CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-503

CHEMISTRY REVIEW(S)

NDA 21-503

Nelfinavir Mesylate

Agouron Pharmaceuticals, Inc.

George Lunn
Division of Anti-Viral Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-503

2. REVIEW #: 1

3. REVIEW DATE: 25-APR-2003

4. REVIEWER: George Lunn

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	6/28/02
BC	7/25/02
BC	9/27/02
BC	12/4/02
BC	12/16/02
BL	12/20/02
BC	2/27/03
BC	4/10/03
BC	4/11/03
BL	4/16/03
BC	4/17/03
BC	4/24/03

APPEARS THIS WAY ON ORIGINAL

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Agouron Pharmaceuticals, Inc.
Address:	10350 North Torrey Pines Road La Jolla, CA 92037-1020
Representative:	Marie-Do Mompas, Pharm.D.
Telephone:	(858) 622 7360; fax (858) 678 8285

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Viracept®
b) Non-Proprietary Name (USAN): nelfinavir mesylate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5 (new formulation)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-viral

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 625 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

APPEARS THIS WAY ON ORIGINAL

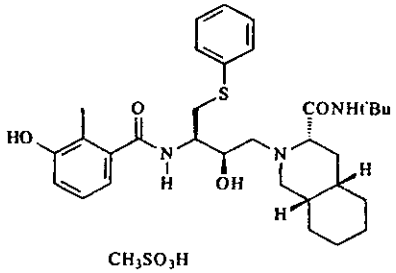
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note8]:

_____SPOTS product – Form Completed

__X__ Not a SPOTS product

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

[3S-[2(2S*,3S*,3α,4aβ,8aβ]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino-4-(phenylthio)butyl]-3-isoquinolinecarboxamide, monomethanesulfonate (salt)



$C_{32}H_{45}N_3O_4S.CH_3SO_3H$

Formula weight: 663.90

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	[ ]	[ ]	3	Adequate	9/27/00	Acceptable for solid oral dosage forms
—	III	[ ]	[ ]	7	Adequate		Used for currently approved 250 mg tablets; acceptable
—	III	[ ]	[ ]	7	Adequate		Used for currently approved 250 mg tablets;
—	III	[ ]	[ ]	3	Adequate	10/30/97	
—	III	—	—	3	Adequate	9/7/00	Acceptable for

Chemistry Review Data Sheet

							solid oral dosage forms
—	III	[ ]	[ ]	3	Adequate	7/28/99	Acceptable for —

[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
Review of original NDA and Amendments	NDA 20-779	Drug substance manufacture and testing

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-503

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

The manufacturing process, quality control testing, and suppliers of the drug substance remain unchanged from those described in the approved NDA 20779 for nelfinavir mesylate 250 mg tablets, as amended.

Drug Product

The drug product is a 625 mg film-coated tablet. The inactive ingredients are calcium silicate, crospovidone, colloidal silicon dioxide, magnesium stearate, ——— and — The 625 mg tablets are very similar to the currently approved 250 mg tablets with the addition of colloidal silicon dioxide and the deletion of the blue color. However, the relative amounts of the components are quite different. The 625 mg tablets are not bioequivalent to the currently approved 250 mg tablets.

All inactive ingredients are compendial except for the ——— The —— is composed of compendial ingredients and is the same component as used in the currently approved 625 mg tablets (NDA 20-779). The —— is covered by a DMF.

The tablets are manufactured using a ——— method and the core tablets are ——— ——— The commercial scale is — kg or —— tablets. The in-process controls consist of

The specifications are virtually the same as for the currently approved 250 mg tablet. After some discussion the dissolution acceptance criterion remains at Q = — % in 45 min. — included as a test to be conducted for information only. — not a specification for the 250 mg tablet. At the request of FDA some of the impurity acceptance criteria were reduced to a modest extent. These reduced acceptance criteria will also be applied to the currently marketed 250 mg tablets.

The analytical methods are virtually the same as those for the currently approved 250 mg tablets. Sample preparations are adjusted to accommodate the increased strength. The methods are fully described and validation details are provided. The methods were validated for the 625 mg tablets. A complete Methods Validation package is provided. However, since the methods are so similar to the currently approved methods for the 250 mg tablets, no Methods Validation is necessary.

The same container-closure system is used as for the currently approved 250 mg tablets. The tablets are packaged in 120 count 325 cc — bottles fitted with child-resistant closures and a ——— The product contact materials (——— have been reviewed and found to be adequate for solid oral dosage forms. — . of satisfactory stability data for tablets stored at 5°C, 25°C/60% RH, and 30°C/60% RH and — . of satisfactory data for tablets stored at 40°C/75% RH are provided for three registrational batches of 625 mg tablets and one comparative batch of 250 mg tablets. The registrational batch sizes are ——— tablets. — of the commercial scale. There are no obvious trends and the changes in degradants are minimal. Minor cosmetic defects — were observed and attributed to ——— —— The —— will be modified.

