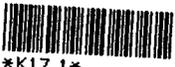


20-685 / S-043

K17.1

NDA 20-685/SE8-043

N20685



K17.1

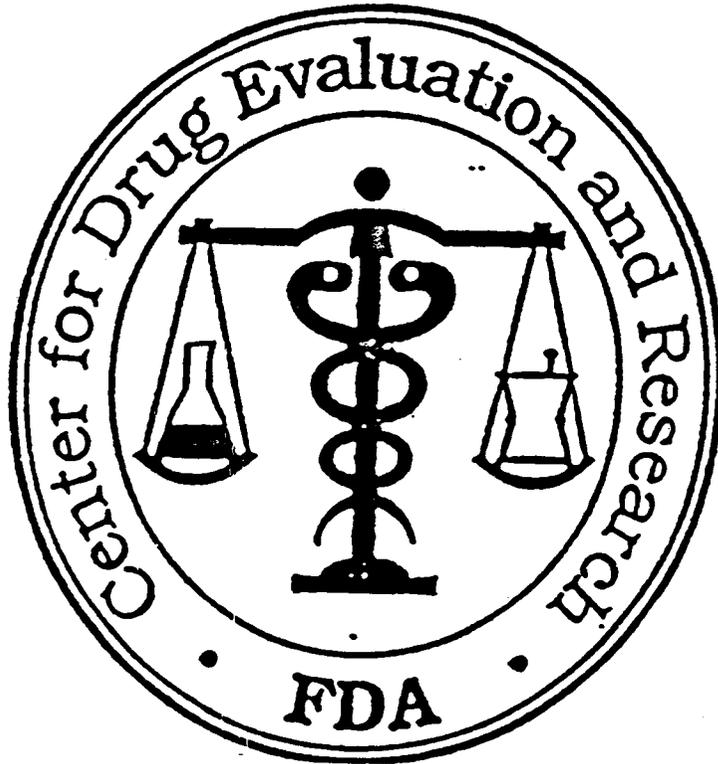
IXIVAN™ (Indinavir Sulfate) Tab.



N20685

Indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients.

*RBE
12/4/00
1:41PM*



**DIVISION OF ANTIVIRAL
DRUG PRODUCTS
HFD-530**

**Melisse Baylor, M.D.
Reviewing Medical Officer**

**Christine K. Lincoln, RN, MS, MBA
Regulatory Health Project Manager**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>20-685</u> / SE <u>8</u> - <u>043</u>	
Drug <u>Crixivan (indinavir sulfate)</u>	Applicant <u>Merck & Co., Inc.</u>
RPM <u>Christine Lincoln</u>	Phone <u>301-827-2335</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) <u>41,413</u>	
Application classifications: Chem Class _____ Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>October 23, 2000</u> Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information:
 - User Fee Paid
 - User Fee Waiver (attach waiver notification letter)
 - User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	✓
Original proposed labeling (package insert, patient package insert)	N/A
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling?	<input checked="" type="checkbox"/> Yes (include review) <input checked="" type="checkbox"/> No
Immediate container and carton labels	N/A
Nomenclature review	N/A

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.

Exception for review (Center Director's memo).....	N/A
OC Clearance for approval.....	N/A

◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	<input type="checkbox"/> Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	N/A
Copy of Applicant's commitments	N/A
◆ Was Press Office notified of action (for approval action only)?.....	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Copy of Press Release or Talk Paper.....	
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	X
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	N/A
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	N/A
Disclosable information – indicate where review is located	X
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	X
Date of EOP2 Meeting _____	45 day filing
Date of pre NDA Meeting _____	
Date of pre-AP Safety Conference _____	
◆ Advisory Committee Meeting	N/A
Date of Meeting	N/A
Questions considered by the committee	N/A
Minutes or 48-hour alert or pertinent section of transcript	N/A
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	N/A X
◆ Clinical review(s) and memoranda	X

- ◆ Safety Update review(s) X
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... X
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda N/A
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) N/A
 Recommendation for scheduling N/A
- ◆ Microbiology (efficacy) review(s) and memoranda N/A
- ◆ DSI Audits N/A
 Clinical studies bioequivalence studies N/A

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda N/A
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/A
- ◆ DMF review(s) N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda N/A
- ◆ Facilities Inspection (include EES report)
 Date completed N/A Acceptable Not Acceptable
- ◆ Methods Validation N/A Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda N/A
- ◆ Memo from DSI regarding GLP inspection (if any) N/A

- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A

NDA 20-685/S-043

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

OCT 23 2000

Dear Dr. Kloss:

Please refer to your supplemental new drug application dated December 22, 1999, received December 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crixivan (indinavir sulfate) 100, 200, 333, and 400mg capsules.

We acknowledge receipt of your submissions dated:

January 24, 2000	May 3, 2000	September 7, 2000
January 31, 2000	May 4, 2000	September 22, 2000
March 10, 2000	August 10, 2000	September 28, 2000
March 31, 2000	August 25, 2000	October 10, 2000
April 14, 2000	August 28, 2000	October 19, 2000
April 26, 2000	August 31, 2000	October 23, 2000

This supplemental new drug application provides for pediatric safety data in the **CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS** sections of the label.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on October 23, 2000.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-685/S-043." In addition, please provide a clean text MS Word version of the label as a desk copy. Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. 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-42
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

Please submit one market 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, please call Christine Lincoln, RN, MS, MBA, Regulatory Project Manager, at (301) 327-2335.

Sincerely,

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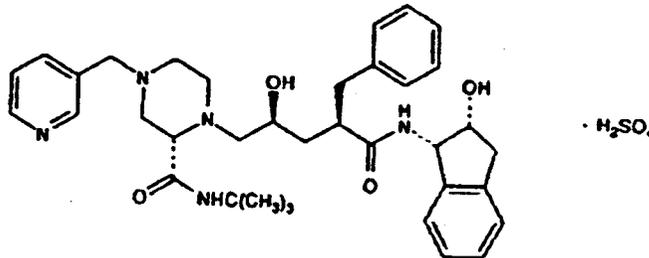
Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

XIVAN®
JINAVIR SULFATE)
APSULES

DESCRIPTION

CRIXIVAN® (indinavir sulfate) is an inhibitor of the human immunodeficiency virus (HIV) protease. CRIXIVAN Capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide and sodium lauryl sulfate.

The chemical name for indinavir sulfate is [1(1*S*,2*R*),5(*S*)]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-*D*-erythro-pentonamide sulfate (1:1) salt. Indinavir sulfate has the following structural formula:



Indinavir sulfate is a white to off-white, hygroscopic, crystalline powder with the molecular formula $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ and a molecular weight of 711.88. It is very soluble in water and in methanol.

MICROBIOLOGY

Mechanism of Action: HIV protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV. Indinavir binds to the protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious viral particles.

Antiretroviral Activity In Vitro: The relationship between *in vitro* susceptibility of HIV to indinavir and inhibition of HIV replication in humans has not been established. The *in vitro* activity of indinavir was assessed in cell lines of lymphoblastic and monocytic origin and in peripheral blood lymphocytes. HIV variants used to infect the different cell types include laboratory-adapted variants, primary clinical isolates and clinical isolates resistant to nucleoside analogue and nonnucleoside inhibitors of the HIV reverse transcriptase. The IC_{95} (95% inhibitory concentration) of indinavir in these test systems was in the range of 25 to 100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, as well as with an investigational nonnucleoside (L-697.661), indinavir showed synergistic activity in cell culture.

Drug Resistance: Isolates of HIV with reduced susceptibility to the drug have been recovered from some patients treated with indinavir. Viral resistance was correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions in the viral protease. Eleven amino acid residue positions, at which substitutions are associated with resistance, have been identified. Resistance was mediated by the co-expression of multiple and variable substitutions at these positions. In general, higher levels of resistance were associated with the co-expression of greater numbers of substitutions.

Cross-Resistance to Other Antiviral Agents: Cross-resistance was noted between indinavir and the protease inhibitor ritonavir. Varying degrees of cross-resistance have been observed between indinavir and other HIV-protease inhibitors.

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CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Indinavir was rapidly absorbed in the fasted state with a time to peak plasma concentration (T_{max}) of 0.8 ± 0.3 hours (mean \pm S.D.) ($n=11$). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-1000 mg dose range. At a dosing regimen of 800 mg every 8 hours, steady-state area under the plasma concentration time curve (AUC) was $30,691 \pm 11,407$ nM \cdot hour ($n=16$), peak plasma concentration (C_{max}) was $12,617 \pm 4037$ nM ($n=16$), and plasma concentration eight hours post dose (trough) was 251 ± 178 nM ($n=16$).

Effect of Food on Oral Absorption: Administration of indinavir with a meal high in calories, fat, and protein (784 kcal, 48.6 g fat, 31.3 g protein) resulted in a $77\% \pm 8\%$ reduction in AUC and an $84\% \pm 7\%$ reduction in C_{max} ($n=10$). Administration with lighter meals (e.g., a meal of dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) resulted in little or no change in AUC, C_{max} or trough concentration.

Distribution: Indinavir was approximately 60% bound to human plasma proteins over a concentration range of 81 nM to 16,300 nM.

Metabolism: Following a 400-mg dose of 14 C-indinavir, $83 \pm 1\%$ ($n=4$) and $19 \pm 3\%$ ($n=6$) of the total radioactivity was recovered in feces and urine, respectively; radioactivity due to parent drug in feces and urine was 19.1% and 9.4%, respectively. Seven metabolites have been identified, one glucuronide conjugate and six oxidative metabolites. *In vitro* studies indicate that cytochrome P-450 3A4 (CYP3A4) is the major enzyme responsible for formation of the oxidative metabolites.

Elimination: Less than 20% of indinavir is excreted unchanged in the urine. Mean urinary excretion of unchanged drug was $10.4 \pm 4.9\%$ ($n=10$) and $12.0 \pm 4.9\%$ ($n=10$) following a single 700-mg and 1000-mg dose, respectively. Indinavir was rapidly eliminated with a half-life of 1.8 ± 0.4 hours ($n=10$). Significant accumulation was not observed after multiple dosing at 800 mg every 8 hours.

