CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-945

ADMINISTRATIVE DOCUMENTS

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491 AP6B-1SW
Abbott Park, Illinois 60064-6108

June 8, 1999

Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
1st Floor Document Control Room
Rockville, Maryland 20850

Re: Norvir (ritonavir capsules) soft gelatin
NDA 20-945

Response to
Request for Information

Dear Sir or Madam:

The purpose of this submission is to provide the patent certification for the Norvir soft gelatin capsules. No patents on the soft gelatin formulation have issued yet. Of the ritonavir related patents which have been issued, the following are relevant and should be listed relative to the soft gelatin capsule NDA.

Please call me at the number provided below if you have any concerns regarding this information.

Sincerely,

Rebecca A. Welch

Rebecca A. Welch
Associate Director
PPD Regulatory Affairs
(847) 937-8971

Declaration of Patent

The undersigned declares that the following patents, which have been previously submitted, cover the drug, composition, and/or method of use for Norvir. These patents are published in the current "Orange Book". Norvir is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Patent #	Expiration Date	Topic of Patent
5,541,206	Jul 30, 2013	Drug, composition and method of use
5,635,523	Jun 03, 2014	Method of Use
5,648,497	Jul 15, 2014	Drug
5,846,987	Dec 29, 2012	Method of use

The sponsor, Abbott Laboratories, certifies that no previous patent claim this method of use.

Rebecca A Welch 6/7/99

Rebecca A. Welch
Associate Director
PPD Regulatory Affairs
Abbott Laboratories

EXCLUSIVITY SUMMARY FOR NDA # 20-945 SUPPL #000

Trade Name Norvir(ritonavir capsules) soft gelatin 100 mg capsules Generic Name Ritonavir

Applicant Name Abbott Laboratories HFD # 530

Approval Date If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO //

b) Is it an effectiveness supplement?

YES // NO /X/

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES // NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

This application was a new dosage form.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /__/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES // NO /X/

If yes, NDA # Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-659 Norvir oral solution

NDA# 20-680 Norvir (ritonavir) hard gelatin capsule

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS N/A

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
! -
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__/

If yes, explain: _____

_____

/S/

6/25/99

Signature Date

Title: Regulatory Project Officer

/S/

MD 6/29/99

Signature of Office/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-945 Supplement # 000 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Norvir (ritonavir capsules) soft gelatin 100 mg Action: (AP) AE NA

Applicant Abbott Laboratories Therapeutic Class 7030140 Antiviral/AIDS/Systemic

Indication(s) previously approved ~~N/A~~ Norvir is indicated in combination with other antiretroviral agents for the treatment of HIV infection

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application NORVIR (ritonavir capsules) soft gelatin 100 mg is indicated in combination with other antiretroviral agents for the treatment of HIV infections.

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

X c. The applicant has committed to doing such studies as will be required.
- X (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[signature] Hem.D. Regulatory Management Officer 6-25-99

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-945
Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

Certification Requirement for all Applications

For Approval of a Drug Product

Concerning Using Services of Debarred Persons

- DEBARMENT STATEMENT -

Any application for approval of a drug product submitted on or after June 1, 1992, must include:

> "A certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) (sections 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act), in connection with this application for approval of a drug product."

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)].

Rebecca A. Welch

3/1/99
Date

Rebecca A. Welch
Associate Director, PPD Regulatory Affairs
Abbott Laboratories
Dept. 491, Bldg. AP6B-1
(847) 937-8971
100 Abbott Park Road
Abbott Park, Illinois 60064

Regulatory Review Officer's Review of New Drug Application 20-945:
Norvir SEC 100 mg Capsules:

Date Submitted: March 1, 1999
Date Received: March 5, 1999
Amendments: March 30, 1999
Date Completed: June 29, 1999

Sponsor: Abbott Laboratories
Pharmaceutical Products Division
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

Drug: Ritonavir SEC 100 mg Capsules

Indication: Treatment of HIV Infection

Materials Reviewed:

