonavir tablets can be administered with tipranavir at the approved 500 mg tipranavir/200 mg ritonavir twice daily regimen, under fed conditions. The safety concerns with increases in tipranavir concentrations

warrant the following actions: (1) the precautionary language regarding tipranavir hepatic toxicity will be included in the tipranavir plus ritonavir drug interaction information in the ritonavir tablet label, (2) the ritonavir label will indicate ritonavir must be taken with meals, which may lessen the impact of the switch from ritonavir capsules to tablets, (3) and strategies for evaluating potential safety issues with tipranavir and ritonavir tablet coadministration will be discussed with tipranavir's sponsor (post-ritonavir tablet approval).

Administration of the new ritonavir tablet with tipranavir poses some safety concerns that will be addressed as outlined above. Incorporation of the above actions allows administration of tipranavir 500 mg with ritonavir 200 mg (2 x 100 mg tablets) under fed conditions.

Saquinavir: (approved regimen: 1000 mg saquinavir/100 mg ritonavir twice daily; administered under fed conditions)

There are no pharmacokinetic data that compare saquinavir concentrations following administration of saquinavir 1000 mg/ritonavir 200 mg to concentrations following administration of saquinavir 1000 mg/ritonavir 100 mg. Data from a parallel design study compare saquinavir concentrations following administration of saquinavir 1200 mg/ritonavir 200 mg once daily to concentrations following saquinavir 1200 mg/ritonavir 100 mg once daily. The Fortovase formulation of saquinavir (no longer marketed) was used in this study. The results of the study indicate saquinavir concentrations were lower when 1200 mg saquinavir was coadministered with 200 mg ritonavir instead of 100 mg ritonavir. Saquinavir AUC,  $C_{max}$ , and  $C_{min}$  geometric mean values were 30 to 40% lower with the higher dose of ritonavir. It is difficult to interpret the results because of the parallel study design and the variability in saquinavir concentrations. (Reference: Kilby JM, et al; Antimicrobial Agents and Chemotherapy, 2000; 2672-2678)

The review team evaluated additional information submitted by Abbott to determine whether lower saquinavir concentrations may result if ritonavir concentrations are increased. Abbott submitted a paper that describes a regression analysis conducted by Kilby, et al (HIV Med, 2002: Apr; 3(2):97-104). The regression analysis evaluated saquinavir concentrations following administration saquinavir (400 to 800 mg) in combination with ritonavir (200 mg to 400 mg). A statistically significant relationship was not observed between ritonavir dose and saquinavir  $C_{min}$  and  $C_{max}$  values.

Although results from Kilby, et al suggest higher ritonavir concentrations do not alter saquinavir concentrations, the review team considered the clinical significance of the lower saquinavir concentrations observed for saquinavir 1200 mg/ritonavir 200 mg compared to saquinavir 1200 mg/ritonavir 100 mg. The team determined that potential decreases in saquinavir exposure are not expected to result in saquinavir exposure that is lower than exposure following saquinavir 1200 mg administered three times a day without ritonavir coadministration. Clinical efficacy for saquinavir was established with saquinavir 1200 mg administered three times a day.

Administration of the new ritonavir tablet with saquinavir does not present safety or efficacy concerns.

Atazanavir (approved regimens: 300 mg atazanavir/100 mg ritonavir once daily; 400 mg once daily without ritonavir; administered under fed conditions)

Twenty-eight patients with subtherapeutic atazanavir concentrations following atazanavir 300 mg/ritonavir 100 mg once daily had their dose increased to atazanavir 300 mg/ritonavir 200 mg once daily. Blood samples were collected up to 3 hours post dose. Atazanavir concentrations were similar before and after the increase in ritonavir dose. (Reference: Harris M, et al; 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment, 2005) Other clinical pharmacology information indicates the use of concentrations up to 3 hours post dose is acceptable.

Administration of the new ritonavir tablet with atazanavir does not present safety or efficacy concerns.

Fosamprenavir (approved regimens: 700 mg fosamprenavir/100 mg ritonavir twice daily; 1400 mg fosamprenavir/100 mg ritonavir once daily; 1400 mg fosamprenavir/200 mg ritonavir once daily; 1400 mg fosamprenavir twice daily without ritonavir; administered under fasted or fed conditions)

When fosamprenavir 1400 mg/ritonavir 200 mg was compared with fosamprenavir 1400 mg/ritonavir 100 mg once daily, there was no significant change in amprenavir  $AUC_{(0-24h)}$  or  $C_{max}$ . Fosamprenavir  $C_{min}$  is higher by approximately 70% with the doubling of ritonavir doses. (Reference: Lexiva (fosamprenavir) prescribing information, April 2009). Because there is no change in total or maximum amprenavir exposure, we do not expect higher ritonavir concentrations to alter the safety profile of fosamprenavir/ritonavir.

Administration of the new ritonavir tablet with fosamprenavir does not present safety or efficacy concerns. The conclusion is relevant under fasted and fed conditions.

**REVIEW CONCLUSION:**

The information provided by the applicant, supplemented by review of approved drug product labels, supports the use of the ritonavir tablet formulation at the 600 mg twice daily dose or as a pharmacokinetic enhancer at 100 to 200 mg once or twice daily. The ritonavir tablet label will indicate the tablets need to be taken with a meal. Following approval of the tablet, the FDA will initiate discussion with tipranavir's sponsor regarding strategies for evaluating potential safety issues with tipranavir and ritonavir tablet coadministration.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20659	SUPPL-45	ABBOTT LABORATORIES PHARMACEUTICAL PRODUCTS DIV	NORVIR (RITONAVIR) ORAL SOLUTION
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/

---

KELLIE S REYNOLDS  
10/02/2009

JOHN A LAZOR  
10/14/2009