CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-779 / S-026
20-778 / S-012

Trade Name: Viracept

Generic Name: (nelfinavir mesylate)

Sponsor: Pfizer Inc.

Approval Date: May 17, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 20-778/S-012
NDA 20-779/S-026

Agouron Pharmaceuticals, Inc.
Attention: Patricia Rizun
Senior Regulatory Affairs Specialist
10350 North Torrey Pines Road
La Jolla, CA 92037-1020

Dear Ms. Rizun:

Please refer to your supplemental new drug applications dated July 15 and July 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viracept→ (nelfinavir mesylate) Oral Powder 50 mg/g and Viracept→ (nelfinavir mesylate) Tablet 250 mg.

The User fee goal date for this application is July 19, 2000.

We acknowledge receipt of your submissions dated:

September 9, 1999	March 24, 2000	May 9, 2000	May 15, 2000
October 15, 1999	May 1, 2000	May 10, 2000	May 16, 2000
February 16, 2000	May 3, 2000	May 11, 2000	May 17, 2000

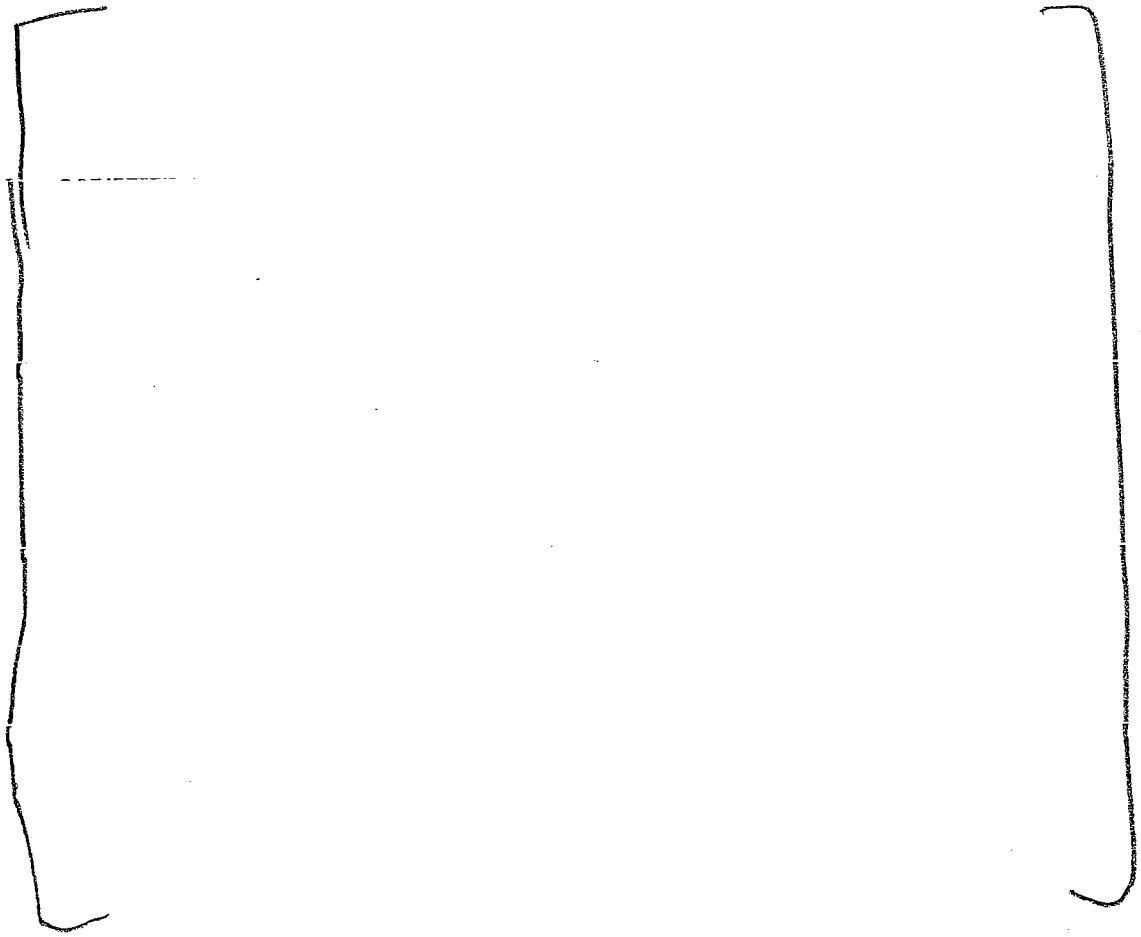
These supplemental applications provide information to fulfill the accelerated approval commitments as required under CFR 314.510. Specifically, this new drug application provides for the use of Viracept→ in combination with other antiretroviral agents, for the treatment of HIV-1 infection.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling submitted on May 17, 2000. Accordingly, these supplemental applications are approved effective on the date of this letter. Approval of these supplements fulfills your commitments made under 21 CFR 314.510.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-778/SE2-012, 20-779/SE2-026." In addition, please submit an electronic copy of the label in MS Word. Approval of these submissions by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your outstanding Phase 4 commitments specified in your submission dated March 14, 1997 for accelerated approval; in the FDA action letter, dated November 24, 1999 for approval of the twice daily dosing regimen for Viracept; and also as specified in the submission, dated May 10, 2000 for the traditional approval supplements. Outstanding phase 4 commitments, including new phase 4 commitments specified in the May 10, 2000 submission, are listed below, along with any agreed upon completion dates:



Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data, and final reports to these NDAs as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of

patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27), and therefore we are deferring submission of your pediatric studies until July 1, 2001.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). Please refer to the Pediatric Written Request dated May 26, 1999. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please submit one marketed package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Sylvia Lynche, Pharm.D., Regulatory Management Officer, at (301) 827-2335.

Sincerely,

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-026
20-778 / S-012

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-778

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Agouron Pharmaceuticals, Inc.
10350 North Torrey Pines Road
La Jolla, CA 92037-1022

4. AF NUMBER

5. SUPPLEMENT(S)

NUMBER(S)	DATE(S)
SE7-012	15-Jul-98

6. NAME OF DRUG

VIRACEPT[R] Oral powder

7. NONPROPRIETARY NAME

nelfinavir mesylate oral powder

8. SUPPLEMENT(S) PROVIDES FOR:

Traditional approval of Viracept (nelfinavir mesylate) oral powder.

9. AMENDMENTS / REPORTS

10. PHARMACOLOGICAL CATEGORY

Anti-HIV

11. HOW DISPENSED

|X| Rx | | OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM(S)

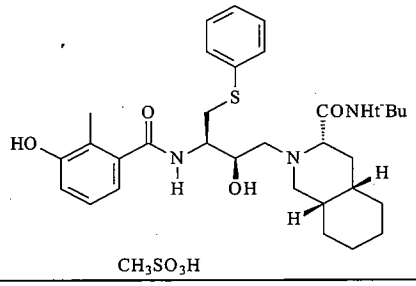
Oral Powder

14. POTENCY(IES)

50 mg/g

15. CHEMICAL NAME AND STRUCTURE

[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)



16. MEMORANDA

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

This Supplement provides for traditional approval of Viracept (nelfinavir mesylate) oral powder. No new CMC data are supplied. This Supplement is therefore recommended for approval from a CMC perspective.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
George Lunn, Ph.D.		9/8/99

20. CONCURRENCE: HFD-530/SMiller

DISTRIBUTION						
	X	Original Jacket	X	GLunn	X	SLynche
	X	Division File	X	SMiller	X	TWu
	X	HFD-830/CChen	X	KHastings	X	LIacono-Connors

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-026
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MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA 20-778 SE7-012 **Reviewer:** Lauren C. Iacono-Connors
NDA 20-779 SE7-026

Date submitted: 07-19-99 **Date received:** 07-20-99
Date assigned: 07-26-99 **Date reviewed:** 04-28-00

Sponsor: Agouron Pharmaceuticals, Inc.
10350 North Torrey Pines Road
La Jolla, CA 92037

Proprietary Name(s): Viracept™
Nonproprietary: Nelfinavir Mesylate
Chemical Name: [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).

Molecular Formula: $C_{32}H_{45}N_3O_4S \cdot CH_4O_3S$ **Molecular Weight:** 663.90 (567.79 as free base)

Structural Formula: N/A

Indication: Treatment of HIV infection

Dosage Form/Route of Administration: Tablet and Powder/Oral

Drug Category: HIV Protease Inhibitor

Supporting Documents: IND [redacted] NDA 20-778/779

Background/Summary

VIRACEPT received accelerated approval for marketing on March 14, 1997. The sponsor has submitted a Supplemental NDA (SNDA) for VIRACEPT (Tablets and Oral Powder) to fulfill the requirements for full traditional approval. All supportive technical information is either contained in the SNDA 20-779/20-778 or is cross-referenced to earlier submissions. Upon review it was determined that the majority of the supportive microbiology data were previously submitted to the division for review. Therefore, the review of these previously submitted reports will not be reproduced here. Instead those reviews will be appropriately cross-referenced.