Special Populations

Hepatic Insufficiency: Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of indinavir resulting in approximately 60% higher mean AUC following a single 400-mg dose ($n=12$). The half-life of indinavir increased to 2.8 ± 0.5 hours. Indinavir pharmacokinetics have not been studied in patients with severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*).

Renal Insufficiency: The pharmacokinetics of indinavir have not been studied in patients with renal insufficiency.

Gender: The effect of gender on the pharmacokinetics of indinavir was evaluated in 10 HIV seropositive women who received CRIXIVAN 800 mg every 8 hours with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day for one week. Indinavir pharmacokinetic parameters in these women were compared to those in HIV seropositive men (pooled historical control data). Differences in indinavir exposure, peak concentrations, and trough concentrations between males and females are shown in Table 1 below:

PK Parameter	% change in PK parameter for females relative to males	90% Confidence Interval
AUC _{0-8h} (nM \cdot hr)	↓13%	(↓32%, ↑12%)
C _{max} (nM)	↓13%	(↓32%, ↑10%)
C _{8h} (nM)	↓22%	(↓47%, ↑15%)

↓Indicates a decrease in the PK parameter; ↑Indicates an increase in the PK parameter.

The clinical significance of these gender differences in the pharmacokinetics of indinavir is not known.

Race: Pharmacokinetics of indinavir appear to be comparable in Caucasians and Blacks based on pharmacokinetic studies including 42 Caucasians (26 HIV-positive) and 16 Blacks (4 HIV-positive).

Pediatric: The optimal dosing regimen for use of indinavir in pediatric patients has not been established. In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m² every 8 hours, produced AUC_{0-8h} of $38,742 \pm 24,098$ nM \cdot hour ($n=34$), C_{max} of $17,181 \pm 9809$ nM ($n=34$), and trough concentrations of 134 ± 91 nM ($n=28$). The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults.

receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50% of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

Drug Interactions (also see PRECAUTIONS, Drug Interactions)

Specific drug interaction studies were performed with indinavir and a number of drugs.

Drugs That Should Not Be Coadministered With CRIVAN

Administration of indinavir (800 mg every 8 hours) with rifampin (600 mg once daily) for one week resulted in an 89% \pm 9% decrease in indinavir AUC.

In a published study, eight HIV-negative volunteers received indinavir 800 mg every eight hours for four doses prior to and at the end of a 14-day course of St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg three times daily. Indinavir plasma pharmacokinetics were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC_{0-8h} of indinavir was decreased 57% \pm 19% and the C_{8h} of indinavir was decreased 81% \pm 16% compared to when indinavir was taken alone. All subjects demonstrated a decrease in AUC_{0-8h} (range 36 to 79%) and a decrease in C_{8h} (range 49 to 99%). (See WARNINGS.)

Drugs Requiring Dose Modification

Delavirdine: Preliminary data (n=14) indicate that delavirdine inhibits the metabolism of indinavir such that coadministration of a 400-mg single dose of indinavir with delavirdine (400 mg three times a day) resulted in indinavir AUC values slightly less than those observed following administration of an 800-mg dose of indinavir alone. Also, coadministration of a 600-mg dose of indinavir with delavirdine (400 mg three times a day) resulted in indinavir AUC values approximately 40% greater than those observed following administration of an 800-mg dose of indinavir alone. Indinavir had no effect on delavirdine pharmacokinetics (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Delavirdine*).

Efavirenz: When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg once daily) for two weeks, the indinavir AUC and C_{max} were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Efavirenz*.)

Itraconazole: In a multiple-dose study, administration in the fasted state of itraconazole capsules 200 mg twice daily with indinavir 600 mg every 8 hours resulted in an indinavir AUC similar to that observed during administration of indinavir 800 mg every 8 hours alone for one week (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Itraconazole*).

Ketoconazole: In a single-dose study, administration of a 400-mg dose of ketoconazole with a 400-mg dose of indinavir resulted in a 68% \pm 48% increase in indinavir AUC compared to a 400-mg dose of indinavir alone. In a multiple-dose study, administration of ketoconazole 400 mg once daily with indinavir 600 mg every 8 hours resulted in an 18% \pm 17% decrease in indinavir AUC compared to an 800-mg dose of indinavir alone every 8 hours (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Ketoconazole*).

Rifabutin: The coadministration of indinavir 800 mg every 8 hours with rifabutin either 300 mg once daily or 150 mg once daily was evaluated in two separate clinical studies. The results of these studies showed a decrease in indinavir AUC (32% \pm 19% and 31% \pm 15%, respectively) vs. indinavir 800 mg every 8 hours alone and an increase in rifabutin AUC (204% \pm 142% and 60% \pm 47%, respectively) vs. rifabutin 300 mg once daily alone. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Rifabutin*.)

Drugs Not Requiring Dose Modification

Cimetidine, Quinidine, Grapefruit Juice: Administration of a single 400-mg dose of indinavir following six days of cimetidine (600 mg every 12 hours) did not affect indinavir AUC. Administration of a single 400-mg dose of indinavir with 8 oz. of grapefruit juice resulted in a decrease in indinavir AUC (26% \pm 18%). Administration of a single 400-mg dose of indinavir with 200 mg of quinidine sulfate resulted in a 10% \pm 26% increase in indinavir AUC.

Methadone: Administration of indinavir (800 mg every 8 hours) with methadone (20 mg to 60 mg daily) for one week resulted in no change in methadone AUC and little or no change in indinavir AUC.

Nucleoside analogue antiretroviral agents: Administration of indinavir (1000 mg every 8 hours) with zidovudine (200 mg every 8 hours) for one week resulted in a 13% \pm 48% increase in indinavir AUC and a 17% \pm 23% increase in zidovudine AUC. In another study, administration of indinavir (800 mg every 8

hours) with zidovudine (200 mg every 8 hours) in combination with lamivudine (150 mg twice daily) for one week resulted in no change in indinavir AUC, a 36% increase in zidovudine AUC, and a 6% decrease in lamivudine AUC. Administration of indinavir (800 mg every 8 hours) in combination with stavudine (40 mg every 12 hours) for one week resulted in no change in indinavir AUC and a 25% ± 26% increase in stavudine AUC.

ORTHO-NOVUM 1/35: Administration of indinavir (800 mg every 8 hours) with ORTHO-NOVUM 1/35 for one week resulted in a 24% ± 17% increase in ethinyl estradiol AUC and a 26% ± 14% increase in norethindrone AUC.

Trimethoprim/Sulfamethoxazole, Fluconazole, Isoniazid, Clarithromycin: Administration of indinavir (400 mg every 6 hours) with trimethoprim/sulfamethoxazole (one double strength tablet every 12 hours) for one week resulted in no change in indinavir AUC, a 19% ± 31% increase in trimethoprim AUC, and no change in sulfamethoxazole AUC. Administration of indinavir (1000 mg every 8 hours) with fluconazole (400 mg once daily) for one week resulted in a 19% ± 33% decrease in indinavir AUC and no change in fluconazole AUC. Administration of indinavir (800 mg every 8 hours) with isoniazid (300 mg once daily) for one week resulted in no change in indinavir AUC and a 13% ± 15% increase in isoniazid AUC. Administration of indinavir (800 mg every 8 hours) with clarithromycin (500 mg every 12 hours) for one week resulted in a 29% ± 42% increase in indinavir AUC and a 53% ± 36% increase in clarithromycin AUC.

INDICATIONS AND USAGE

CRIXIVAN in combination with antiretroviral agents is indicated for the treatment of HIV infection.

This indication is based on two clinical trials of approximately 1 year duration that demonstrated: 1) a reduction in the risk of AIDS defining illnesses or death; 2) a prolonged suppression of HIV RNA.

Description of Studies

In all clinical studies, with the exception of ACTG 320, the AMPLICOR HIV MONITOR assay was used to determine the level of circulating HIV RNA in serum. This is an experimental use of the assay. HIV RNA results should not be directly compared to results from other trials using different HIV RNA assays or using other sample sources.

Study ACTG 320 was a multicenter, randomized, double-blind clinical endpoint trial to compare the effect of CRIXIVAN in combination with zidovudine and lamivudine with that of zidovudine plus lamivudine on the progression to an AIDS-defining illness (ADI) or death. Patients were protease inhibitor and lamivudine naive and zidovudine experienced, with CD4 cell counts of ≤200 cells/mm³. The study enrolled 1156 HIV-infected patients (17% female, 28% Black, 18% Hispanic, mean age 39 years). The mean baseline CD4 cell count was 87 cells/mm³. The mean baseline HIV RNA was 4.95 log₁₀ copies/mL (89,035 copies/mL). The study was terminated after a planned interim analysis, resulting in a median follow-up of 38 weeks and a maximum follow-up of 52 weeks. Results are shown in Table 2 and Figures 1 & 2.