- NDA — dated March 1, 1999
- Amendments dated March 30, 1999
- Clinical Pharmacology/Biopharmaceutics review prepared by Drs. Kumi, Davit, Lazor and Reynolds for NDA 20-569 and 20-680.
- Clinical Pharmacology/Biopharmaceutics review prepared by Dr. Gillespie for NDA 20-945

1.0 BACKGOUND:

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV infection. Since the original approval ritonavir was marketed as a semi-solid 100-mg capsule (SSC) and as an oral solution (80mg/mL). The applicant submitted an application for a new, soft-elastic (SEC) 100 mg — capsule on November 21, 1997. During the review, the applicant notified the division that the formation of a Form II polymorph had spontaneously occurred during manufacturing. The Form II crystal dramatically reduced the solubility of ritonavir such that the sponsor could no longer manufacturer the proposed 100 mg — SEC formulation or the SSC formulation; however the oral solution was successfully reformulated with the new polymorph. The applicant subsequently received a non-approval action for this application on November 23, 1998. The applicant has reformulated the SEC formulation to allow for Form I and Form II polymorph and resubmitted an application for ritonavir 100 mg SEC on March 1, 1999.

2.0 CLINICAL STUDIES

2.1. STUDY M98-966

"Assessment of the bioequivalence of and the effect of food on a new ritonavir soft elastic capsule formulation compared to the marketed liquid formulation"

2.2 STUDY OBJECTIVES:

- To assess the bioequivalence of the 100 mg ritonavir soft elastic capsule formulation to the currently marketed liquid formulation (K-5) under non-fasting conditions
- To evaluate the effect of food on the bioavailability of the SEC formulation

2.3 STUDY DESIGN:

This was an open-label, randomized, single-dose, three-treatment, three-period crossover study. Sixty healthy adult male and female subjects were enrolled in the trial. The three regimens in the study were:

Regimen A:	7.5 mL of 80 mg/mL ritonavir liquid (reference formulation) administered under non fasting conditions
Regimen B:	Six 100 mg SECs (test formulation) administered under nonfasting conditions
Regimen C:	Six 100 mg SECs (test formulation) administered under fasting conditions

Pharmacokinetic assessments were performed at 0, 0.5, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 32, and 40 hours after study drug administration.

2.4 STUDY RESULTS:

Please refer to the biopharm review prepared by Dr. Gillespie and the statistical report prepared by Dr. Hu for further details on the applicant's study analysis and conclusions.

Fifty-seven of the 60 patients enrolled in the study completed all phases of the study. Two subjects were dropped due to a positive drug screen and a third was lost to follow-up. Pharmacokinetic results of this trial are presented in Table 1. The mean and individual bioavailability parameters (C_{max}, AUC and C_{min}) are presented graphically in Figures 1 - 3.

Table 1. Pharmacokinetic Parameters (±SD)

	Fed Liquid	*Fed SEC*	*Difference*
T_{max}	4.1±1.6	5.5±2.0	+34%
C_{max}	11.9±5.3	13.6±5.4	+14%
$AUC_{0-\infty}$	109.6±60	121.7±54	+11%
C_{min}	3.9±2.6	5.9±2.7	+51%
$T_{1/2}$	4.2	3.96	-6%

Figure 1. Individual and Mean C_{max} Values (mean values denoted by horizontal line)

