

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-785

CHEMISTRY REVIEW(S)

Memorandum

To: Stephen P. Miller

CC:

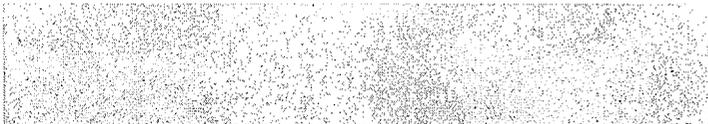
From: Lorenzo Rocca

Date: 12/17/2004

Re: NDA 21-785 Methods Validation

As we discussed today (Thursday, December 16, 2004) the methods for the analytical testing of saquinavir mesylate drug substance and INVERASE® (saquinavir mesylate), 500 mg Film Coated Tablet will not be submitted to the Office of New Drug Chemistry (HFD-800) for evaluation and final decision as to which (if any) of the sponsor's analytical release methods for drug substance and drug product should be submitted to the appropriate FDA Laboratory for validation.

This decision is based on evaluation of the test methods and the method validation reports provided in NDA 21-785. Based on the results of this evaluation it can be concluded, with reasonable certainty, that the sponsor's proposed test methods will allow an analyst to accurately and reproducibly perform the analysis of saquinavir mesylate drug substance and INVERASE® (saquinavir mesylate), 500 mg Film Coated Tablet.



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

/s/

Lorenzo Rocca
12/17/04 09:43:55 AM
CHEMIST

Stephen Paul Miller
12/17/04 01:42:24 PM
CHEMIST

I concur that it is not necessary for FDA
laboratories to validate the analytical methods in NDA
21-785.

NDA 21-785

**INVIRASE® (saquinavir mesylate) 500 mg
Film Coated Tablet**

Hoffman-La Roche Inc.

**Lorenzo Rocca, Ph.D.
Division of Anti-Viral Drug Products**

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Chemistry Review Data Sheet

1. NDA 21-785
2. REVIEW #: 1
3. REVIEW DATE: December 10, 2004
4. REVIEWER: Lorenzo Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Amendment (N-000(BC))

Document Date

18-June-2004

21-September-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Hoffman-La Roche Inc.

Address: 340 Kingsland Street
Nutly, NJ 07110-1199

Representative: Matthew Lamb, Pharm. D.

Telephone: 973-562-2833

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: INVIRASE®
- b) Non-Proprietary Name (USAN): Saquinavir mesylate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-viral: Anti-HIV

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

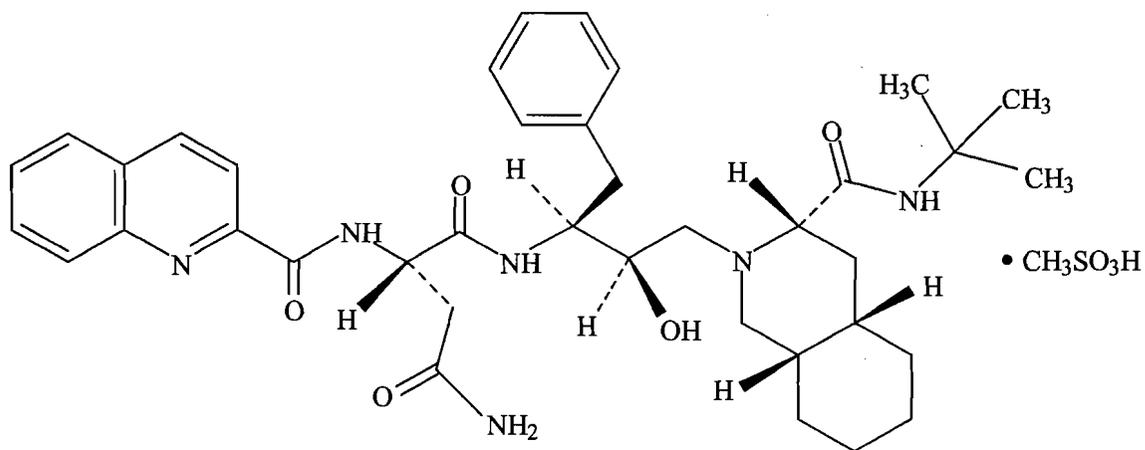
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-[(αS)-α-[(1R)-2-[(3S,4aS,8aS)-3-(*tert*-Butylcarbonyl)octahydro-2(1H)-isoquinoly]-1-hydroxyethyl]phenethyl]-2-quinaldamidossuccinamide monomethanesulfonate (salt)
(C₃₈H₅₀N₆O₅.CH₄O₃S; Mol. Wt. 766.95)