Table 2
ACTG 320

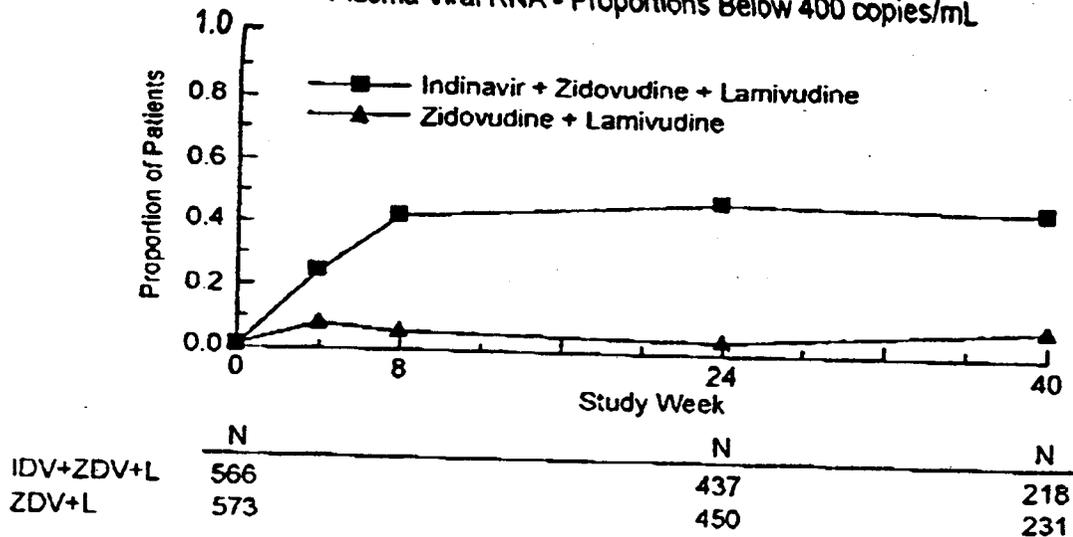
Endpoint	Number (%) of Patients with AIDS-defining Illness or Death	
	IDV+ZDV+L (n=577)	ZDV+L (n=579)
HIV Progression or Death	35 (6.1)	63 (10.9)
Death*	10 (1.7)	19 (3.3)

* The number of deaths is inadequate to assess the impact of indinavir on survival.
IDV = Indinavir, ZDV = Zidovudine, L = Lamivudine

Registered trademark of Ortho Pharmaceutical Corporation

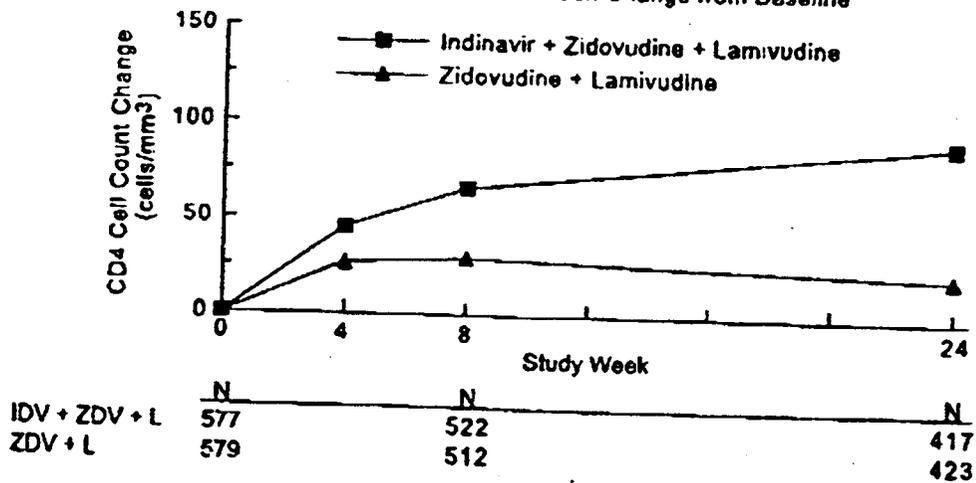
Study ACTG 320: Figure 1

Indinavir Protocol ACTG 320 Zidovudine Experienced
Plasma Viral RNA - Proportions Below 400 copies/mL



Study ACTG 320: Figure 2

ACTG 320 Zidovudine Experienced
CD4 Cell Counts - Mean Change from Baseline



Study 028, a double-blind, multicenter, randomized, clinical endpoint trial conducted in Brazil, compared the effects of CRIXIVAN plus zidovudine with those of CRIXIVAN alone or zidovudine alone on the progression to an ADI or death, and on surrogate marker responses. All patients were antiretroviral naive with CD4 cell counts of 50 to 250 cells/mm³. The study enrolled 996 HIV-1 seropositive patients [28% female, 11% Black, 1% Asian/Other, median age 33 years, mean baseline CD4 cell count of 152 cells/mm³, mean serum viral RNA of 4.44 log₁₀ copies/mL (27,824 copies/mL)]. Treatment regimens containing zidovudine were modified in a blinded manner with the optional addition of lamivudine (median time: week 40). The median length of follow-up was 56 weeks with a maximum of 97 weeks. The study was terminated after a planned interim analysis, resulting in a median follow-up of 56 weeks and a maximum follow-up of 97 weeks. Results are shown in Table 3 and Figures 3 and 4.

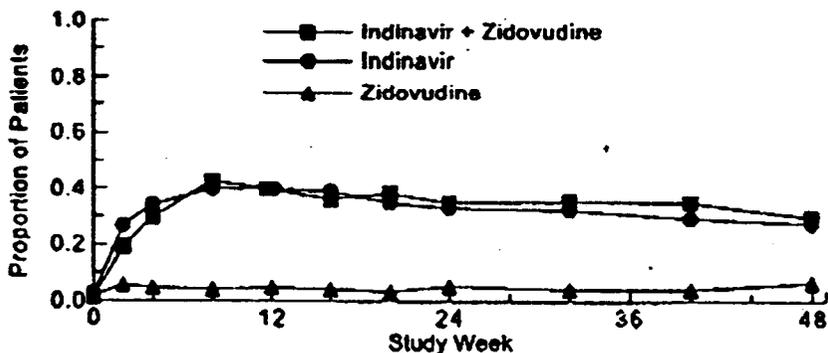
Table 3
Protocol 028

Endpoint	Number (%) of Patients with AIDS-defining illness or Death		
	IDV+ZDV (n=332)	IDV (n=332)	ZDV (n=332)
HIV Progression or Death	21 (6.3)	27 (8.1)	62 (18.7)
Death*	8 (2.4)	5 (1.5)	11 (3.3)

* The number of deaths is inadequate to assess the impact of indinavir on survival.

Study 028: Figure 3

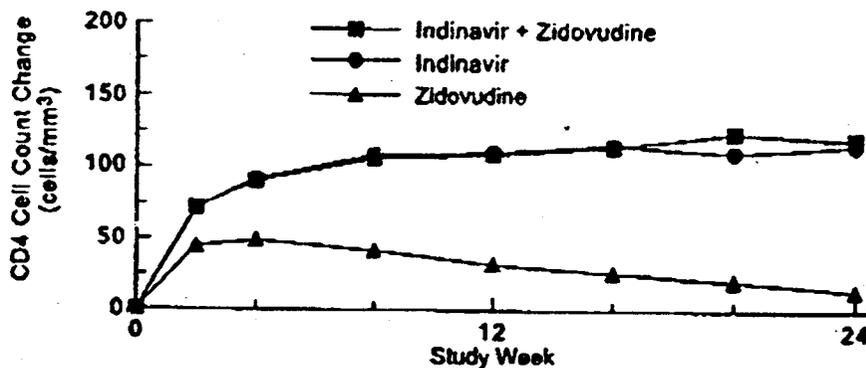
Indinavir Protocol 028 Zidovudine Naive
Viral RNA - Proportions Below 500 Copies/mL in Serum



	N	N	N
IDV + ZDV	328	319	261
IDV	329	318	244
ZDV	328	317	253

Study 028: Figure 4

Indinavir Protocol 028 Zidovudine Naive
CD4 Cell Counts - Mean Change from Baseline



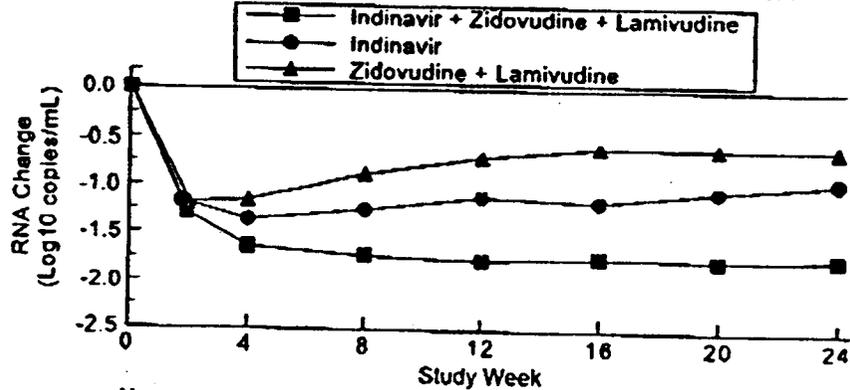
	N	N
IDV + ZDV	332	277
IDV	332	298
ZDV	332	295

Study 035 was a multicenter randomized trial in 97 HIV-1 seropositive patients who were zidovudine-experienced (median exposure 30 months), protease-inhibitor- and lamivudine-naive, with mean baseline CD4 count 175 cells/mm³ and mean baseline serum viral RNA 4.62 log₁₀ copies/mL (41,230 copies/mL).

Comparisons included CRIXIVAN plus zidovudine plus lamivudine vs. CRIXIVAN alone vs. zidovudine plus lamivudine. After at least 24 weeks of randomized, double-blind therapy, patients were switched to open-label CRIXIVAN plus lamivudine plus zidovudine. Mean changes in log₁₀ viral RNA in serum, the proportions of patients with viral RNA below 500 copies/mL in serum, and mean changes in CD4 cell counts, during 24 weeks of randomized, double-blinded therapy are summarized in Figures 5, 6, and 7, respectively. A limited number of patients remained on randomized, double-blind treatment for longer periods; based on this extended treatment experience, it appears that a greater number of subjects randomized to CRIXIVAN plus zidovudine plus lamivudine demonstrated HIV RNA levels below 500 copies/mL during one year of therapy as compared to those in other treatment groups.

