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: _____

_____

Signature: /S/ *Date:* 3/22/99
Title: Regulatory Project Manager

Signature of Office/Division Director
Signature: /S/ *Date:* 4/2/99

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Extended Market Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Submission of Reports of Clinical Studies of Amprenavir in Pediatric Patients

Glaxo Wellcome Inc. requests a determination that marketing submissions and approvals under subsections (b) (2) or (j) of Section 505 of the Federal Food, Drug, and Cosmetic Act (the "FFDCA"), for any product containing amprenavir, will be fully subject to the market exclusivity extension provisions of new Section 505A of the FFDCA (as added by Section 111 of the Food and Drug Administration Modernization Act of 1997). This request is made on the basis of Glaxo Wellcome Inc.'s submission of reports of clinical studies of amprenavir in pediatric patients, as described in the PROPOSED PEDIATRIC STUDY REQUEST submitted to [redacted]) on August 18, 1998.

A copy of the request is attached.

Although the proposed "Written Request" pertaining to amprenavir has yet to be issued, Glaxo Wellcome Inc. is proceeding in good faith with the submission of NDA 21-007, on the assumption that delayed submission would not well serve the interests of either the adult or pediatric patient populations who may benefit from therapy with the new drug. Prior communications with the Reviewing Division have given us confidence that amprenavir is considered an appropriate candidate for extended exclusivity, in light of our program of pediatric development, and that we can expect a Written Request before approval of NDA 21-007, pursuant to subsection 505A(a) of the FFDCA. The anticipated Written Request is expected to call for and can precede the submission of significant pediatric data not being submitted at this time, *viz.*, presently unavailable 48-week data from Protocol PROB2004 and PROAB3004, both open label trials of amprenavir in combination with other antiviral products in HIV-infected children (PROB2004 to enroll minimum of 60 patients and PROAB3004 to enroll 100 patients). In any event, Glaxo Wellcome Inc.'s decision not to delay submission of NDA 21-007 pending receipt of a Written Request should not prejudice our ability to qualify for extended exclusivity under Section 505A. Such an adverse outcome is certainly not mandated by the statute, would in fact contravene congressional intent, and would be unfair and inappropriate from a policy standpoint.

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

August 18, 1998

Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

Re: ——— Amprenavir (141W94) for HIV Infection
General Correspondence: Other; PROPOSED PEDIATRIC STUDY REQUEST;
Serial No.: 275

Dear Dr. Jolson:

Reference is made to the recent guidance document for industry, as issued by the Center for Drug Evaluation and Research on June 29, 1998, entitled, Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act. This guidance describes how studies may qualify for pediatric exclusivity under section 505A of the Act. This provision of the Act (signed into law by President Clinton on November 21, 1997) permits certain drugs to obtain an additional period of exclusivity if the sponsor submits requested information relating to use of the drug in the pediatric population. This provision of the Act became effective immediately. The purpose of this submission is to seek a Written Request for pediatric studies for AGENERASE (amprenavir) capsules and AGENERASE Oral Solution (amprenavir oral solution) for treatment of HIV infection in accordance with this Guidance.

Glaxo Wellcome has a record of commitment to discovery, development, and manufacturing of new antiretroviral drug products for the entire range of patients with HIV. To this end, we have previously worked with your Division on the development of zidovudine (Retrovir®) as parenteral, oral capsule, oral tablet, and syrup formulations to serve neonates, infants, children, adolescents, and adult patients (including pregnant women). We are continuing to work on pediatric development of ——— ——— products for patients with HIV. For amprenavir, the main rationale for pediatric development is the clear medical need for antiretroviral drugs that are both safe and effective for use in highly active combination regimens. Glaxo Wellcome has diligently pursued clinical studies designed to assess the pharmacokinetic properties, safety, and effectiveness of amprenavir in pediatric patients with HIV infection. We have also developed 50 mg capsules (a small capsule amenable to acceptance by many older

Glaxo Wellcome Research and Development
Five Moore Drive
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Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

children and adolescents) and a well-accepted liquid formulation of amprenavir for this patient population.

These efforts in pediatrics are progressing concurrently with the clinical development program in adult patients. We have appreciated the close interaction with your Division on this pediatric program. These interactions have been productive, mutually beneficial, and quite long lived.