CHEMISTRY REVIEW

Chemistry Review Data Sheet



Saquinavir Mesylate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
C	3	/		3	Adequate	NA	None
	3			3	Adequate	NA	None
	3			3	Adequate	NA	None
	3			3	Adequate	NA	None
	4			1	Adequate	Aug. 16, 2004	None

CHEMISTRY REVIEW

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	Susan Zhou, Ph.D.
EES	All sites approved by OC	12/9/04	Office of Compliance (OC) (Establishment Report Appended to this review)
Pharm/Tox	N/A	N/A	Kuei Meng Wu, Ph.D.
Clinical Pharmacology	Approved	pending	Jenn Digiacinto, Pharm. D.
LNC	USAN available	N/A	N/A
Methods Validation	Will be submitted to ONDC upper management for consideration	pending	Lorenzo Rocca, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical exclusion granted	12/9/04	Lorenzo Rocca, Ph.D.
Microbiology	Approved	pending	Narayana Battula, Ph.D.

The Chemistry Review for NDA 21-785

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The chemistry, manufacturing and controls for saquinavir mesylate drug substance are described in the approved NDA 20-628 for INVIRASE® 200 mg Capsule (approved December 6, 1995). All chemical and quality control information pertaining to the drug substance which is described in NDA 20-628 is applicable to this new dosage form.

INVIRASE® (saquinavir mesylate) 500 mg Film Coated Tablets contain saquinavir mesylate, equivalent to 500 mg of the free base, in a light orange to grayish or brownish orange oval cylindrical, biconvex tablet imprinted (i.e., imbossed) above SQV 500 and below ROCHE. INVIRASE® (saquinavir mesylate) 500 mg Film Coated tablets will be packaged in a standard bottle with a . The inactive ingredients are povidone K30 USP , lactose : , croscarmellose NF , microcrystalline cellulose NF and magnesium stearate NF . The inactive ingredients are all compendial except for the film coat. The sponsor plans to use a commercially available coating material manufacturer has provided LOA . to support NDA 21-785. has been reviewed by Lorenzo Rocca, Ph.D. (HFD-530) and found adequate to support NDA 21-785. The sponsor has also stated that the inactive ingredients, with the exception of lactose are not derived from human or animal origin. The inactive ingredient lactose is derived from cow's milk the same as milk collected for human consumption. The sponsor's statement confirms there is low risk from BSE contamination to the patient.

The first saquinavir mesylate market formulation was INVIRASE® (saquinavir mesylate) 200 mg Hard-Gelatine Capsule (i.e., NDA 20-628, approved December 6, 1995). However, to improve patient compliance the sponsor is proposing a 500 mg film-coated tablet (10 x 200 mg capsules/day vs. 4 x 500 mg tablets/day). Both the

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capsule and tablet use similar but not identical inactive ingredients. The ingredients, in both cases, are all _____ used to manufacture solid dosage form. Presumably a 500 mg film coated tablet formulation is more desirable from a patient compliant stand point than a 500 mg hard gelatin capsule. During formulation development tablet core composition remained unchanged whereas the coating material _____

_____ produced at Hofmann-La Roche (Basel, Switzerland) and batches _____ at the commercial manufacturing site Roche Farma Leganés (Madrid, Spain). The manufacturing process has remained essentially unchanged throughout the development of INVIRASE® (saquinavir mesylate) 500 mg Film Coated Tablets with only minor adjustments in equipment to accommodate batch size. The manufacturing process involves :

_____ . The manufacturing steps represent conventional pharmaceutical operations and the sponsor has demonstrated that during the development process they have adequately evaluated the critical process parameters and instituted appropriate in process controls to ensure a robust and reproducible commercial scale manufacturing process. As mentioned above the sponsor has confirmed their control of the manufacturing process by production of multiple batches (_____) of drug product at the scale-up site at Hofmann-La Roche (Basel, Switzerland) and the production of the registration batches _____ at the final manufacturing site Roche Farma Leganés (Madrid, Spain). The three batches manufactured at Basel were manufactured at approximately _____ commercial scale. The three batches manufactured at Roche Farma two batches were produced at _____ of commercial scale while the third batch represented commercial scale (Batch Size = Theoretical Yield of Tablets : _____). The batch analysis data for these multiple batches provides evidence that the sponsor can produce a product that meets release specifications on a consistent basis.

Manufacturing, testing, labeling and packaging of INVIRASE® (saquinavir mesylate) 500 mg Film-Coated Tablets will take place at Roche Farma, S.A. (Madrid, Spain). The Roche Farma facility has been inspected for cGMP and found acceptable by the Office of Compliance (OC). The Establishment Evaluation Request Detail Report is appended to this review.