Study 035: Figure 5

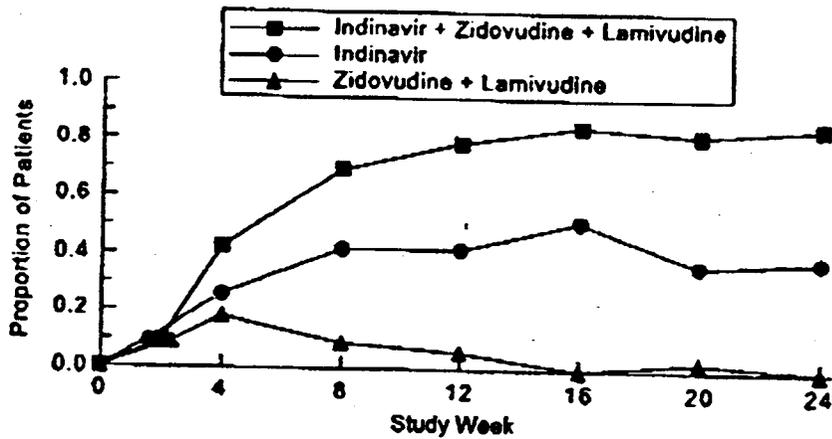
Indinavir Protocol 035 Zidovudine Experienced
Viral RNA - Mean Log₁₀ Change from Baseline in Serum



	N	N	N
IDV + ZDV + L	32	30	30
IDV	31	31	28
ZDV + L	33	33	30

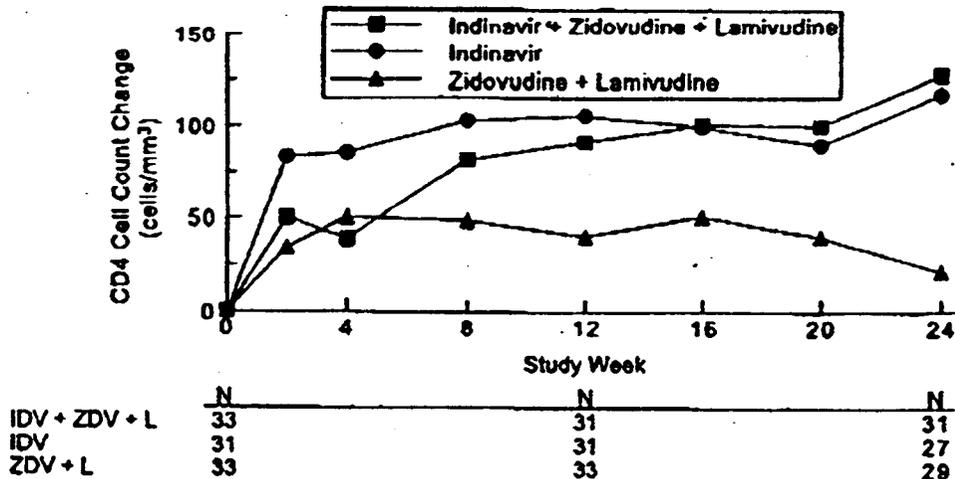
Study 035: Figure 6

Indinavir Protocol 035 Zidovudine Experienced
Viral RNA - Proportions Below 500 Copies/mL In Serum



Study 035: Figure 7

Indinavir Protocol 035 Zidovudine Experienced
CD4 Cell Counts - Mean Change from Baseline



Genotypic Resistance in Clinical Studies

Study 006 (10/15/93-10/12/94) was a dose-ranging study in which patients were initially treated with CRIXIVAN at a dose of <2.4 g/day followed by 2.4 g/day. Study 019 (6/23/94-4/10/95) was a randomized comparison of CRIXIVAN 600 mg every 6 hours, CRIXIVAN plus zidovudine, and zidovudine alone. Table 4 shows the incidence of genotypic resistance at 24 weeks in these studies.

Table 4
Genotypic Resistance at 24 Weeks

Treatment Group	Resistance to IDV n/N	Resistance to ZDV n/N
IDV	—	—
<2.4 g/day	31/37 (84%)	—
2.4 g/day	9/21 (43%)	1/17 (6%)
IDV/ZDV	4/22 (18%)	1/22 (5%)
ZDV	1/18 (6%)	11/17 (65%)

* N - includes patients with non-amplifiable virus at 24 weeks who had amplifiable virus at week 0.

CONTRAINDICATIONS

CRIXIVAN is contraindicated in patients with clinically significant hypersensitivity to any of its components.

CRIXIVAN should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam, pimozone, or ergot derivatives. Inhibition of CYP3A4 by CRIXIVAN could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

WARNINGS

Nephrolithiasis/Urolithiasis

Nephrolithiasis/urolithiasis has occurred with CRIXIVAN therapy. The frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (9.3%). In some cases, nephrolithiasis/urolithiasis has been associated with renal insufficiency or acute renal failure. If signs or symptoms of nephrolithiasis/urolithiasis occur, (including flank pain, with or without hematuria or microscopic hematuria), temporary interruption (e.g., 1-3 days) or discontinuation of therapy may be considered. Adequate

hydration is recommended in all patients treated with CRIXIVAN. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION, *Nephrolithiasis/Urolithiasis*.)

Hemolytic Anemia

Acute hemolytic anemia, including cases resulting in death, has been reported in patients treated with CRIXIVAN. Once a diagnosis is apparent, appropriate measures for the treatment of hemolytic anemia should be instituted, including discontinuation of CRIXIVAN.

Hepatitis

Hepatitis including cases resulting in hepatic failure and death has been reported in patients treated with CRIXIVAN. Because the majority of these patients had confounding medical conditions and/or were receiving concomitant therapy(ies), a causal relationship between CRIXIVAN and these events has not been established.

Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

Drug Interactions

Concomitant use of CRIXIVAN with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including CRIXIVAN, are used in combination with these drugs.

Concomitant use of CRIXIVAN and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Coadministration of CRIXIVAN and St. John's wort has been shown to substantially decrease indinavir concentrations (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drugs That Should Not Be Coadministered With CRIXIVAN*) and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

PRECAUTIONS

General

Indirect hyperbilirubinemia has occurred frequently during treatment with CRIXIVAN and has infrequently been associated with increases in serum transaminases (see also ADVERSE REACTIONS, *Clinical Trials and Post-Marketing Experience*). It is not known whether CRIXIVAN will exacerbate the physiologic hyperbilirubinemia seen in neonates. (See *Pregnancy*.)

Coexisting Conditions

Patients with hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established. (See ADVERSE REACTIONS, *Post-Marketing Experience*.)

Patients with hepatic insufficiency due to cirrhosis: In these patients, the dosage of CRIXIVAN should be lowered because of decreased metabolism of CRIXIVAN (see DOSAGE AND ADMINISTRATION).

Patients with renal insufficiency: Patients with renal insufficiency have not been studied.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients

CRIXIVAN is not a cure for HIV infection and patients may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of CRIXIVAN are unknown at

this time. CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using CRIXIVAN and should not modify or discontinue treatment without first consulting the physician. Therefore, if a dose is missed, patients should take the next dose at the regularly scheduled time and should not double this dose. Therapy with CRIXIVAN should be initiated and maintained at the recommended dosage.

CRIXIVAN may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

For optimal absorption, CRIXIVAN should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, CRIXIVAN may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar (see CLINICAL PHARMACOLOGY, *Effect of Food on Oral Absorption and DOSAGE AND ADMINISTRATION*). Ingestion of CRIXIVAN with a meal high in calories, fat, and protein reduces the absorption of indinavir.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

CRIXIVAN Capsules are sensitive to moisture. Patients should be informed that CRIXIVAN should be stored and used in the original container and the desiccant should remain in the bottle.

Drug Interactions

Delavirdine

Due to an increase in indinavir plasma concentrations (preliminary results), a dosage reduction of indinavir should be considered when CRIXIVAN and delavirdine are coadministered. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Delavirdine*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Delavirdine*.)

Efavirenz

Due to a decrease in the plasma concentrations of indinavir, a dosage increase of indinavir is recommended when CRIXIVAN and efavirenz are coadministered. No adjustment of the dose of efavirenz is necessary when given with indinavir. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Efavirenz*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Efavirenz*.)

Itraconazole

Itraconazole is an inhibitor of P-450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN and itraconazole are coadministered (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Itraconazole*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Itraconazole*).

Ketoconazole

Ketoconazole is an inhibitor of P-450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN and ketoconazole are coadministered (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Ketoconazole*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Ketoconazole*).

Rifabutin

When rifabutin and CRIXIVAN are coadministered, there is an increase in the plasma concentrations of rifabutin and a decrease in the plasma concentrations of indinavir. A dosage reduction of rifabutin and a dosage increase of CRIXIVAN are necessary when rifabutin is coadministered with CRIXIVAN. The suggested dose adjustments are expected to result in rifabutin concentrations at least 50% higher than typically observed when rifabutin is administered alone at its usual dose (300 mg/day) and indinavir concentrations which may be slightly less than typically observed when indinavir is administered alone at its usual dose (800 mg every 8 hours). (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Rifabutin*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Rifabutin*.)

Rifampin

Rifampin is a potent inducer of P-450 3A4 that markedly diminishes plasma concentrations of indinavir. Therefore, CRIVAN and rifampin should not be coadministered (see CLINICAL PHARMACOLOGY, *Drugs That Should Not Be Coadministered With CRIVAN*).

Other

If CRIVAN and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach; a normal (acidic) gastric pH may be necessary for optimum absorption of indinavir, whereas acid rapidly degrades didanosine which is formulated with buffering agents to increase pH (consult the manufacturer's product circular for didanosine).

Interactions between indinavir and less potent CYP3A4 inducers than rifampin, such as phenobarbital, phenytoin, carbamazepine, and dexamethasone have not been studied. These agents should be used with caution if administered concomitantly with indinavir because decreased indinavir plasma concentrations may result.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumor type was observed. The highest dose tested in rats was 640 mg/kg/day, at this dose a statistically significant increased incidence of thyroid adenomas was seen only in male rats. At that dose, daily systemic exposure in rats was approximately 1.3 times higher than daily systemic exposure in humans. No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, *in vitro* and *in vivo* chromosomal aberration studies, and *in vitro* mammalian cell mutagenesis assays. No treatment-related effects on mating, fertility, or embryo survival were seen in female rats and no treatment-related effects on mating performance were seen in male rats at doses providing systemic exposure comparable to or slightly higher than that with the clinical dose. In addition, no treatment-related effects were observed in fecundity or fertility of untreated females mated to treated males.

Pregnancy

Pregnancy Category C: Developmental toxicity studies were performed in rabbits (at doses up to 240 mg/kg/day), dogs (at doses up to 80 mg/kg/day), and rats (at doses up to 640 mg/kg/day). The highest doses in these studies produced systemic exposures in these species comparable to or slightly greater than human exposure. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs (at exposures at or below those in humans) and of cervical ribs (at exposures comparable to or slightly greater than those in humans) were seen in rats. In all three species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rabbits, at a maternal dose of 240 mg/kg/day, no drug was detected in fetal plasma 1 hour after dosing. Fetal plasma drug levels 2 hours after dosing were approximately 3% of maternal plasma drug levels. In dogs, at a maternal dose of 80 mg/kg/day, fetal plasma drug levels were approximately 50% of maternal plasma drug levels both 1 and 2 hours after dosing. In rats, at maternal doses of 40 and 640 mg/kg/day, fetal plasma drug levels were approximately 10 to 15% and 10 to 20% of maternal plasma drug levels 1 and 2 hours after dosing, respectively.

Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1 to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

Hyperbilirubinemia has occurred during treatment with CRIVAN (see PRECAUTIONS and ADVERSE REACTIONS). It is unknown whether CRIVAN administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates.

There are no adequate and well-controlled studies in pregnant women. CRIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to CRIXIVAN, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

Studies in lactating rats have demonstrated that indinavir is excreted in milk. Although it is not known whether CRIXIVAN is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving CRIXIVAN. This is consistent with the recommendation by the U.S. Public Health Service Centers for Disease Control and Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m² every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adults receiving the recommended dose (see **CLINICAL PHARMACOLOGY, Pediatric**). Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see **WARNINGS, Nephrolithiasis/Urolithiasis**). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

ADVERSE REACTIONS

Clinical Trials in Adults

Nephrolithiasis/urolithiasis, including flank pain with or without hematuria (including microscopic hematuria), has been reported in approximately 9.3% (193/2071) of patients receiving CRIXIVAN in clinical trials at the recommended dose, compared to 1.8% in the control arms. Of the patients treated with CRIXIVAN who developed nephrolithiasis/urolithiasis, 3.1% (6/193) were reported to develop hydronephrosis and 3.1% (6/193) underwent stent placement. Following the acute episode, 3.6% (7/193) of patients discontinued therapy. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION, Nephrolithiasis/Urolithiasis**.)

Asymptomatic hyperbilirubinemia (total bilirubin \geq 2.5 mg/dL), reported predominantly as elevated indirect bilirubin, has occurred in approximately 14% of patients treated with CRIXIVAN. In <1% this was associated with elevations in ALT or AST.

Hyperbilirubinemia and nephrolithiasis/urolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses \leq 2.4 g/day.

Clinical adverse experiences reported in \geq 2% of patients treated with CRIXIVAN alone, CRIXIVAN in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 5.

Table 5
Clinical Adverse Experiences Reported in ≥2% of Patients

Adverse Experience	Study 028 Considered Drug-Related and of Moderate or Severe Intensity			Study ACTG 320 of Unknown Drug Relationship and of Severe or Life-threatening Intensity	
	CRIXIVAN Percent (n=332)	CRIXIVAN plus Zidovudine Percent (n=332)	Zidovudine Percent (n=332)	CRIXIVAN plus Zidovudine plus Lamivudine Percent (n=571)	Zidovudine plus Lamivudine Percent (n=575)
<i>Body as a Whole</i>					
Abdominal pain	16.6	16.0	12.0	1.9	0.7
Asthenia/fatigue	2.1	4.2	3.6	2.4	4.5
Fever	1.5	1.5	2.1	3.8	3.0
Malaise	2.1	2.7	1.8	0	0
<i>Digestive System</i>					
Nausea	11.7	31.9	19.6	2.8	1.4
Diarrhea	3.3	3.0	2.4	0.9	1.2
Vomiting	8.4	17.8	9.0	1.4	1.4
Acid regurgitation	2.7	5.4	1.8	0.4	0
Anorexia	2.7	5.4	3.0	0.5	0.2
Appetite increase	2.1	1.5	1.2	0	0
Dyspepsia	1.5	2.7	0.9	0	0
Jaundice	1.5	2.1	0.3	0	0
<i>Hemic and Lymphatic System</i>					
Anemia	0.6	1.2	2.1	2.4	3.5
<i>Musculoskeletal System</i>					
Back pain	8.4	4.5	1.5	0.9	0.7
<i>Nervous System/Psychiatric</i>					
Headache	5.4	9.6	6.0	2.4	2.8
Dizziness	3.0	3.9	0.9	0.5	0.7
Somnolence	2.4	3.3	3.3	0	0
<i>Skin and Skin Appendage</i>					
Pruritus	4.2	2.4	1.8	0.5	0
Rash	1.2	0.6	2.4	1.1	0.5
<i>Respiratory System</i>					
Cough	1.5	0.3	0.6	1.6	1.0
Difficulty breathing/ dyspnea/shortness of breath	0	0.6	0.3	1.8	1.0
<i>Urogenital System</i>					
Nephrolithiasis/uroolithiasis*	8.7	7.8	2.1	2.6	0.3
Dysuria	1.5	2.4	0.3	0.4	0.2
<i>Special Senses</i>					
Taste perversion	2.7	8.4	1.2	0.2	0

* Including renal colic, and flank pain with and without hematuria

In Phase I and II controlled trials, the following adverse events were reported significantly more frequently by those randomized to the arms containing CRIXIVAN than by those randomized to nucleoside analogues: rash, upper respiratory infection, dry skin, pharyngitis, taste perversion.

Selected laboratory abnormalities of severe or life-threatening intensity reported in patients treated with CRIXIVAN alone, CRIXIVAN in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 6.

Table 6
Selected Laboratory Abnormalities of Severe or Life-threatening Intensity
Reported in Studies 028 and ACTG 320

	CRIXIVAN	Study 028 CRIXIVAN plus Zidovudine	Zidovudine	Study ACTG 320 CRIXIVAN plus Zidovudine plus Lamivudine	Zidovudine plus Lamivudine
	Percent (n=329)	Percent (n=320)	Percent (n=330)	Percent (n=571)	Percent (n=575)
<i>Hematology</i>					
Decreased hemoglobin <7.0 g/dL	0.6	0.9	3.3	2.4	3.5
Decreased platelet count <50 THS/mm ³	0.9	0.9	1.8	0.2	0.9
Decreased neutrophils <0.75 THS/mm ³	2.4	2.2	6.7	5.1	14.6
<i>Blood chemistry</i>					
Increased ALT >500% ULN*	4.9	4.1	3.0	2.6	2.8
Increased AST >500% ULN	3.7	2.8	2.7	3.3	2.8
Total serum bilirubin >250% ULN	11.9	9.7	0.6	6.1	1.4
Increased serum amylase >200% ULN	2.1	1.9	1.8	0.9	0.3
Increased glucose >250 mg/dL	0.9	0.9	0.6	1.6	1.9
Increased creatinine >300% ULN	0	0	0.6	0.2	0

* Upper limit of the normal range.

Post-Marketing Experience

Body As A Whole: redistribution/accumulation of body fat (see PRECAUTIONS, *Fat Redistribution*).

Cardiovascular System: cardiovascular disorders including myocardial infarction and angina pectoris.

Digestive System: liver function abnormalities; hepatitis including reports of hepatic failure (see WARNINGS); pancreatitis; jaundice; abdominal distention; dyspepsia.

Hematologic: increased spontaneous bleeding in patients with hemophilia (see PRECAUTIONS); acute hemolytic anemia (see WARNINGS).

Endocrine/Metabolic: new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia (see WARNINGS).

Hypersensitivity: anaphylactoid reactions; urticaria.

Musculoskeletal System: arthralgia.

Nervous System/Psychiatric: oral paresthesia; depression.

Skin and Skin Appendage: rash including erythema multiforme and Stevens-Johnson Syndrome; hyperpigmentation; alopecia; ingrown toenails and/or paronychia; pruritus.

Urogenital System: nephrolithiasis/urolithiasis; in some cases resulting in renal insufficiency or acute renal failure (see WARNINGS); interstitial nephritis sometimes with indinavir crystal deposits; in some patients, the interstitial nephritis did not resolve following discontinuation of CRIXIVAN; crystalluria; dysuria.

Laboratory Abnormalities

Increased serum triglycerides; increased serum cholesterol.

OVERDOSAGE

There have been more than 60 reports of acute or chronic human overdosage (up to 23 times the recommended total daily dose of 2400 mg) with CRIXIVAN. The most commonly reported symptoms were renal (e.g., nephrolithiasis/urolithiasis, flank pain, hematuria) and gastrointestinal (e.g., nausea, vomiting, diarrhea).

It is not known whether CRIXIVAN is dialyzable by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended dosage of CRIXIVAN is 800 mg (usually two 400-mg capsules) orally every 8 hours.

CRIXIVAN must be taken at intervals of 8 hours. For optimal absorption, CRIXIVAN should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, CRIXIVAN may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar. (See CLINICAL PHARMACOLOGY, *Effect of Food on Oral Absorption*.)

To ensure adequate hydration, it is recommended that adults drink at least 1.5 liters (approximately 48 ounces) of liquids during the course of 24 hours.

Concomitant Therapy (See CLINICAL PHARMACOLOGY, *Drug Interactions*, and/or PRECAUTIONS, *Drug Interactions*.)

Delavirdine

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day.

Didanosine

If indinavir and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach (consult the manufacturer's product circular for didanosine).

Efavirenz

Dose increase of CRIXIVAN to 1000 mg every 8 hours is recommended when administering efavirenz concurrently (consult the manufacturer's product circular for efavirenz).

Itraconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently.

Ketoconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering ketoconazole concurrently.

Rifabutin

Dose reduction of rifabutin to half the standard dose (consult the manufacturer's product circular for rifabutin) and a dose increase of CRIXIVAN to 1000 mg (three 333-mg capsules) every 8 hours are recommended when rifabutin and CRIXIVAN are coadministered.

Hepatic Insufficiency

The dosage of CRIXIVAN should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis.

Nephrolithiasis/Urolithiasis

In addition to adequate hydration, medical management in patients who experience nephrolithiasis/urolithiasis may include temporary interruption (e.g., 1 to 3 days) or discontinuation of therapy.

HOW SUPPLIED

CRIXIVAN Capsules are supplied as follows:

No. 3755 — 100 mg capsules: semi-translucent white capsules coded "CRIXIVAN™ 100 mg" in green and a radial green band on the body. Available as:

NDC 0006-0570-62 unit of use bottles of 180 (with desiccant).

No. 3756 — 200 mg capsules: semi-translucent white capsules coded "CRIXIVAN™ 200 mg" in blue. Available as:

NDC 0006-0571-42 unit-of-use bottles of 270 (with desiccant)

NDC 0006-0571-43 unit-of-use bottles of 360 (with desiccant).