Thus, we believe that Glaxo Wellcome has progressed pediatric development of amprenavir for HIV infection in good faith with due diligence in the interest of concurrent development of this drug for both adult and pediatric patient populations. The guidance of June 29, 1998 is the first document published by the Food and Drug Administration to provide industry with specific instructions for pursuing exclusivity based on appropriate pediatric studies. Therefore, we are submitting the enclosed **Proposed Pediatric Study Request** in accordance with FDA's June 29, 1998 Guidance in order to seek a Written Request for pediatric studies with amprenavir for treatment of HIV infection. We believe our efforts merit a Written Request as a step toward seeking exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act. We previously submitted a statement of our view that amprenavir merits such exclusivity (May 29, 1998, Serial No. 252). The table included in Attachment 1 summarizes each element of protocols PROA1006, PROB2004, and PROAB3004 as requested in the guidance of June 29, 1998. The table in Attachment 2 provides the timeframe for key events for these protocols. Therefore, we are asking you to work with the Office Director to issue a Written Request for pediatric studies with amprenavir for treatment of HIV infection.

We appreciate your cooperation and support on this important matter. We request that you issue the Written Request suggested in the paragraphs above.

This submission is provided in quadruplicate. Four desk copies have been sent directly to Mr. Zeccola for use by the review team. Please contact me at (919)-483-6972 for any matters regarding this request. Thank you.

Sincerely,

Robert S. Watson
Product Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Attachment 1. Information to Facilitate FDA's Issuance of a Written Request for Studies of Amprenavir in Pediatric Patients with HIV Infection.

Issue in Section IV (A) of FDA's Guidance on Pediatric Exclusivity	Glaxo Wellcome's Proposal
Type of studies to be performed	1. Characterize the pharmacokinetic properties of amprenavir in pediatric patients from 2 to 16 years of age 2. Assess the effects of amprenavir on surrogate endpoints of HIV disease in pediatric patients from 2 to 16 years of age in two clinical trials 3. Assess the safety of amprenavir in pediatric patients in three clinical studies
Objective/rationale	The main rationale for pediatric development of amprenavir is the clear medical need for antiretroviral drugs that are both safe and effective for use in highly active combination regimens. An additional rationale for pediatric development of amprenavir is its suitability for formulation in a palatable, oral solution that will be accepted by most pediatric patients. Currently, only 6 of the 13 antiretroviral drug products approved in the US are available in pediatric formulations. These 6 products are Retrovir, Videx, Epivir, Zerit, Norvir, and Viracept. Additional pediatric labeling is needed to expand the choices available for treatment of pediatric patients.
Indication(s) to be studied	Use of amprenavir for treatment of HIV-1 infection

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ON ORIGINAL

Attachment 1. Information to Facilitate FDA's Issuance of a Written Request for Studies of Amprenavir in Pediatric Patients with HIV Infection.

Issue in Section IV (A) of FDA's Guidance on Pediatric Exclusivity	Glaxo Wellcome's Proposal
Study design	Protocol PROA1006 "A Phase I Open Label, Dose-Escalation Clinical Study to Assess the Pharmacokinetics and Tolerability of Single Oral Doses of 141W94 in HIV-Infected Children" – This study assessed the pharmacokinetic properties of single doses of amprenavir capsules in pediatric patients from 4 to 12 years old. This study has been completed. Protocol PROB2004 "A Phase II Trial to Assess the Preliminary Antiviral Effect, Pharmacokinetics, Safety and Tolerability of Multiple Oral Doses of 141W94 Liquid Formulation in Combination with NRTIs in HIV Infected Children below 13 Years Old" – This study assesses the pharmacokinetics of multiple doses of amprenavir oral solution. Safety and efficacy data will be collected for a 48 week study period. Protocol PROAB3004 "A Phase III, Open label Trial to Evaluate the Safety, antiviral Efficacy and Pharmacokinetics of 141W94 Plus Current Therapy in HIV-Infected Children" – This multicenter, multi-national study will collect safety and efficacy data in pediatric patients using capsules or oral solution, based on age and/or weight, for a 48 week study period.
Age groups in which the studies will be performed	The following groups are eligible for enrollment in one or more of the pediatric studies on amprenavir: Children (2 to 12 years) Adolescents (12 to 16 years)

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Attachment 1. Information to Facilitate FDA's Issuance of a Written Request for Studies of Amprenavir in Pediatric Patients with HIV Infection (continued).