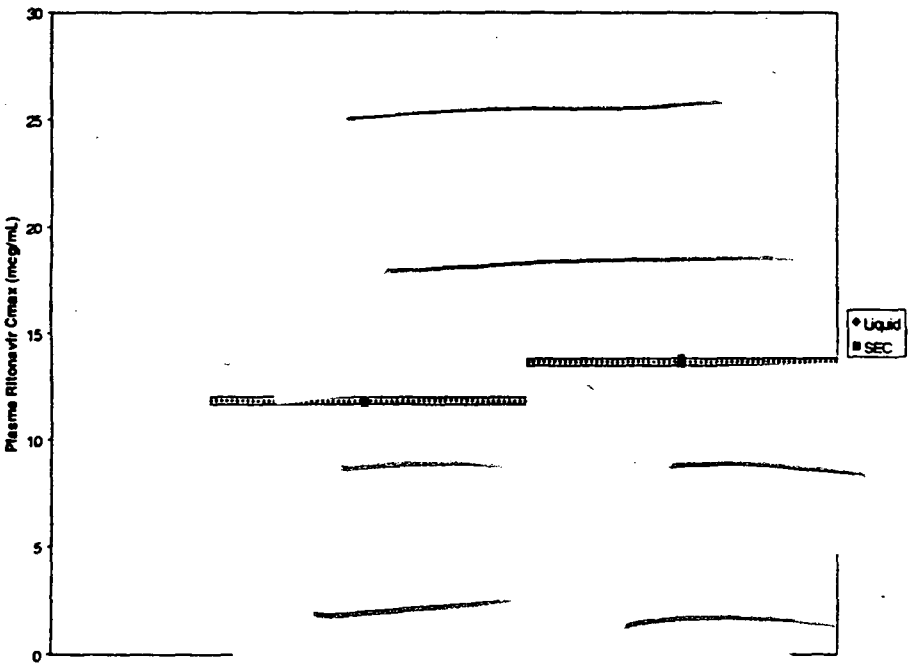
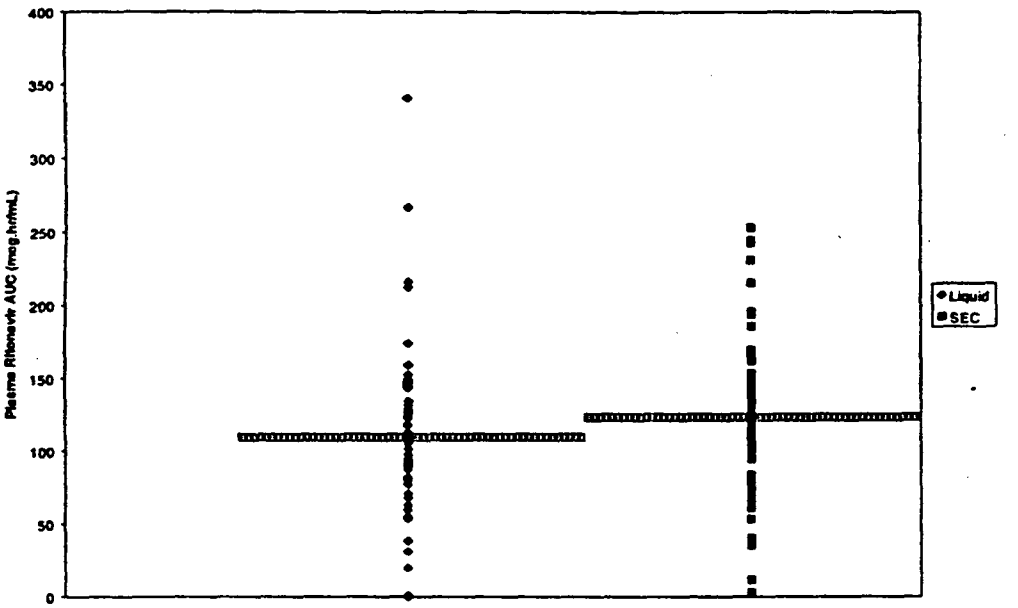
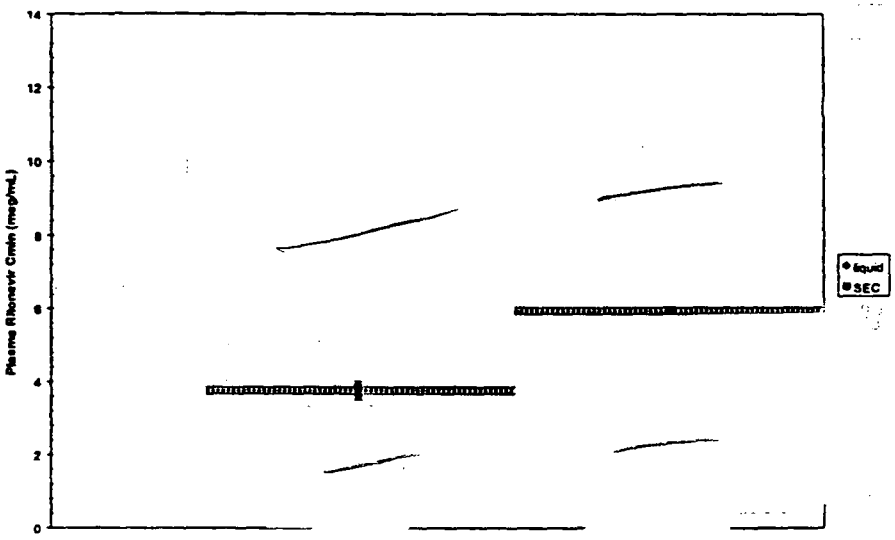