No. 3802 — 333 mg capsules: semi-translucent white capsules coded "CRIXIVAN™ 333 mg" in red and a radial red band on the body. Available as:

NDC 0006-0574-65 unit-of-use bottles of 135 (with desiccant).

No. 3758 — 400 mg capsules: semi-translucent white capsules coded "CRIXIVAN™ 400 mg" in green. Available as:

NDC 0006-0573-42 unit-dose packages of 42

NDC 0006-0573-62 unit-of-use bottles of 180 (with desiccant)

NDC 0006-0573-54 unit-of-use bottles of 90 (with desiccant)

NDC 0006-0573-18 unit-of-use bottles of 18 (with desiccant).

Storage

Bottles: Store in a tightly-closed container at room temperature. 15-30°C (59-86°F). Protect from moisture.

CRIXIVAN Capsules are sensitive to moisture. CRIXIVAN should be dispensed and stored in the original container. The desiccant should remain in the original bottle.

Unit-Dose Packages: Store at room temperature, 15-30°C (59-86°F). Protect from moisture.

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CRIXIVAN® (indinavir sulfate) Capsules
Patient Information about
CRIXIVAN (KRIK-sih-van)
for HIV (Human Immunodeficiency Virus) Infection
 Generic name: indinavir (in-DIH-nuh-veer) sulfate

Please read this information before you start taking CRIXIVAN. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss CRIXIVAN when you start taking your medication and at regular checkups. You should remain under a doctor's care when using CRIXIVAN and should not change or stop treatment without first talking with your doctor.

What is CRIXIVAN?

CRIXIVAN is an oral capsule used for the treatment of HIV (Human Immunodeficiency Virus). HIV is the virus that causes AIDS (acquired immune deficiency syndrome). CRIXIVAN is a type of HIV drug called a protease (PRO-tee-ase) inhibitor.

How does CRIXIVAN work?

CRIXIVAN is a protease inhibitor that fights HIV. CRIXIVAN can help reduce your chances of getting illnesses associated with HIV. CRIXIVAN can also help lower the amount of HIV in your body (called "viral load") and raise your CD4 (T) cell count. CRIXIVAN may not have these effects in all patients.

CRIXIVAN is usually prescribed with other anti-HIV drugs such as ZDV (also called AZT), 3TC, ddI, ddC, or d4T. CRIXIVAN works differently from these other anti-HIV drugs. Talk with your doctor about how you should take CRIXIVAN.

How should I take CRIXIVAN?

There are six important things you must do to help you benefit from CRIXIVAN:

1. **Take CRIXIVAN capsules every day as prescribed by your doctor.** Continue taking CRIXIVAN unless your doctor tells you to stop. Take the exact amount of CRIXIVAN that your doctor tells you to take, right from the very start. To help make sure you will benefit from CRIXIVAN, you must not skip doses or take "drug holidays". If you don't take CRIXIVAN as prescribed, the activity of CRIXIVAN may be reduced (due to resistance).
2. **Take CRIXIVAN capsules every 8 hours around the clock, every day.** It may be easier to remember to take CRIXIVAN if you take it at the same time every day. If you have questions about when to take CRIXIVAN, your doctor or health care provider can help you decide what schedule works for you.
3. **If you miss a dose by more than 2 hours, wait and then take the next dose at the regularly scheduled time.** However, if you miss a dose by less than 2 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of CRIXIVAN at any one time.
4. **Take CRIXIVAN with water.** You can also take CRIXIVAN with other beverages such as skim or non-fat milk, juice, coffee, or tea.

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- CRIXIVAN (crizotinib sulfate) capsules
5. Ideally, take each dose of CRIXIVAN without food but with water at least one hour before or two hours after a meal. Or you can take CRIXIVAN with a light meal. Examples of light meals include:

dry toast with jelly, juice, and coffee (with skim or non-fat milk and sugar if you want)

cornflakes with skim or non-fat milk and sugar

Do not take CRIXIVAN at the same time as any meals that are high in calories, fat, and protein (for example — a bacon and egg breakfast). When taken at the same time as CRIXIVAN, these foods can interfere with CRIXIVAN being absorbed into your bloodstream and may lessen its effect.

6. It is critical to drink plenty of fluids while taking CRIXIVAN. Adults should drink at least six 8-ounce glasses of liquids (preferably water) throughout the day, every day. Your health care provider will give you further instructions on the amount of fluid that you should drink. CRIXIVAN can cause kidney stones. Having enough fluids in your body should help reduce the chances of forming a kidney stone. Call your doctor or other health care provider if you develop kidney pains (middle to lower stomach or back pain) or blood in the urine.

Does CRIXIVAN cure HIV or AIDS?

CRIXIVAN is not a cure for HIV or AIDS. People taking CRIXIVAN may still develop infections or other conditions associated with HIV. Because of this, it is very important for you to remain under the care of a doctor. Although CRIXIVAN is not a cure for HIV or AIDS, CRIXIVAN can help reduce your chances of getting illnesses, including death, associated with HIV. CRIXIVAN may not have these effects in all patients.

Does CRIXIVAN reduce the risk of passing HIV to others?

CRIXIVAN has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination.

Who should not take CRIXIVAN?

Do not take CRIXIVAN if you have had a serious allergic reaction to CRIXIVAN or any of its components.

What other medical problems or conditions should I discuss with my doctor?

Talk to your doctor if:

- You are pregnant or if you become pregnant while you are taking CRIXIVAN. We do not yet know how CRIXIVAN affects pregnant women or their developing babies.
- You are breast-feeding. You should stop breast-feeding if you are taking CRIXIVAN.

Also talk to your doctor if you have:

- Problems with your liver, especially if you have mild or moderate liver disease caused by cirrhosis.
- Problems with your kidneys.
- Diabetes
- Hemophilia
- High cholesterol and you are taking cholesterol-lowering medicines called "statins".

Tell your doctor about any medicines you are taking or plan to take, including non-prescription medicines, herbal products including St. John's wort (*Hypericum perforatum*), or dietary supplements.

Can CRIXIVAN be taken with other medications?*

Drugs you should not take with CRIXIVAN:

SELDANE®
(terfenadine)
VERSED®
(midazolam)
ORAP®
(pimozide)
PROPULSID®
(cisapride)

HISMANAL®
(astemizole)
HALCION®
(triazolam)
Ergot medications
(e.g., Wigraine® and Cafergot®)

Taking CRIXIVAN with the above medications could result in serious or life-threatening problems (such as irregular heartbeat or excessive sleepiness).

In addition, you should not take CRIXIVAN with the following:

Rifampin, known as RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE®.

It is not recommended to take CRIXIVAN with the cholesterol-lowering drugs MEVACOR® (lovastatin) or ZOCOR® (simvastatin) because of possible drug interactions. There is also an increased risk of drug interactions between CRIXIVAN and LIPITOR® (atorvastatin) and BAYCOL® (cerivastatin); talk to your doctor before you take any of these cholesterol-reducing drugs with CRIXIVAN.

Taking CRIXIVAN with St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort is not recommended. Taking St. John's wort has been shown to decrease CRIXIVAN levels and may lead to increased viral load and possible resistance to CRIXIVAN or cross resistance to other antiretroviral drugs.

Drugs you can take with CRIXIVAN include:

RETROVIR®
(zidovudine, ZDV
also called AZT)

EPIVIR™
(lamivudine, 3TC)

ZEFIT®
(stavudine, d4T)

isoniazid
(INH)

BACTRIM®/SEPTRA®
(trimethoprim/sulfamethoxazole)

DIFLUCAN®
(fluconazole)

BIAXIN®
(clarithromycin)

ORTHO-NOVUM 1/35®
(oral contraceptive)

TAGAMET®
(cimetidine)

Methadone

VIDEX® (didanosine, ddI) — If you take CRIXIVAN with VIDEX, take them at least one hour apart.

MYCOBUTIN® (rifabutin) — If you take CRIXIVAN with MYCOBUTIN, your doctor may adjust both the dose of MYCOBUTIN and the dose of CRIXIVAN.

NIZORAL® (ketoconazole) — If you take CRIXIVAN with NIZORAL, your doctor may adjust the dose of CRIXIVAN.

RESCRIPTOR® (delavirdine) — If you take CRIXIVAN with RESSCRIPTOR, your doctor may adjust the dose of CRIXIVAN.

SPORANOX® (itraconazole) — If you take CRIXIVAN with SPORANOX, your doctor may adjust the dose of CRIXIVAN.

SUSTIVA™ (efavirenz) — If you take CRIXIVAN with SUSTIVA, your doctor may adjust the dose of CRIXIVAN.

Talk to your doctor about any medications you are taking.

What are the possible side effects of CRIXIVAN?

Like all prescription drugs, CRIXIVAN can cause side effects. The following is not a complete list of side effects reported with CRIXIVAN when taken either alone or with other anti-HIV drugs. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

Some patients treated with CRIXIVAN developed kidney stones. In some of these patients this led to more severe kidney problems, including kidney failure or inflammation of the kidneys. Drinking at least six 8-ounce glasses of liquids (preferably water) each day should help reduce the chances of forming a kidney stone (see How should I take CRIXIVAN?). Call your doctor or other health care provider if you develop kidney pains (middle to lower stomach or back pain) or blood in the urine.

Some patients treated with CRIXIVAN have had rapid breakdown of red blood cells (hemolytic anemia) which in some cases was severe or resulted in death.

Some patients treated with CRIXIVAN have had liver problems including liver failure and death. Some patients had other illnesses or were taking other drugs. It is uncertain if CRIXIVAN caused these liver problems.

Diabetes and high blood sugar (hyperglycemia) have occurred in patients taking protease inhibitors. In some of these patients, this led to ketoacidosis, a serious condition caused by poorly controlled blood sugar. Some patients had diabetes before starting protease inhibitors, others did not. Some patients required adjustments to their diabetes medication. Others needed new diabetes medication.

In some patients with hemophilia, increased bleeding has been reported.

Severe muscle pain and weakness have occurred in patients taking protease inhibitors, including CRIXIVAN, together with some of the cholesterol-lowering medicines called "statins". Call your doctor if you develop severe muscle pain or weakness.

Changes in body fat have been seen in some patients taking protease inhibitors. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs and arms may also happen. The cause and long term health effects of these conditions are not known at this time.