The sponsor proposes that data collected and submitted to date, "provides evidence that genotypic changes correlate strongly with phenotypic response to antiretroviral therapy, and demonstrate the benefit of VIRACEPT therapy in patients who have previously failed other protease inhibitors." A number of study reports, manuscripts, and abstracts were cited to support this conclusion. The sponsor has also proposed significant changes in the current package insert for VIRACEPT regarding statements on drug resistance. The sponsor-cited study reports are listed below.

PH-1201-096: Incidence of genotypic mutations associated with nelfinavir therapy in pivotal clinical trials. Microbiology review of NDAs 20-778/20-779 (received December 23 1996).

PH-1004-096: Genotypic and phenotypic characterization of HIV-1 variants isolated from patients treated with nelfinavir mesylate in pilot phase I/II dose-ranging studies. Microbiology review of NDAs 20-778/20-779 (received December 23 1996).

AG1343-VI-001: Susceptibility of nevirapine, AZT, or 3TC resistant HIV-1 isolates to nelfinavir. Microbiology review of SNDAs 20-778 SE2-011/20-779 SE2-022 (received January 28 1999).

AG1343-VI-002: Correlation between HIV genotypic resistance and clinical response in patients receiving nelfinavir monotherapy or nelfinavir in combination with 3TC and AZT. Microbiology review of SNDAs 20-778 SE2-011/20-779 SE2-022 (received January 28 1999).

AG1343-VI-003: Virologic response to a ritonavir/saquinavir-containing regimen in patients who had previously failed nelfinavir-containing regimens. Microbiology review of SNDAs 20-778 SE2-011/20-779 SE2-022 (received January 28 1999). With respect to inclusion of these data in the current labeling for VIRACEPT the clinical reviewer has determined that the subjects enrolled in this study should be without bias. The selection method was not clear from this study report. The submission of this information is pending but will determine the suitability of these data for inclusion in the product label.

AG1343-VI-004: Correlation of virologic response with genotype of plasma HIV-1 variants in patients treated with nelfinavir in the U.S. expanded access program. Microbiology review of SNDAs 20-778 SE2-011/20-779 SE2-022 (received January 28 1999). The clinical reviewer has recommended that the discussion of patients from the Expanded Access Program be deleted because 0.5 $\log_{10}$ reduction in viral load at any time point before 12 weeks may not be clinically relevant, especially if it is only short-lived.

CPCRA 046 (GART) Abstract and Study Summary: The impact of drug resistance mutations in plasma virus of patients failing on PI-containing HAART regimens on subsequent virologic response to next HAART regimen: results of the CPCRA 046 (GART).

The sponsor originally submitted an abstract reproduced from the *Third International Workshop on HIV Drug Resistance and Treatment Strategies* (June 23-26, 1999, San Diego, CA). The data described in the abstract was intended to support VIRACEPT proposed labeling claims. On March 3, 2000 the sponsor was requested to provide a complete study report on CPCRA 046 study results so that those data may be reviewed and considered for inclusion in the label. The sponsor submitted a "study

summary" on March 24, 2000. Upon review by the medical officer it was determined that the viral load response was only followed out to 8 weeks, [redacted] analysis was not durable at longer term follow-up.

In an effort to assist in the review of complex genotypic data found across numerous study reports the sponsor provided a couple of summary tables describing the studies from which they derived data for 195 patients referred to in the Microbiology Summary Section of the SNDA and in the draft label. The tables are reproduced in enclosures 1 and 2 with FDA corrections noted in the tables. The data for 191 patients were submitted in the cited study reports included in the SNDA. Data for the remaining 4 patients were included in this March 24, 2000 submission. However, the data generated on these 4 patients is in the form of a table and lacks sufficient detail to permit an independent review. Therefore, due to the lack of supporting information and experimental detail provided with this data set, the data cannot be reviewed in support of VIRACEPT labeling claims. If the sponsor wishes to include these 4 patients' data in the label a complete study report should be submitted to the division for review as soon as possible.