Figure 2. Individual and Mean AUC Values (mean values denoted by horizontal line)



APPEARS THIS WAY
ON ORIGINAL

Figure 3. Individual and Mean C_{min} (concentration at end of dosing interval) Values (mean values denoted by horizontal line)



In summary, the results of this study showed that the SEC and liquid formulations are not bioequivalent. However, it appears that several anomalous data points may be skewing the results. I agree with Dr. Gillespie's assessment that visual inspection of individual plots of the bioavailability parameters shows that each distribution is similar between the different treatment groups. Therefore, it seems unlikely that differences in mean C_{max} and AUC would produce any significant sequelae.

It appeared that the skewed distribution of the pharmacokinetic parameters were due, in part, to extremely low plasma concentrations obtained in five subjects. Three subjects who received the reference liquid formulation had AUC values of 0.1, 1.2 and 0.8 μg •h/mL, one subject who received the SEC formulation under nonfasting conditions had an AUC value of 3.1 μg •h/mL and one subject who received the SEC formulation under fasting conditions had an AUC value of 1.7 μg •h/mL.

The applicant states that it is unlikely that the low values seen in this study were a result of the new formulation, given that three of the five low AUC values were seen in subjects who received the liquid formulation. Doses were dispensed to multiple subjects from the same bottle; therefore these low values cannot be explained by formulation inconsistency alone. The applicant also states that it is improbable that these low values represent reduced absorption or higher clearance of ritonavir or a food effect, since these values were generally observed in only one of the three study periods, and identical meals and study conditions were employed in all three periods. The applicant notes that the same ritonavir liquid lot was given to 28 subjects in a separate bioavailability study and the lowest observed AUC was 74.9 μg •h/mL.

Emesis or non-compliance was not documented in the trial. These low values may have occurred if the dose was not ingested or if subjects vomited shortly after dosing. The applicant notes that in previous bioequivalence studies of ritonavir, two low values were observed in a single-dose bioequivalence study, one with the SSC formulation under nonfasting conditions and one with a previous SEC formulation under fasting conditions. Such low values have not been observed in any multiple dose pharmacokinetic studies in healthy or HIV infected patients who received ritonavir 600 mg BID.

In two analyses performed by the applicant, one in which all five low values were excluded and the second in which the three lowest values with the liquid formulation were excluded showed that the SEC formulation of ritonavir met the bioequivalence criteria relative to the reference liquid formulation. The results are summarized in Table 2 below.