Issue in Section IV (A) of FDA's Guidance on Pediatric Exclusivity	Glaxo Wellcome's Proposal
Number of patients to be studied or power of the study to be achieved	• Study PROA1006 enrolled 20 pediatric patients in this dose escalation study. Experience was obtained with doses of amprenavir of 5, 10, 15, and 20 mg/kg (capsules). The study provided sufficient pharmacokinetic and safety information to enable dose selection and initiation of subsequent pediatric studies. • Study PROB2004 will enroll 60 subjects in this trial assessing the pharmacokinetics, safety and antiviral effect of amprenavir. • Study PROAB3004 will enroll 100 HIV-1 infected children. Taken together, these studies will provide data for approximately 180 amprenavir-treated patients
Inclusion/exclusion criteria	• Study PROA1006 has been completed. It enrolled patients between 4 and 12 years of age who were infected with HIV-1. Patients were eligible if able to take solid medication (capsules) and willing to provide informed consent. • PROB2004 will enroll HIV-1 infected children (NRTI naïve or experienced. PI naïve or experienced. NNRTI experienced if stopped 28 days prior to enrollment) less than 13 years of age with HIV RNA viral load greater than 400 copies/ml. • PROAB3004 will enroll children aged 4 years and older with HIV-1 RNA viral load ≥ 400 copies/ml and who require a protease inhibitor-containing antiretroviral regimen. Each protocol is available to provide complete details on inclusion/exclusion criteria.

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Attachment 1. **Information to Facilitate FDA's Issuance of a Written Request for Studies of Amprenavir in Pediatric Patients with HIV Infection (continued).**

Issue in Section IV (A) of FDA's Guidance on Pediatric Exclusivity	Glaxo Wellcome's Proposal
Primary efficacy endpoint	• Study PROA1006 was a single dose pharmacokinetic, dose-escalation study. • PROB2004 will evaluate the pharmacokinetics of multiple doses of amprenavir. It will also assess the antiviral effect of amprenavir in combination therapy at 16 weeks as measured by changes in plasma HIV-1 RNA and CD4+ cell count and durability, safety and tolerability over 48 weeks. • PROAB3004 will evaluate the efficacy of amprenavir in combination therapy as proportions of subjects with HIV-1 RNA levels below 400 copies/ml at 48 weeks. Secondary efficacy measures include AAUCMB of $\log_{10}$ HIV-1 RNA and CD4+ cell counts, changes from baseline in HIV-1 RNA viral load and CD4+ cell counts, and clinical disease progression.
Study evaluations	• Pharmacokinetic parameters • Plasma HIV RNA and CD4 cell count as surrogate endpoints • Routine hematology, clinical chemistry, and urinalysis tests • Physical examination and interview on symptoms/adverse reactions
Drug information (dosage form, regimen, route of administration, formulation)	*Dosage Form and Formulation:* Amprenavir 50 mg or 150 mg capsules are oblong, opaque off-white to cream colored soft gelatin capsules. Each capsule contains the inactive ingredients d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400), and propylene glycol. The capsule shell contains the inactive ingredients - sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. Amprenavir oral solution is a clear, pale yellow to yellow, grape bubblegum peppermint-flavored liquid, containing 15 mg of amprenavir in each ml. It contains the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor , polyethylene glycol 400 (PEG 400), propylene glycol, saccharin sodium, sodium chloride, and sodium citrate (dihydrate). *Regimen:* 20 mg/kg twice a day (to a maximum of 1200 mg twice daily) *Route of Administration:* oral
Safety concerns	• There are no additional or different safety concerns for pediatric patients relative to adults. All current safety information on amprenavir is in the Investigator's Brochure.
Statistical information (power of the study; statistical analyses)	• Detailed information on statistical analyses of the data is contained in the protocols and study reports.

Attachment 1. Information to Facilitate FDA's Issuance of a Written Request for Studies of Amprenavir in Pediatric Patients with HIV Infection (continued).