In addition tablets were stored under — —— There was no appreciable change after — The conditions did lead to an increase in impurities (although well within the specifications). Tablets from — batch were also stored open for ——— At 5°C/amb RH and 40°C/75% RH dissolution failures occurred and at 40°C/75% RH and 60°C/amb RH Storage open clearly produces unacceptable results under a number of conditions. For this reason, the container label contains the statement "Dispense in original container" for both 250 and 625 mg tablets.

Supporting stability data are offered for other batches of 250 mg and 625 mg tablets. The only obvious trend is to — with time and temperature.

A statistical analysis was carried out for the registrational and supporting stability batches using the data obtained at 25°C/60% RH and 30°C/60% RH. The values for assay and total degradants were found not to change over time. Based on a 95% confidence band the upper bound at 36 months was found to be well within specification for the degradants ——— The expiration dating period for the currently approved 250 mg tablets is 36 months. An expiration dating period of 36 months is reasonable.

An exclusion from the environmental assessment requirements is claimed under 21 CFR 25.31(a). The new NDA is not expected to increase the use of the active moiety, nelfinavir mesylate, since the total daily dose remains the same.

Representations were made by FDA that the proposed bottle label might be difficult to distinguish from the label for the currently approved 250 mg tablets. In an Amendment the sponsor changed the label so as to make it readily distinguishable. The package insert is essentially the package insert for the currently approved 250 mg formulation, modified to include the new 625 mg formulation. In particular, the Description, Dosage and Administration, and How Supplied sections have been modified to reflect the new formulation.

An Establishment Evaluation Request was entered into EES for the [redacted] sites. At FDA request a [redacted] were withdrawn because these sites no longer perform these functions. On 4/14/03 an Overall Recommendation of Acceptable was made.

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

In combination with other antiretroviral agents Viracept (nelfinavir mesylate) tablets are indicated for the treatment of HIV infection. This NDA describes a 625 mg film-coated tablet. The recommended dose of nelfinavir is 1250 mg bid. Instead of consuming five of the 250 mg tablets twice a day the patient will now consume two of the 625 mg tablets twice a day. Thus the daily pill count will decrease from ten to four. The tablets are packaged in 120 count 325 cc [redacted] bottles fitted with child-resistant closures and a [redacted] This represents a 30 day supply. The expiration dating period is 36 months and the recommended storage conditions are 15-30°C.

C. Basis for Approvability or Not-Approval Recommendation

In this NDA the composition of the 625 mg nelfinavir mesylate tablets and the manufacturing process are adequately described. The composition, specifications, and analytical methods of the 625 mg tablets are very similar to those of the currently approved 250 mg tablets. The same container-closure system is used as for the currently approved 250 mg tablets and the 36 month expiry is appropriate and is supported by [redacted], of satisfactory stability data for the 625 mg tablets, 36 months of satisfactory stability data for the similar 250 mg tablets, and a statistical analysis. The package insert is essentially the package insert for the currently approved 250 mg formulation with the Description, Dosage and Administration, and How Supplied modified to reflect the new formulation. After evaluation all manufacturing sites were found to acceptable, particularly the [redacted] site [redacted] and

the drug product testing laboratory [redacted] This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature George Lunn, Ph.D. {Signed Electronically in DFS} Date of draft review 4/15/03

B. Endorsement Block Stephen P. Miller, Ph.D., {Signed Electronically in DFS}

C. CC Block Chi-wan Chen, Ph.D.

22 Page(s) Withheld

1 § 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/

George Lunn
5/6/03 12:01:51 PM
CHEMIST

Nelfinavir 625 mg NDA

Stephen Paul Miller
5/6/03 04:59:40 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21503/000	Action Goal:	
Stamp:	01-JUL-2002	District Goal:	02-MAR-2003
Statutory Due:	01-MAY-2003	Brand Name:	VIRACEPT(NELFINAVIR
Applicant:	AGOURON PHARMACEUTICALS INC 10350 NORTH TORREY PINES RD LA JOLLA, CA 92037	Estab. Name: Generic Name:	MESYLATE) 625MG TABS NELFINAVIR MESYLATE
Priority:	S	Dosage Form:	(TABLET)
Org Code:	530	Strength:	625 MG

Application Comment: THIS NDA IS FOR A HIGHER STRENGTH 625 MG NELFINAVIR TABLET. THIS TABLET IS NOT BIOEQUIVALENT TO THE CURRENTLY APPROVED 250 MG NELFINAVIR TABLETS THEREFORE A NEW NDA IS REQUIRED. THE COMPONENTS OF THE NEW TABLET ARE VIRTUALY THE SAME AS THOSE OF THE CURRENTLY APPROVED TABLET BUT THE PROPORTIONS OF THESE COMPONENTS ARE DIFFERENT. THE MANUFACTURING PROCESSES ARE VERY SIMILAR. THE MANUFACTURE OF THE DRUG SUBSTANCE IS NOT AFFECTED BY THIS NDA. (on 16-JUL-2002 by G. LUNN (HFD-530) 301-827-2393)

FDA Contacts:	S. BELOUIN	(HFD-530)	301-827-2335	, Project Manager
	G. LUNN	(HFD-530)	301-827-2393	, Review Chemist
	S. MILLER	(HFD-530)	301-827-2392	, Team Leader