Table 2: Bioequivalence and Food Effect Assessment Based on ANOVA

Comparison	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate*	90% Confidence Interval
Including All Values			
Test SEC non fasting vs Ref. Liquid Nonfasting	C_{max}	1.351	1.036-1.762
	AUC_t	1.351	1.027-1.775
	AUC_∞	1.350	1.028-1.773
Excluding All Five Low Extreme Values			
Test SEC non fasting vs Ref. Liquid Nonfasting	C_{max}	1.082	0.972-1.204
	AUC_t	1.068	0.956-1.194
	AUC_∞	1.068	0.957-1.193
Excluding the Three Low Extreme Values of the Reference Liquid Formulation			
Test SEC non fasting vs Ref. Liquid Nonfasting	C_{max}	1.045	0.877-1.244
	AUC_t	1.038	0.870-1.239
	AUC_∞	1.038	0.877-1.238

*Antilogarithm of the difference (test minus reference) of the least squares means for logarithms
Source NDA 20-945 Bio section vol 1 page 008

SAFETY OUTCOMES:

The most commonly reported treatment-emergent adverse events reported during the study were nausea, constipation, diarrhea, and circumoral paresthesia. Table 3 summarizes the numbers and percentages of subjects experiencing treatment-emergent adverse events. Treatment-emergent adverse events reported by only one subject per regimen are not included in the table.

Table 3: Treatment-Emergent Adverse Events

Body System	Liquid Formulation 600 mg ritonavir Nonfasting (N=59)	Test SEC Formulation 600 mg ritonavir Nonfasting (N=58)	Test SEC Formulation 600 mg ritonavir fasting (N=57)
All Systems	21 (35.6%)	20 (34.5%)	21 (36.8%)
Body as a Whole			
Abdominal Pain	1 (1.7%)	3 (5.2%)	1 (1.8%)
Headache	5 (8.5%)	4 (6.9%)	2 (3.5%)
Neck Pain	1 (1.7%)	0	2 (3.5%)
Digestive			
Constipation	6 (10.2%)	2 (3.4%)	7 (12.3%)
Diarrhea	3 (5.1%)	3 (5.2%)	7 (12.3%)
Nausea	7 (11.9%)	8 (13.8%)	4 (7%)
Vomiting	3 (5.1%)	3 (5.2%)	1 (1.8%)
Nervous			
Circumoral Paresthesia	10 (16.9%)	2 (3.4%)	5 (8.8%)
Dizziness	2 (3.4%)	2 (3.4%)	3 (5.3%)
Peripheral Paresthesia	1 (1.7%)	0	3 (5.3%)
Skin and Appendages			
Rash	2 (3.4%)	1 (1.7%)	0
Sweating	0	0	2 (3.5%)

Source NDA 20-945 bio section vol 1 page 208

There were no serious adverse events reported during the trial and no subject prematurely discontinued the study due to adverse events. No new or unexpected adverse events were observed with the SEC formulation or with the liquid formulation.

2.5 CONCLUSIONS:

When conventional criteria are used (two one-sided test procedures with 90% confidence interval analysis) the SEC formulation is not bioequivalent to the currently approved liquid. However, in analyses performed by the applicant in which all five low values were excluded or in which three low values for the liquid formulation were excluded showed that the SEC formulation of ritonavir met the bioequivalence criteria relative to the reference liquid formulation.

3.0 DISCUSSION:

In an effort to better understand the results of study m98-966 a review of previous bioequivalence studies with the ritonavir oral solution formulation was conducted to assess the AUC and C_{max} parameters. Listed below is a summary of the results from single-dose bioequivalence trials in which patients received 600 mg of ritonavir administered as an oral solution. The results of the oral solution arm from the bioequivalence study of the soft elastic capsule formulation compared to the marketed liquid formulation is depicted in bolded italics for comparison.

Study	Parameter					
	Formulation	Patient Population	Conditions	Total number of subjects	C_{max} (µg /mL)	AUC_∞ (µg •h/mL)
M98-966: Bioequivalence	***Marketed Oral Solution***	***Healthy***	***Fed***	***60***	***11.9±5.3***	***109.6±60***
Study M95-284: Mass Balance	Oral solution – Formulation not specified	Healthy	Fed State	5	13.8 ± 2.5	125 ± 26*
M93-052: Dose Escalation	A	HIV +	Fed State	8	12.54 ± 4.57	132.2 ± 82.6
M95-279: Bioequivalence	K-4Y	Healthy	Fed State	15	15.2 ± 4.2	138.7 ± 47.9
	A	Healthy	Fed State	15	15.2 ± 3.9	139.0 ± 46.0
	K-5	Healthy	Fed State	15	14.6 ± 3.8	132.0 ± 42.5
M95-378	A	Healthy	Fed State	21	14.2 ± 3.3	135.3 ± 42.0
M95-350	A	Healthy	Fed State	23	14.2 ± 3.4	151.4 ± 43.4