Issue in Section IV (A) of FDA's Guidance on Pediatric Exclusivity	Glaxo Wellcome's Proposal
Labeling that may result from the studies	These clinical studies and capsule/liquid formulations are intended to result in labeling that provides pediatric information in the following sections: Clinical Pharmacology Indications Precautions: Pediatric Use Adverse Reactions How Supplied The exact nature of this labeling will be determined by the results of the studies.
Format of report to be submitted to the Agency	Each completed study will be reported to FDA in a format consistent with FDA's guideline (*Guideline for Format and Content of Clinical and Statistical Sections of New Drug Applications*).
Timeframes	Please see the separate table in Attachment 2

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ON ORIGINAL

Attachment 2. **Proposed timeframes for various activities on pediatric studies of amprenavir.**

Study and Activity	Timeframe
Protocol PROA1006 "A Phase I Open Label, Dose-Escalation Clinical Study to Assess the Pharmacokinetics and Tolerability of Single Oral Doses of 141W94 in HIV-Infected Children"	
Submitting the protocol to an IND	[redacted] November 15, 1996 (Serial No. 068)
Begin enrolling study participants	November, 1996
Completing the study	June, 1997
Drafting report of the study	1Q 1998
Submitting report of the study	NDA 21-007 – May 29, 1998
Protocol PROB2004 "A Phase II Trial to Assess the Preliminary Antiviral Effect, Pharmacokinetics, Safety and Tolerability of Multiple Oral Doses of 141W94 Liquid Formulation in Combination with NRTIs in HIV Infected Children below 13 Years Old"	
Submitting the protocol to an IND	[redacted] April 8, 1998 (Serial No. 234)
Begin enrolling study participants	April, 1998
Completing the study	1998
Drafting report of the study	Interim 3Q 1998
Submitting report of the study	Final report to be submitted in NDA 21-007 in October, 1998
Protocol PROAB3004 "A Phase III, Open label Trial to Evaluate the Safety, antiviral Efficacy and Pharmacokinetics of 141W94 Plus Current Therapy in HIV-Infected Children"	
Submitting the protocol to an IND	[redacted] June 3, 1997 (Serial No. 132)
Begin enrolling study participants	September , 1997
Completing the study	1999
Drafting report of the study	Interim 3Q 1998
Submitting report of the study	Final report to be submitted in NDA 21-007 in October, 1998

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21039	**Trade Name:**	AGENERASE(AMPRENAVIR)15MG/ML ORAL SOLUTI
Supplement Number:		**Generic Name:**	AMPRENAVIR
Supplement Type:		**Dosage Form:**	Solution; Oral
Regulatory Action:	PN	**Proposed Indication:**	Indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Children (25 Months-12 years)
____Infants (1-24 Months)
_X_Adolescents (13-16 Years)
_X_Other Age Groups (listed): 4-12 years

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

1.Phase 4 Commitment from original submission: The completion of pediatric studies in patients less than 4 years of age including neonates. 4/6/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELISSA TRUFFA

/S/

Signature

4-15-99

Date

APPEARS THIS WAY ON ORIGINAL

NDA 21-039

AGENERASE™ (amprenavir)
Oral Solution

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

22 OCT 98

Charles E. Mueller
Head, US Clinical Compliance
World Wide Compliance

Date

APPEARS THIS WAY
ON ORIGINAL

x

Division Director Memorandum

NDA:	**21-007 (capsules) and 21-039 (solution)**
Drug and indication:	**Amprenavir (50 and 100 mg capsules and 15 mg/mL solution) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection**
Dose:	**Adults and adolescents (age 13-16 years) - 1200 mg twice daily** **Pediatric patients (4-12 years) or patients over age 13 but with weight ≤50 kg:** ***Capsule dose* - 20 mg/kg twice daily or 15 mg/kg three times daily up to a maximum of 2400 mg daily;** ***Solution dose* - 22.5 mg/kg twice daily or 17 mg/kg three times daily up to a maximum of 2800 mg daily.**
Applicant:	**Glaxo Wellcome Inc.**
Submission dated:	**October 16, 1998 (NDA 21-007)** **December 7, 1998 (NDA 21-039)**
Date of Memorandum:	**April 14, 1999**

In these applications, the sponsor has requested accelerated approval for amprenavir capsules and solution for the treatment of HIV-infection. In support of this request, the sponsor has submitted reports of interim results from two ongoing, randomized, controlled studies, which enrolled a total of 232 antiretroviral-naive (trial PROAB3001) and 504 NRTI and (NNRTI-) experienced (trial PROAB3006) adults. Pediatric use is further supported by safety, pharmacokinetic and limited activity data on 118 pediatric patients, ages 4 - 18 years.

I am in concurrence with the consensus of the review team that these applications should be approved under the 21 CFR 314 Subpart H provisions for accelerated approval. Approval of amprenavir capsules and solution will provide adults and pediatric patients another therapeutic option for management of HIV-infection.