The drug product specifications are acceptable. Specifications for INVIRASE® (saquinavir mesylate) 500 mg Film-Coated Tablets are similar but not identical to those for the INVIRASE® (saquinavir mesylate) 200 mg Capsule. The sponsor has provided sufficient justification for their proposed specifications. Biopharm's (HFD-880) review of NDA 21-785 has been completed (see NDA _____ Clinical Pharmacology/Biopharmaceutics Review, October, 2004). Biopharm has found the sponsor's proposed dissolution specifications (i.e., _____ (Q), _____) and dissolution conditions (USP Apparatus _____ rpm _____) acceptable. The impurities specifications for the drug product reflect the fact that saquinavir mesylate has demonstrated long term stability. Two degradation

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products, _____, have been qualified through tox testing and will be controlled at a spec of NMT _____. Each Unspecified, Total Unspecified Impurities and Total All Impurities are set at NMT _____ each, NMT _____, and NMT _____, respectively, which are identical to the specifications set for the approved capsule formulation and also recommended by ICH Q3BR.

The analytical methods are adequately described and the sponsor has validated the methods for their intended use. A complete method validation package is supplied. Validation of the proposed analytical methods by the FDA is not expected before NDA approval.

The tablet container closure system is similar but not identical to the container/closure system used to package the approved capsule formulation. The INVIRASE® (saquinavir mesylate) 500 mg Film-Coated Tablets container/closure system is a 120-count _____ bottle _____.

The packaging components have previously been found safe for use in packaging solid oral dosage formulation, and the stability data shows that the container/closure system provides appropriate protection for this product.

The available primary drug product stability data includes up to nine months room temperature and six months accelerated ICH stability data on drug product manufactured at pilot-scale as well as full scale batch at the proposed commercial site of drug product manufacture. The photostability, assay values, content of degradation products and the physical properties (appearance, color and dissolution) of the tablets remained within specification during storage at all tested conditions with no trends observed in any of the values. Based on the primary stability data as well as _____ months of supportive stability data for two development batches produced at the original development site and packaged in the commercial/container closure system, the stability data supports the sponsor's proposed 24 month shelf life for INVIRASE® (saquinavir mesylate) 500 mg Film-Coated Tablets. The sponsor's expiration dating, namely "Store at 25°C (77°F): excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room temperature]" is acceptable.

Categorical exclusion from the requirement to file an Environment Assessment is requested by the sponsor and is reasonable based on the sponsor's claim being in accordance with 21 CFR 25.31(b). The sponsors proposed container label is in accordance with the CFR for labeling (201.10 (g)(2)).

The Quality Overall Summary in NDA 21-785 Module 2 comprised a twenty page summary of the data presented in NDA 21-785 Module 3. The summary in Module 2 was well crafted and clearly highlighted the key points covered in Module 3 including pharmaceutical development, description and composition of the drug product, control of excipients and drug product, drug product specifications, drug product container closure system and drug product stability.



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B. Description of How the Drug Product is Intended to be Used

INVIRASE® (saquinavir mesylate) 500 mg Film Coated Tablets may only be used if it is combined with ritonavir. The recommended dosage of INVIRASE® in combination with Norvir® (ritonavir) is a twice daily dosing of 2 tablets of INVIRASE® (saquinavir mesylate) 500 mg taken with 1 capsule of Norvir® (ritonavir) 100 mg. INVIRASE must be taken along with Norvir® (ritonavir), and INVIRASE® must be taken with meals or up to 2 hours after a meal. The tablets are supplied in _____ bottles containing 120 tablets. INVIRASE® tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. The bottles should be kept tightly closed.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-785 is approved for CMC. All sites involved in the manufacture of the drug substance and drug product have been approved by the Office of Compliance (OC). The Establishment Evaluation Request Detail Report is appended to this review. The package insert, patient package insert and drug product label have been reviewed for CMC and found acceptable.

The CMC for drug substance saquinavir mesylate is adequately described in the approved NDA 20-628 for INVIRASE® 200 mg Capsule (approved December 6, 1995). The composition, manufacturing process and specifications for INVIRASE® (saquinavir mesylate) 500 mg Film Coated Tablets are adequate to assure the identity and quality of the drug product. The container/closure system is adequate to assure the drug product will be stable, protected and properly identified. The sponsor's proposed 24 month expiration dating period is acceptable and is supported by the available primary and supportive drug product stability data.

III. Administrative

A. Reviewer's Signature

Lorenzo Rocca, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Stephen P. Miller, Ph.D. {Signed Electronically in DFS}/Date

C. CC Block

David Lin, Ph.D.

Kenny Shade, R.N., J.D.

34 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

/s/

Lorenzo Rocca
12/10/04 07:02:38 PM
CHEMIST

Stephen Paul Miller
12/13/04 11:13:25 AM
CHEMIST
NDA 21-785 is approved from the CMC perspective.