*Note 24hr AUC value

The mean C_{max} and AUC values for studies M95-284, M93-052, M95-279, M95-378 and M95-350 are approximately 14.2 µg /mL and 136.0 µg •h/mL respectively. In comparison, the C_{max} and AUC values for these studies were approximately 19 % and 25 % greater than the C_{max} and AUC values observed in study M98-966. Although cross study comparisons should be made with caution, results from previous single-dose studies using 600 mg of ritonavir oral solution suggest that concentrations for the oral solution in study M98-966 were uncharacteristically low.

In addition, a second analysis was performed which compared C_{max} and AUC values for the SEC formulation to that of single-dose bioequivalence trials in patients receiving 600 mg of ritonavir administered as a semi solid formulation. The results are summarized below.

Study	Parameter				
	Formulation	Conditions	Total number of subjects	C_{max} (µg /mL)	AUC_∞ (µg •h/mL)
M98-966: Bioequivalence	***SEC***	***Fed State***	***60***	***13.64 ± 5.4***	***121.7 ± 54***
M95-378: Bioequivalence	L (semi-solid capsule)	Fed State	21	14.5 ± 4.1	129.5 ± 47.1
M95-350: Bioequivalence	L (semi-solid capsule)	Fed State	23	13.7 ± 2.3	133.8 ± 31.82

This analysis provides reassurance that the SEC formulation produces similar C_{max} and AUCs compared to the semi-solid capsule formulation when administered under similar conditions. The C_{max} and AUC values from the SEC formulation are not higher than those observed in previous studies and therefore should not pose any additional safety concerns.

4.0 RECOMMENDED REGULATORY ACTION:

Although the AUC and C_{max} levels for the SEC formulation were approximately 35% higher compared to the liquid formulation in study M98-996, these levels were comparable to those seen in previous bioequivalence studies with the oral solution and semi solid capsule formulations. Based on these findings, the SEC levels should not pose any additional safety concerns and are comparable to historical controls; therefore, approval of the ritonavir 100-mg SEC capsules is recommended.

Kimberly Struble, Pharm.D.
Regulatory Review Officer

Concurrence:
HFD-530/MOTL/Murray /S/ 6/29/99
HFD-530/DivDir/Jolson /S/ 7/2/99

cc:
Original NDA
Division File
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/CSO/Lynche
HFD-530/Biopharm/Reynolds,Rajagopalan

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1044	HFD#	530	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	KO-YU LO			NORVIR	Ritonavir Capsules, 100 mg, 600 mg bid Ritonavir Oral Solution 80 mg/mL

A. Look-alike/Sound-alike

NORVASC

Potential for confusion:

____ Low XXX Medium ____ High

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

THE — IS UNNECESSARY.

D. Established Name

XXX Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

____ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date S 9/3/98

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: **February 9, 1999**

NDA: **20-945**

Drug: **Norvir SEC**

Indication: **Treatment of HIV Infection**

Sponsor: **Abbott Laboratories**

Type of Meeting: **Chemistry and Manufacturing/Pre-NDA Meeting**

DAVDP Attendees:
Heidi Jolson, M.D., M.P.H., Director
Debra Birnkrant, M.D., Deputy Director
Jeff Murray, M.D., Medical Team Leader
Kim Struble, Pharm.D., Regulatory Review Officer
Stephen Miller, Ph.D., Chemistry Team Leader
Ko-yu Lo, Ph.D., Chemistry Reviewer
Chi-wan Chen, Ph.D., Director, Div New Drug Chemistry III
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader
Walla Dempsey, Ph.D., Associate Director
Zi Qiang Gu, Ph.D., Chemist
George Lunn, Ph.D., Chemist
Sylvia D. Lynche, Pharm.D., Regulatory Project Manager
Virginia L. Yoerg, Regulatory Project Manager
Marsha Holloman, Regulatory Project Manager