The following issues pertaining to this regulatory action merit comment:

1. Demonstration of Efficacy

As noted above, evidence of the efficacy of amprenavir as a component of combination therapy for HIV, is provided by the results of two randomized, controlled clinical trials. In both of these trials, the primary efficacy endpoint was the proportion of patients having <400 HIV RNA copies/mL and without progression to a CDC Class C event or death at 16 weeks. Data through 24 weeks of treatment was subsequently requested and the results form the basis of this

regulatory decision.

Trial 3001 provides a blinded comparison of adults treated with the combination of amprenavir+zidovudine+lamivudine vs. zidovudine+lamivudine treatment alone. Although it is recognized that this trial design would not be consistent with current recommendations for HIV-treatment, these results nonetheless demonstrate the relative antiviral contribution of amprenavir in suppressing HIV RNA through 24 weeks of treatment (54% vs. 11% in amprenavir vs. placebo recipients, respectively).

Trial 3006 provides a non-blinded comparison of adults treated with the combination of amprenavir+zidoovudine+lamivudine vs. indinavir+zidovudine+lamivudine treatment. Interpretation of these results is more complex than trial 3001 because of its open-label design and high, disproportionate discontinuation rates (36% vs. 22% in the amprenavir and indinavir groups, respectively by 24 weeks). In the FDA analysis, a significantly lower rate of viral suppression was demonstrated in the amprenavir group compared to the indinavir group (42.5% vs 53.2%, respectively). This difference was largely due to the higher rate of discontinuation due to adverse events in amprenavir-recipients.

From the regulatory perspective, two statements can be made based on these results. First, comparability of amprenavir with indinavir has not been established for the reasons noted above. Second, evidence of the antiviral activity of amprenavir may be still inferred from these results because it is assumed that the rate of suppression (42.5%) in amprenavir-recipients is higher than would have been achieved by use of zidovudine+lamivudine alone in this nucleoside-experienced population.

2. Adult patient populations represented

The principal controlled trials were conducted in HIV-infected adults with generally less advanced disease, and who had either no antiretroviral experience or previous NRTI (and NNRTI) experience, only. No information on the safety and efficacy of amprenavir in patients with prior protease inhibitor (PI) experience has been provided. As a phase IV commitment, the sponsor has committed to further study of amprenavir in patients with more advanced HIV-disease and prior PI experience.

3. Safety concerns

The primary safety issues that have been identified in controlled trials include: rash (including Stevens-Johnson syndrome in approximately 1% of amprenavir recipients), gastrointestinal events (including nausea, vomiting, diarrhea and abdominal discomfort and that were frequent reasons for drug discontinuation), and perioral and peripheral paresthesias. These issues are adequately addressed in the package insert

The prescriber will additionally need to be aware of the numerous potentially important drug-drug interactions between amprenavir (or other approved protease inhibitors) and concomitant medications. This includes a recently-reported interaction between sildenafil and ritonavir or

saquinavir, which results in substantially increased exposure to sildenafil. This issue was raised when results of drug-interaction studies conducted by Pfizer were submitted in March 1999 in support of revised labeling for sildenafil. Although the clinical relevance of these pharmacokinetic changes is currently unknown and the interaction of amprenavir with sildenafil has not been studied, there is concern that higher and more prolonged serum levels may place patients at higher risk for sildenafil-associated adverse events, such as hypotension, visual disturbances and priapism.

Although this issue is still under review by the Division of Reproductive and Urologic Drug Products, it is appropriate to describe these initial findings and recommendations for sildenafil dosing in the amprenavir label in a Warning and Precaution about concomitant use. Based on the outcome of this review, future revisions to the amprenavir label, to strengthen or further discuss this interaction, may be necessary.