PROPOSED MICROBIOLOGY LABEL: The following is the proposed label that can be supported by the data submitted.

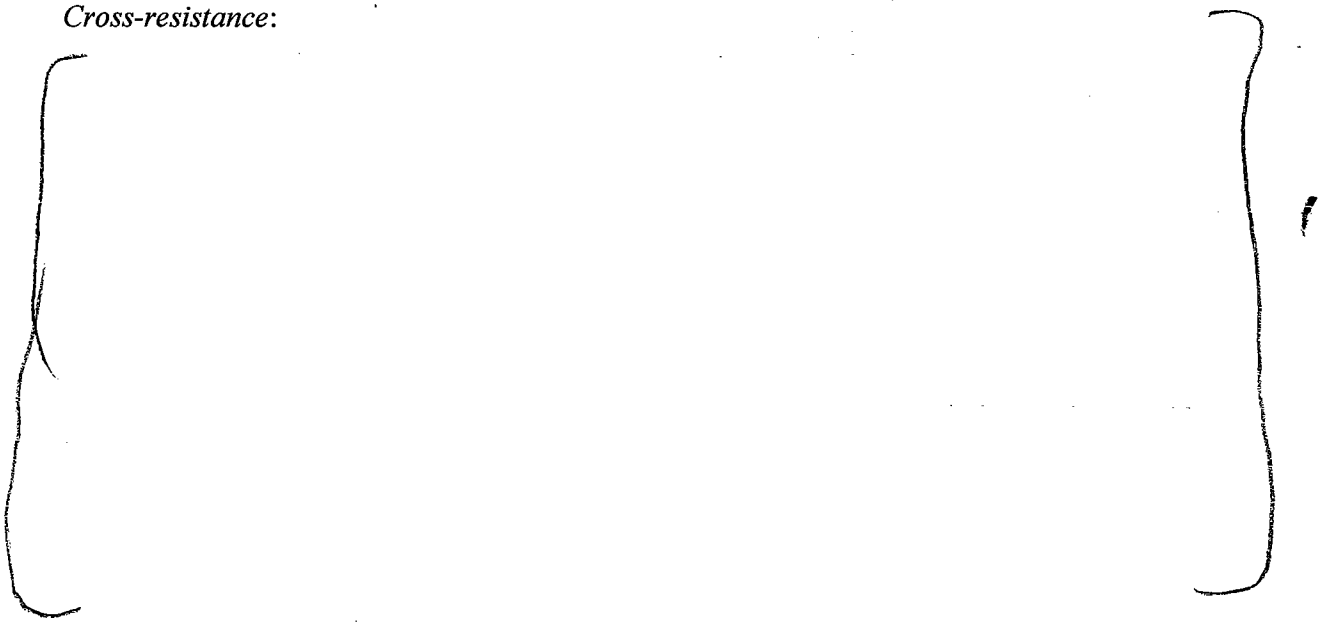
Mechanism of Action: Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Antiviral Activity In Vitro: The antiviral activity of nelfinavir *in vitro* has been demonstrated in both acute and/or chronic HIV infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against several laboratory strains of HIV-1 and several clinical isolates of HIV-1 and the HIV-2 strain ROD. The EC_{95} (95% effective concentration) of nelfinavir ranged from 7 to 196 nM. In combination with reverse transcriptase inhibitors, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (zidovudine, lamivudine or zalcitabine) antiviral activity *in vitro* without enhanced cytotoxicity. Drug combination studies with protease inhibitors (ritonavir, saquinavir or indinavir) showed variable results ranging from antagonistic to synergistic.

Drug Resistance: HIV-1 isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=191; 154 of which were evaluable) changes in clinical trials over period of 2 to 82 weeks. One or more virus protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in >10% of patients with evaluable isolates. Of 19 patients for which both phenotypic and genotypic analyses were performed on clinical isolates, 9 showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. All 9 patients possessed one or more mutations in the virus protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

confirm that these 154 subjects were virologic failures) was 55%. The overall incidence of the L90M substitution was 10%.

Cross-resistance:



Conclusions

With respect to microbiology, this supplemental NDA is approved pending acceptance of final draft labeling.

Lauren C. Iacono-Connors, Ph.D.
Microbiology Team Leader

CONCURRENCES:
HFD-530/Div Dir

HFD-530/TLMicro

CC:
HFD-530/Original NDA 20-778/779
HFD-530/TLMicro/
HFD-530/CSO/S. Lynche