Abbott Attendees:
John Morris, M.D., Research Investigator
Eugene Sun, M.D., Antiviral Venture Head
Rebecca Welch, Associate Director Regulatory Affairs
Roland Catherall, V.P. Regulatory Affairs
Efraim Shek, V.P. Pharm. Analyst, RDD
Rick Granneman, Director of Pharmacokinetics
Charles Locke, Manager Statistics
Laman Al-Razzak, Sr. Project Manager PARD

Background:

The sponsor requested this meeting on January 22, 1999, to facilitate discussion regarding the content and timing of the amendment submitted under NDA 20-945. This amendment addresses the issues raised in the action letter dated November 23, 1998.

Objective:

1. To discuss the adequacy of the data to substantiate an NDA re-submission with [redacted] of stability data and two bioequivalence studies (plus two amendments) in support of the review and approval of NORVIR [redacted] ritonavir soft gelatin capsules).

Discussion:

Following a presentation by the sponsor, the following items were discussed: timing of the application; the physical stability data available on this product; and the bioequivalence studies that will be submitted with the application. The sponsor proposed submitting the NDA by February 28, 1999 with [redacted] of stability data and two bioequivalence studies. Two amendments would be filed on March 30, 1999 and April 30, 1999. The first amendment would contain a third bioequivalence study that compared the capsules containing [redacted] crystals with the oral solutions as the reference. The second amendment would contain the [redacted] stability data.

1. FDA indicated that under the proposed timeline, the [redacted] stability data would not be available until July, which would not allow sufficient time for review under the review clock. Abbott expressed a willingness to go to the marketplace with a [redacted] expiration date and would provide the FDA with [redacted] stability data during the review period. FDA requested that the sponsor submit a proposal by fascimile for the [redacted] shelf life and outline a timeline. The FDA also requested that the sponsor include the stability commitments in the NDA package.

2. FDA questioned how well the stability studies project the [redacted] The sponsor agreed to consolidate the data by the end of February for presentation to the Division.

3. More information was requested on the bioequivalence study to ensure that the study is completed with capsules containing [redacted] Form II crystals. Information was requested on the rate that crystallization occurred. The sponsor indicated that no additional growth of crystals occurred after [redacted] and that these data would be included with the NDA re-submission.

Decisions/Agreements Reached:

1. The sponsor will submit a proposal for marketing the product with a [redacted] shelf life and outline a timeline for additional data. The FDA will review and comment at that time.

2. The sponsor will include commitments about the stability testing in the NDA package.

3. The sponsor will submit data on the projection of ——— from the stability studies by the end of February.

4. The sponsor agreed to submit data on the crystallization rates and levels.

Minutes preparer: |S| **Date:** 7/29/99

Conference Chair: **Date:** 7/29/99

Concurrence:
HFD-530/MTL/Murray-eso 7/19/99
HFD-530/RRO/Struble- 7/20/99
HFD-530/CTL/Miller- 7/26/99
HFD-530/CR/Lo- 7/29/99
HFD-530/PTL/Reynolds
HFD-530/Dempsey-

cc:
HFD-530/Lynche
HFD-530/Struble
HFD-530/Lo
HFD-530/Miller
Original NDA 20-945
Division file
HFD-530

Meeting Minutes

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996.

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Attn: D-491, AP6B-1
Pharmaceutical Products Division
Regulatory Affairs

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Attn: Pete Noblin
D-491, AP6B-1
Regulatory Affairs

3. TELEPHONE NUMBER *(Include Area Code)*
847-937-5091

4. PRODUCT NAME
Norvir

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☑ NO
(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☑ YES ☐ NO
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

ATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Rebecca A Welch for Peter W. Noblin for PPD User Fees	Associate Director, Regulatory Affairs	March 1, 1999

FORM FDA 3397 (12/93)

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