4. Other potential safety issues

Three additional issues of potential safety concern merit comment:

a. Sulfonamide sensitivity

As discussed in the clinical review, amprenavir has the structure of a sulfonamide. Limited information in individuals with a reported history of sulfa allergy and who were treated with amprenavir suggests that the occurrence of rash was no different in these individuals. However, there is insufficient information currently to exclude the potential for allergic manifestations in patients with a history of sulfa allergy. Therefore, the label will recommend that these individuals be treated with particular caution. Additionally, the sponsor has agreed to further prospective investigation of this issue in Phase IV.

b. Vitamin E content in the excipient

Both formulations of amprenavir utilize the excipient tocopherol propylene glycol succinate, which is hydrolyzed to vitamin E. The vitamin E exposure provided by amprenavir exceeds the recommended daily dose of this vitamin for both adults and children. Although no adverse experience clearly attributable to vitamin E exposure has been identified in the provided animal and human data, the sponsor has agreed to additional preclinical and clinical investigation of this issue during phase IV. Additionally, the package insert will indicate that use of vitamin E supplementation in patients receiving amprenavir is not recommended, that the long-term safety of chronic, high dose vitamin E is not known and that high dose vitamin E has been reported to exacerbate the blood coagulation defect of vitamin K deficiency.

c. Fat redistribution and abnormalities in lipid metabolism

The syndrome of fat redistribution has been recognized post-marketing in all approved protease inhibitors. The currently available database on amprenavir is insufficient in both size and treatment duration to evaluate whether this syndrome will occur. However, higher rates of hypertriglyceridemia and hyperglycemia in amprenavir (vs. placebo)

recipients and the occurrence of lipodystrophy in a patient in trial 3006, raise suspicion that amprenavir can induce metabolic abnormalities similar to other products in this class. The package insert will include class labeling for this adverse event and the sponsor has committed to further investigation during phase IV.

5. Pediatric Use

The sponsor has provided data on the safety and pharmacokinetics of amprenavir in 118 pediatric patients, ages 4-18. The basis of the pediatric dosing recommendation for the capsule and solution formulations is discussed in the clinical pharmacology group leader memorandum. Limited safety data does not suggest unique safety issues in the pediatric population compared with adult experience.

[ ]

6. Resistance

As discussed in the microbiology review, this application contains insufficient information to address the potential for cross-resistance between amprenavir and marketed protease inhibitors. This important issue will be further investigated in phase IV.

7. Lack of bioequivalence between formulations

As noted in the clinical pharmacology review, the capsule and solution formulations are not bioequivalent, and the solution is approximately 14% less bioavailable. The implications for prescribing are as follows:

a. The two formulations are not interchangeable on a mg-to-mg basis and labeling and cartons reflect this information;
b. The package insert will provide two different dosing recommendations for pediatric patients depending on whether they are receiving capsules or solution.

8. Traditional approval

In order to provide evidence of clinical benefit with amprenavir to support traditional approval, the sponsor has committed to submission of results from ongoing trials 3001 and 3006 through at least 48 weeks of treatment. This proposal is acceptable to satisfy this regulatory requirement.

9. Phase IV commitments

In addition to the previously noted requirements for traditional approval, the sponsor has agreed to further investigation of amprenavir post-marketing to address the following issues: safety and efficacy of amprenavir in combination with other antiretrovirals and in protease-inhibitor experienced patients; the potential for drug-drug interactions between amprenavir and ritonavir, efavirenz, nevirapine, methadone and oral contraceptives; development of resistance and cross-resistance; potential for development of lipid and other metabolic abnormalities; carcinogenicity;

use in pediatric patients younger than 4 years; safety of use in patients with a history of sulfa allergy; long-term implications of vitamin E exposure; investigation of any gender-related differences in safety and efficacy; and ———————

The outstanding effort of the amprenavir review team merits acknowledgment. Although the NDA for the solution formulation was received almost three months after the submission of the capsule application, the review team committed to simultaneous action on both applications to meet the capsule-NDA's earlier PDUFA date. The team's efforts toward the simultaneous approval should be commended. As a result, pediatric patients will have access to a liquid formulation many months earlier than required by PDUFA goal-dates.

APPEARS THIS WAY
ON ORIGINAL

There are no additional outstanding regulatory issues at the time of this action.

/S/

Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products

cc:
NDA 21-007, 21-039
HFD-530/Martin/Cvetkovich
HFD-104/Kweder

APPEARS THIS WAY
ON ORIGINAL

Group Leader Memorandum

NDA:	21-007 (capsule) 21-039 (solution)
Drug:	Agenerase™ (amprenavir) soft-gel capsules and oral solution
Dose:	1200mg BID (adults) 20 mg/kg BID (pediatrics)
Indication:	Treatment of HIV infection
Applicant:	Glaxo Wellcome Inc.
Submission received:	October 15, 1998 (21-038) December 7, 1998 (21-039)
Date of Memorandum:	April 4, 1999

In this application, the applicant requests accelerated approval of amprenavir, a protease inhibitor of human immunodeficiency virus (HIV). It is notable that amprenavir was the first HIV protease inhibitor molecule discovered utilizing targeted drug design. Difficulties encountered in formulation have rendered it the fifth protease inhibitor to be approved.