Overall Recommendation: ACCEPTABLE on 14-APR-2003by J. D AMBROGIO(HFD-322)301-827-9054

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
MITTED TO OC	16-JUL-2002				LUNNG
SUBMITTED TO DO	17-JUL-2002	GMP			DAMBROGIOJ
DO RECOMMENDATION	24-JUL-2002			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ
OC RECOMMENDATION	24-JUL-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
SUBMITTED TO DO	17-JUL-2002	GMP			DAMBROGIOJ
DO RECOMMENDATION	08-AUG-2002			ACCEPTABLE BASED ON FILE REVIEW	VMATUSOV
LAST GMP INSPECTION CONDUCTED BETWEEN 7/18/02 & 7/25/02 FOUND THE FIRM TO BE ACCEPTABLE. CONFIRMED THAT THE FIRM IS AWARE OF THE APPLICATION.					
OC RECOMMENDATION	08-AUG-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: TCM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
SUBMITTED TO DO	17-JUL-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	01-AUG-2002	PS			MTORRES
INSPECTION SCHEDULED	16-OCT-2002		15-NOV-2002		MTORRES
INSPECTION PERFORMED	10-FEB-2003		17-DEC-2002		MTORRES

This unannounced GMP inspection of this was made according to [redacted] Workplan. A concurrent inspection of [redacted] drug products manufactured by [redacted] was also conducted. Coverage was given under [redacted]

Two NDA Pre-Approval Inspections were conducted for NDA 21-503, Nelfinavir Mesylate 625mg tabs) and [redacted]. We also conducted a post-approval inspection for [redacted] however, this drug application has not been approved yet. We also evaluated 6 DQRS consumer complaints and completed an [redacted]gnment from the Postmarket Surveillance Team (HFD-332) regarding ADEs. [redacted]mited inspection conducted from 11/26-12/7/01 revealed deficiencies in consumer complaints handling and investigation procedures and was classified VAI. A GMP inspection dated 10/31-11/08/00 was classified NAI. A prior GMP inspection dated 5/1/00 revealed significant deficiencies in [redacted] and investigations of OOS results. An untitled letter was issued.

This inspection revealed deficiencies for not conducting [redacted] [redacted] incomplete or untimely laboratory or manufacturing investigations; failure to submit a FAR; and failure to validate a spreadsheet used for calculations. An FDA-483 was issued to [redacted] President & CEO, who promised immediate corrections and a written response to the District Director. Doc sample 202451was collected to document IS of Viracept Oral Powder, lot DW29001A. NDA Profile samples 205150 & 208547 were also collected.

DO RECOMMENDATION	10-APR-2003	ACCEPTABLE ADEQUATE FIRM RESPONSE	MSOSA
OC RECOMMENDATION	10-APR-2003	ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: CFN [redacted] FEI [redacted]

[redacted]

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:

Profile: CSN OAI Status: NONE

Estab. Comment: FACTS PRE-APPROVAL ASSIGNMENT # 1316859 IS ASSIGNED TO INVESTIGATIONS BRANCH. (on 31-JUL-2002 by M. ROBINSON (HFR-CE740) 313-226-6260)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
SUBMITTED TO DO	17-JUL-2002	10D			DAMBROGIOJ
ASSIGNED INSPECTION T	19-JUL-2002	PS			MROBINSO
DO RECOMMENDATION	03-SEP-2002			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO
GMP EI DATED 4/25-5/6/02 COVERED PROFILE CLASS CSN FOR SEVERAL PRODUCTS. NO OBJECTIONABLE OBSERVATIONS WERE REPORTED AND NO FDA-483 WAS ISSUED. THE EIR WAS CLASSIFIED NAI.					
OC RECOMMENDATION	03-SEP-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: FEI

DMF No: AADA:
Responsibilities:

Profile: CSN OAI Status: NONE

Estab. Comment: I WOULD BE INTERESTED IN PARTICIPATING IN THIS INSPECTION. THIS I HAD OCCASION TO REVIEW THIS PROCESS IN DETAIL FOR A SUPPLEMENT TO A RELATED NDA THERE ARE NUMEROUS CRITICAL PARAMETERS IN THIS PROCESS. THIS IS NOT A TYPICAL ND I FEEL THAT THE EXPERTISE I HAVE GAINED FROM REVIEWING THE RELATED NDAS AND SUPPLEMENTS WOULD BE OF HELP.
(on 08-NOV-2002 by G. LUNN (HFD-530) 301-827-2393)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
SUBMITTED TO DO	17-JUL-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	04-SEP-2002	GMP			MGARCIA1
INSPECTION SCHEDULED	08-OCT-2002		02-MAR-2003		GARCIAM
INSPECTION PERFORMED	09-APR-2003		24-FEB-2003		MGARCIA1

INSPECTION INITIALLY CLASSIFIED OAI. DOWNGRADED TO VAI. FACTS WILL NOT UPDATE INSPECTION DATA.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

RECOMMENDATION	09-APR-2003	ACCEPTABLE ADEQUATE FIRM RESPONSE	MGARCIA1
OC RECOMMENDATION	09-APR-2003	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-JUL-2002				LUNNG
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