Clinical Studies

Increases in bilirubin (one laboratory test of liver function) have been reported in approximately 10% of patients. Usually, this finding has not been associated with liver problems. However, on rare occasions, a person may develop yellowing of the skin and/or eyes.

Side effects occurring in 2% or more of patients included: abdominal pain, fatigue or weakness, low red blood cell count, flank pain, painful urination, feeling unwell, nausea, upset stomach, diarrhea, vomiting, acid regurgitation, increased or decreased appetite, back pain, headache, dizziness, taste changes, rash, itchy skin, yellowing of the skin and/or eyes, upper respiratory infection, dry skin, and sore throat.

Swollen kidneys due to blocked urine flow occurred rarely.

Marketing Experience

Other side effects reported since CRIXIVAN has been marketed include: allergic reactions; severe skin reactions; yellowing of the skin and/or eyes; heart problems including heart attack; abdominal swelling; indigestion; inflammation of the kidneys; inflammation of the pancreas; joint pain; depression; itching; hives; change in skin color; hair loss; ingrown toenails with or without infection; crystals in the urine; painful urination; and numbness of the mouth.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

How should I store CRIXIVAN capsules?

- Keep CRIXIVAN capsules in the bottle they came in and at room temperature (59°-86°F).
- Keep CRIXIVAN capsules dry by leaving the small desiccant "pillow" in the bottle. Keep the bottle closed.

This medication was prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep CRIXIVAN and all medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about CRIXIVAN. If you have any questions or concerns about either CRIXIVAN or HIV, talk to your doctor.

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Issued May-2009

MERCK & CO., INC.
West Point, PA 19486, USA

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Marak & Co., Inc. Sunnyside Pike, BLA-10 P. O. Box 4 West Point, PA 19486	3. PRODUCT NAME <i>Criqiva</i>
2. TELEPHONE NUMBER (include Area Code) (610) 397-2383	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE LD. NUMBER	6. LICENSE NUMBER / NDA NUMBER <i>1020695</i>

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 730(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input checked="" type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 730(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE FHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Bonnie J. Goldmann</i>	TITLE Bonnie J. Goldmann, M.D. Vice President, Domestic Liaison Regulatory Affairs	DATE <i>December 22, 1999</i>
---	---	----------------------------------

**Indinavir Sulfate - Pediatric Use
Item 16 – Debarment Certification**

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



November 10, 1999

Pediatric Formulation of CRIXIVAN®
sNDA No. - Not Yet Assigned (NDA No. 20 685)

ITEM 13

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 (b)(1) and in accordance with Title 21 C.F.R. 314.70(b), attached hereto please find the patent information for the above-identified application.

The undersigned declares that U.S. Patent No. 5,413,999 covers the formulation, composition, and/or method of use of a pediatric formulation of CRIXIVAN® (indinavir sulfate 100 mg capsules), the subject of this application for which approval is being sought. U.S. Patent No. 5,413,999 has an expiration date of May 9, 2012. This patent is owned by Merck & Co., Inc. A claim of infringement could be asserted if a person not licensed by the owner of U.S. Patent No. 5,413,999 engaged in the manufacture, use or sale of CRIXIVAN®.

Sincerely,

A handwritten signature in black ink that reads "Kenneth R. Walton". The signature is written in a cursive style.

Kenneth R. Walton
Senior Patent Attorney

ITEM 13
PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

- | | | |
|----|--|--|
| 1) | Active Ingredient(s) | Indinavir |
| 2) | Strength(s) | 100 mg |
| 3) | Trade Name | CRIXIVAN® |
| 4) | Dosage Form, Route of Administration | Capsules, Oral |
| 5) | Applicant Firm Name | Merck & Co., Inc. |
| 6) | sNDA Number | Not yet assigned |
| 7) | Approval Date | |
| 8) | Exclusivity - Date First ANDA could be approved | Three (3) years from the approval of this sNDA |
| | Length of Exclusivity Period | Three (3) years |
| 9) | Applicable U.S. patent numbers and expiration date of each | 5,413,999
Expiration Date: 9 May 2012 |

Trade Name Crixivan Generic Name indinavir sulfate

Applicant Name Merck & Co., Inc. HFD-530

Approval Date October 19, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES/___/ NO / X /

b) Is it an effectiveness supplement? YES / X / NO / ___ /

If yes, what type(SE1, SE2, etc.)? SE8-043

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

YES / X / NO / ___ /

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

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

This supplemental new drug application provides for additional pediatric safety data in the CLINICAL PHARMACOLOGY and PRECAUTIONS sections of the label

d) Did the applicant request exclusivity?

YES / / NO / /

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / / NO / /

If yes, NDA # 20-685 Drug Name Crixivan

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /___/
 Investigation #2 YES /___/ NO /___/
 Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

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

Investigation #__, Study # _____
 Investigation #__, Study # _____
 Investigation #__, Study # _____

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

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

Investigation #1	!	
IND # _____	!	YES /___/
	!	NO /___/ Explain: _____
	!	_____
	!	_____
Investigation #2	!	
IND # _____	!	YES /___/
	!	NO /___/ Explain: _____
	!	_____
	!	_____

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

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

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

YES / / NO / /

If yes, explain: _____

 151
Signature of Preparer _____
Title: Project Manager

 10/19/00
Date

 151
Signature of Office of Division Director _____

 10/22/00
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**Indinavir Sulfate - Pediatric Use
Item 17- Field Copy Certification**

Pursuant to 21 CFR 314.50(k)(3), a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 4) has been submitted to the FDA Philadelphia District Office (Red Binders). This copy is a true copy of Item 4 as contained in the archival and review copies of this application.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

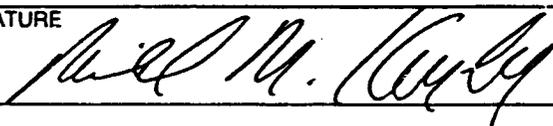
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Tables C-1 and C-2 of	
	"Indinavir Sulfate - Pediatric Use"	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Richard N. Kender	TITLE Vice President, Financial Eval. & Analysis / Business Development
FIRM/ORGANIZATION - Merck & Co., Inc.	
SIGNATURE 	DATE 11/16/99

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Item 19 Financial Disclosure Information

A. Introduction

In compliance with the U.S. Food and Drug Administration's regulation *Financial Disclosure by Clinical Investigators* published February 02, 1998 and revised December 31, 1998, the following sections detail the requested information concerning the financial interests of and compensation to investigators participating in the covered clinical studies presented in this application.

Investigators meeting the definition of Clinical Investigator (Part 54.2 (d)) were requested to complete and return questionnaires related to their financial interest in Merck & Co., Inc. and proprietary interest in the test product. Please note that Merck & Co., Inc. has not entered into any financial arrangement with our clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (21 CFR 54.2(a)). Merck & Co., Inc. Corporate Finance conducted an internal search for all payments that met the definition of "significant payments of other sorts," (21 CFR 54.2 (f)) and reported the information as appropriate.

Data from the following clinical studies are presented in this application:

MK-0639 - A Phase I/II Study of the Protease Inhibitor Indinavir in Children with HIV Infection (National Cancer Institute study) (Protocol 041)

The Last Patient Out (LPO) date for this clinical protocol was July 16, 1998. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of February 02, 1999 through July 16, 1999 and included as appropriate. The cut-off date for financial information provided by the investigators was September 02, 1999.

A Multicenter, Open-Labeled, 24-Week Study to Investigate the Safety, Pharmacokinetics and Efficacy of Indinavir in Combination with Stavudine and Lamivudine in Pediatric Patients with HIV Infection (Protocol 068)

The Last Patient Out (LPO) date for this clinical protocol was February 21, 1999. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of February 02, 1999 through September 02, 1999 and included as appropriate. The cut-off date for financial information provided by the investigators was September 02, 1999. Financial information received from investigators and "significant payments of other sorts" information received between September 02, 1999 and the date of the submission will be provided to the Agency in a subsequent communication.

A Multicenter, Open-Labeled, 48-week Study to Investigate the Safety, PK, and Efficacy of Indinavir in Combination with Stavudine and Lamivudine in Pediatric Patients with HIV-1 Infection (Protocol 106)

The Last Patient Out (LPO) date for this clinical protocol was May 26, 1999. In compliance with the Financial Disclosure requirements, “significant payments of other sorts” information has been reviewed for the time period of February 02, 1999 through September 02, 1999 and included as appropriate. The cut-off date for financial information provided by the investigators was September 02, 1999. Financial information received from investigators and “significant payments of other sorts” information received between September 02, 1999 and the date of the submission will be provided to the Agency in a subsequent communication.

An Open-Label, 3-Period, Crossover Study to Compare the Tolerability and Pharmacokinetics of Single 800 mg Doses of Indinavir Sulfate Salt Capsule Administered Fasted Versus with Applesauce Versus After a Heavy Meal (Protocol 058)

Financial Disclosure information is not provided for this study as it does not meet the definition of a “Covered Study” as defined by the regulation (21 CFR 54.2(a)).

B. Table of All Clinical Investigators/Subinvestigators

Table B-1 provides the names of all identified clinical investigators and subinvestigators listed by protocol and site number; none of the individuals are employees of Merck & Co., Inc. This list includes all subinvestigators listed on the Statement of Investigator Form (FDA 1572).

Table B-1 Table of All Investigators/Subinvestigators for the Crixivan Pediatric, Covered Clinical Trials (Protocols 106, 068, and 041)

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
106-0001		NO
		NO
		NO
		NO
106-0002		NO
		NO
		NO
		NO
106-0003		NO
		NO
		NO
		NO
106-0004		NO
		NO
106-0005		NO
		NO
		NO
106-0006		NO
		NO
		NO
106-0007		NO
		NO
106-0008		NO
		NO
106-0009		NO
		NO
106-0010		NO
		NO

C. Form 3454 – Certification: Financial Interests and Arrangements of Clinical Investigators

Certification for the financial interests of investigator/subinvestigators participating in the covered clinical studies is attached: this information is reflective of the requirements outlined in the Federal Register Volume 63, No. 251, published December 31, 1998.