In support of the request for approval, the applicant has submitted the results of two phase 3 well-controlled studies which provide primary evidence of safety and efficacy. In both studies, the primary efficacy measure utilized was the proportion of subjects whose viral load was < 400 copies/mL (by the Amplicor ™ Monitor HIV RNA assay) at 24 weeks. CD4 count changes were evaluated as a secondary endpoint. Study PROAB 3001 is an ongoing, randomized, double-blind, placebo-controlled, multicenter study conducted in 232 treatment-naïve adults in which the combination of amprenavir/ZDV/3TC is compared to placebo/ZDV/3TC. Study PROAB 3006 is an ongoing, open-label, active-controlled, multicenter study in 504 protease-inhibitor-naïve adults. In this study, the combination of amprenavir/ZDV/3TC is compared to indinavir/ZDV 3TC in an equivalence design..

I concur with Dr. Martin, the primary medical reviewer, that this application is approvable.

Issues of note at the time of this regulatory approval include 1) the rationale for approving the solid and liquid formulations simultaneously, though they were submitted two months apart; 2) finalizing the patient package insert, 3) potential implications of the sulfonamide-like chemical structure of amprenavir, and 4) implications of the high

vitamin E content of both formulations of amprenavir. Each of these issues will be discussed below.

1. Although the NDA for the liquid formulation (NDA 21-039) was submitted two months later than the NDA for the solid formulation (NDA 21-038), these two NDA's will be approved simultaneously. Moving the timeline for approval of the liquid formulation forward shortened the review time available. However, the review team agreed that this was a reasonable course of action for several reasons. First, NDA 21-039 consisted of CMC data to support the liquid formulation, and Dr. Lunn, the chemistry reviewer, was able to review these data within the specified period of time. Additionally, based on our request for rapid conduct of the site inspections, results of these inspections were made available shortly before the targeted approval date for the solid formulation, allowing an action on the liquid formulation to be taken. Second, data supporting the pharmacokinetics of amprenavir in pediatric patients largely drew on evaluation of the liquid formulation. Had an action been taken on the solid formulation alone, labeling for the pediatric population would have been complicated by the need to include information in the label on an unapproved formulation. And, finally, during these times of heightened awareness of the need for appropriate formulations for pediatric patients in general, as well as the need for additional therapeutic options in HIV-infected children, it seemed reasonable to attempt to make the liquid formulation available as soon as possible.

2. Final agreement on the content of a patient package insert which will include important safety information is expected to be reached prior to approval.

3. The chemical structure of amprenavir includes a sulfonamide-like moiety. The adverse event profile of amprenavir is in some respects similar to that of other sulfonamides. The most notable of these is rash, which has occurred in 11% of patients in the phase 3 trials, in 28 % overall, and has included 2 cases of Stevens-Johnson syndrome. While rash has been described in the adverse event profiles of other agents of this class, the rates of rash associated with amprenavir treatment are much higher. In their analysis of the potential for sulfonamide-like related adverse events with amprenavir administration, the applicant made note of several pertinent issues which are presented here, along with our comments on their conclusions:

a. Three non-clinical toxicology studies provided no evidence that amprenavir administration resulted in sensitization. We do not believe that these studies rule out the potential for sensitization, as the relevance of such animal studies to humans is not known.

b. Cross-sensitivity among related compounds is about 20% and therefore, even if cross-sensitization occurred between sulfonamides and amprenavir, the rate of reactions occurring via this mechanism would likely not be clinically significant. It may be true that the adverse events ascribed to cross-sensitization may be small in healthier HIV-infected individuals, but this statement is limited in that it does not address the potential for reactions occurring *de novo* after amprenavir administration and the subsequent sensitization to sulfonamides. Nor does it address the known increased rate and severity of reactions noted in individuals with AIDS.

c. The applicant concluded that rates of sulfonamide-type adverse reactions were much higher in HIV-infected subjects receiving trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis or treatment of *Pneumocystis carinii* pneumonia than those treated with amprenavir. As previously noted, it is well described that HIV-infected patients receiving TMP-SMX as prophylaxis or treatment experience allergic reactions to TMP-SMX at a very high rate. The population represented in the amprenavir safety database included a relatively healthy population of HIV-infected subjects, making the comparison an inappropriate one, as these are not comparable populations.

The applicant agreed to provide information about the sulfonamide structure of amprenavir and the unknown potential for sensitization or cross reactions to sulfonamides in the amprenavir label. We will request that the applicant commit to studying the occurrence of adverse events in sulfonamide sensitive patients receiving amprenavir, as well as the occurrence of sulfonamide sensitization after amprenavir administration.

4. Both formulations provide very high daily doses of vitamin E. The liquid formulation provides more than four times as much vitamin E as the solid formulation at equivalent doses. As an example, a 20 kg child would receive almost 3000 IU vitamin E per day at the recommended dose of 22.5 mg/kg BID of the oral solution of amprenavir. The Recommended Daily Allowance (RDA) of vitamin E for a four-year-old is 7 IU/day. Although administration of oral vitamin E at doses higher than the RDA has not been associated with significant adverse events, we do not have information on what implications there may be associated with the chronic ingestion of these very high doses of vitamin E. The applicant has agreed to provide information in the amprenavir label that describes the doses of vitamin E provided with administration of amprenavir. We will request that the applicant commit to obtaining vitamin E levels in adults and pediatric patients, as well as studying the potential long-term effects of the chronic administration of high dose vitamin E. In addition, we will request

/S/

Therese A. Cvetkovich, MD.
Medical Team Leader
Division of Antiviral Drugs Products, HFD-530

CC:
NDA ——
NDA 21-039
HFD 530-/Jolson
HFD-530/Martin
HFD-530/Cvetkovich

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21007	**Trade Name:**	AGENERASE (AMPRENAVIR) CAPS 50MG/150MG
Supplement Number:		**Generic Name:**	AMPRENAVIR
Supplement Type:		**Dosage Form:**	Capsule; Oral
Regulatory Action:	PN	**Proposed Indication:**	Indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Dosing recommendation in labeling for patients 4 years and older. 4/1/99

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) _X_ Adolescents (13-16 Years)

_X_ Other Age Groups (listed): 4-12 years

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

Applicant has agreed to conduct studies in patients less than 4 year of age, including neonates. 4/1/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELISSA TRUFFA.

/S/

Signature

4-15-99

Date

NDA 21-007

AGENERASE™ (amprenavir) Capsules
Treatment of HIV Infection

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

01-OCT-98

Charles E. Mueller
Head, US Clinical Compliance
World Wide Compliance

Date

.....

The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 28Sep98 Food and Drug Administration Debarment List and the 30Jul98 Disqualified/Restricted/Assurances List for Clinical Investigarors.

Jeanne Kistler

01-Oct-98

Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF PRE-NDA MEETING

IND:

DATE: April 27, 1998

DRUG: Amprenavir (141W94)

SPONSOR: Glaxo Wellcome

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- The Sponsor intends to structure the ISE in accordance with the diagram in Table of the briefing document. At the time of initial submission, this will include data from 300 patients, but will be updated to include 500 patients at the time of final submission of clinical data.

- The Sponsor intends to structure the ISS in accordance with the diagram in Table 2. This will include safety information on approximately 300 patients treated with amprenavir for a minimum of 24 weeks with the initial submission in October.

- The Sponsor intends to update the ISS with additional safety data on patients treated for 24 weeks, including additional patients that were not in the original submission (approximately 500 patients total) See Table 3.

- The Sponsor intends to submit all results of clinical trials using amprenavir oral solution to the NDA for amprenavir capsules so that all clinical data are present in one application. The NDA for amprenavir oral solution will focus on CMC information only.

- The Sponsor will submit SAS datasets for PROAB3001 and PROAB3006 as SAS transport files. Dr. Flyer indicated that it would useful for the Sponsor to submit [redacted] for these studies with the initial submission. This will require further discussion via a teleconference after internal discussions by the Sponsor.

- A teleconference will be scheduled to discuss the analysis plan for the analysis of primary efficacy and safety parameters for PROAB3001.

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Other issues

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- The proposed time line for submission is acceptable

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HFD-530\CSO\Zeccola

CC:
Division File
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Record of Pre-NDA Meeting

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF PRE-NDA MEETING

IND: [redacted]

DATE: April 27, 1998

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