Table C-1 lists all investigators/subinvestigators who have met the certification criteria regarding an absence of financial arrangements as defined in 21 CFR 54.2.

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
106-0001	
106-0002	
106-0003	
106-0004	
106-0005	
106-0007	
106-0008	
106-0009	

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2 (Cont.)

106-0010			
068-0001			
068-0002			
068-0003			
068-0004			
068-0005			
068-0006			

Group Leader Memorandum

NDA: 20-685/S-043

Drug and Indication: Crixivan™ (indinavir sulfate) for the treatment of HIV-1 infection in combination with other antiretroviral agents

Dose: 500 mg/m² every 8 hours

Applicant: Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

Submission received: December 27, 1999

Date review completed: October 19, 2000

Date of Memorandum: October 19, 2000

The applicant has submitted a supplemental New Drug Application to support a new drug indication, for the use of Crixivan™ (indinavir sulfate), a protease inhibitor, for the treatment of HIV-1 infection in pediatric patients 3 years of age and older. The proposed pediatric information would be included in Clinical Pharmacology, Indication and Usage, Warnings, Precautions (Pediatric Use), Adverse Reactions, and Dosage and Administration Sections of the labeling for Crixivan™. This application also responds to the Phase IV commitment outlined in a March 12, 1996 communication between FDA and Merck Research Laboratories.

In support of this indication, the applicant has submitted the safety and efficacy data from three open-label, 24-week, single arm studies and the results of one trial in healthy adult volunteers. The primary support for this indication and a dosing regimen in children came from principles of bioequivalence and the assumption that pharmacokinetic profiles of indinavir in children were similar to indinavir profiles in adults. Therefore, the established efficacy of indinavir sulfate in adults for the treatment of HIV-1 infection would also apply to the pediatric population. However, 500 mg/m² every 8 hours of indinavir in pediatric patients 3 to 18 years of age produced AUC_{0-8hr}, C_{max}, and trough concentrations that were not comparable to AUC_{0-8hr}, C_{max}, and trough concentrations of indinavir previously observed in HIV-infected adults who received the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and trough levels were considerably lower in pediatric patients. Therefore, the principal support of safety and efficacy of indinavir for the treatment of HIV-1 infection in pediatric patients has to be based on the results of clinical trials in children.

The importance of pharmacokinetic/pharmacodynamic relationship in support of dosing regimens in pediatric patients was recently discussed at an Antiviral Drugs Advisory Committee meeting July 25, 2000. Experts at the meeting concluded that C_{min} was the most *likely determinant of virologic outcome*.

This application was originally intended to support an indication and dosing recommendation for indinavir 500 mg/m² every 8 hours in HIV-infected pediatric patients. Because pharmacokinetic, safety and efficacy data did not support indinavir 500 mg/m² every 8 hours for the treatment of HIV-1 infection in pediatric patients, this application was changed to labeling supplement so available safety information regarding indinavir use in the pediatric patients could be included in the indinavir labeling. I am in agreement with recommendations of the primary reviewer that this application is approvable as a labeling supplement and information provided in this application support limited labeling changes in the Clinical Pharmacology, Warnings, and Precautions (Pediatric Use) sections of the product labeling for Crixivan™. Detailed discussion of indinavir pharmacokinetics, safety and efficacy is provided in the medical review of this supplemental labeling application.

Several aspects of pediatric development program for indinavir and approval of this supplemental labeling application warrant comment at the time of this regulatory action:

1. Limited nature of data in support of the proposed dosing regimen and efficacy

The first conducted trial in children (Merck 041) provided support for the indinavir dosing regimen, 500 mg/m² every 8 hours, used in two subsequent principal trials that provided pharmacokinetic, safety and efficacy data in support of the proposed indication. Merck 041 enrolled 54 HIV-infected children who received indinavir 250 mg/m², 350 mg/m², and 500 mg/m² every 8 hours as monotherapy for the first 16 weeks and thereafter, in combination with zidovudine and lamivudine. Because of the 16-week indinavir monotherapy phase, the data were not considered supportive of efficacy. The pharmacokinetic data obtained from this trial that supported selection of 500 mg/m² every 8 hours of indinavir are presented in the table below.

Pharmacokinetic Results for Indinavir Capsules (Fasted State, Week One)

Geometric Mean	250 mg/m ² N=9	350 mg/m ² N=13	500 mg/m ² N=14	800 mg (adults)
AUC _{0-8hr} (nM·hr)	7,987	15,317	27,965	28,719
C _{max} (nM)	5,787	9,543	14,823	11,948
C _{8hr} (nM)	29	42	100	208

Source: Table 13, 15, Volume 1, December 22, 1999 submission

In order to support the steady state pharmacokinetic relationships of indinavir 500 mg/m² every 8 hours (pediatric dosing regimen) and 800 mg every 8 hours in adults (historical controls), the applicant provided geometric mean ratios and 90% confidence intervals for ratios that included AUC, C_{min} , and trough values.

Ratios of Indinavir Pharmacokinetics in Children on indinavir 500 mg/m² q8h and Adults on 800 mg q8h dose

Pharmacokinetic Parameters	Geometric Mean Ratios (90%CI) Pediatric Patients / Adult Patients
AUC _{0-8hr} (total exposure)	0.97 (0.75, 1.26)
C _{max} (peak)	1.24 (0.99, 1.56)
C _{8hr} (trough)	0.48 (0.28, 0.83)

Source: Table 15, Volume 1, December 22, 1999 submission

As it can be concluded from the data presented in the above tables, trough concentrations in pediatric patients were considerably lower compared to those observed in HIV-infected adults. Therefore, in the absence of adequate efficacy data, the indinavir dose of 500 mg/m² every 8 hours can not be considered to be an established dosing regimen for the treatment of HIV-1 infection in pediatric patients.

The safety, efficacy and pharmacokinetics of indinavir in children were evaluated in two clinical trials; 068 and ACTG395. A total of 41 children, 4 to 15 years of age, were enrolled into these multicenter, single arm, open-label studies and received indinavir 500 mg/m² every 8 hours in combination with stavudine and lamivudine. All patients were protease inhibitor naïve and naïve to at least one nucleoside reverse transcriptase inhibitors. The mean baseline plasma RNA was approximately 4.00 log₁₀ copies /mL and mean CD4 cell count was approximately 600 cells/mm³. Thirty-two of these children completed 24 weeks of treatment. In both of these trials, the proportion of patients with plasma HIV RNA <400 copies/ml at 24 weeks using an intent-to-treat (noncompleter=failure) analysis was used as measure of antiretroviral activity. Based on this efficacy endpoint, 59% of patients (95% CI 44% to 74%) had HIV RNA below quantification of the Amplicor™ assay at week 24 of treatment. The mean increase in CD4 cell counts was 242 cells/mm³ in study 068 and 73 cells/mm³ in ACTG 395. The response rates observed in these two pediatric trials are comparable to the response rates demonstrated in adult clinical trials. However, because of small sample size and no comparator arm, the results of these two trials can not support the efficacy of indinavir for the treatment of HIV-1 infection in pediatric patients.

2. Safety

The safety information in this application was provided for 95 children who received indinavir at three different dosing regimens; 70 of these children received 500 mg/m² every 8 hours. The duration of exposure in these children varied from 18 days to 60 weeks.

During the clinical trials no new and unexpected safety issues were observed in the pediatric patients. The adverse experiences in pediatric patients were similar to that observe in adults except for a higher rate of nephrolithiasis 29%, pyuria 58% (24/41), and hematuria 41% (17/41). Some of these events were associated with a mild increase in serum creatinine and interstitial nephritis.

The frequently reported adverse events were abdominal pain, vomiting, nausea, and hyperbilirubinemia.

3. Labeling

The proposed indinavir dose of 500 mg/m² every 8 hours and the proposed indication for the treatment of HIV-infection in children three years of age and older was not supported by pharmacokinetic, safety and efficacy data submitted in this supplemental application. Although the optimal dosing regimen for use of indinavir in children has not been established, the rates of viral RNA suppression and immunologic responses through 24 weeks of treatment in uncontrolled pediatric trials were reasonable and similar to those observed in adult clinical trials. Therefore, limited information regarding pediatric patients was included in the Clinical Pharmacology, Warnings, and Precautions (Pediatric Use) sections of the labeling for Crixivan.

In conclusion, it was considered important to include pediatric safety information in the Crixivan labeling, especially the higher incidence of nephrolithiasis associated with indinavir treatment and also to provide extremely limited information regarding possible benefit of indinavir treatment in this population.

Stanka Kukich, M.D.
Medical Team Leader, HFD-530

cc: NDA 20-363
HFD-530/HJolson/DBirnkrant/MBaylor

**Medical Officer's Review
Supplemental NDA
20-685 / S-043**

**Date of submission: December 22, 1999
Date received: December 27, 1999
Date assigned: December 29, 1999
Draft MOR completed: October 10, 2000
MOR completed: February 13, 2001**

Applicant: Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

Drug Class: HIV-1 Protease Inhibitor

Drug Name Generic: MK-0639, indinavir sulfate
Trade: Crixivan™

Dosage Form: 100, 200, 333 and 400 mg capsule
— liquid suspension (200 mg/ml)
100, 200, and 400 mg capsule contents as slurry in 2
tablespoons of applesauce

Route of Administration: Oral

Proposed Indication: Treatment of HIV-infected pediatric patients

Proposed Dosage: 500 mg / m² every 8 hours

Related INDs: IND 41,413

Amendments: January 24; March 10, 16, and 31; April 14 and 26; May 3;
August 28, 30, and 31; and September 7, 2000

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I. Resume

Indinavir sulfate, a protease inhibitor, was approved for the treatment of HIV infection in combination with other antiretrovirals on March 13, 1996. Merck Research Laboratories has submitted a supplemental New Drug Application (20-685, S-043) to support the use of indinavir capsules, 500 mg/m² every eight hours, for treatment for HIV-infection in children from 3 to 18 years of age. This proposal is supported by the results of three pediatric clinical trials and one pharmacokinetic study in healthy adult volunteers.

In support of this application, a total of 95 HIV-infected children were enrolled into the three pediatric clinical trials. In Merck 041, a dose-finding study, 54 HIV-infected children were randomized to receive one of three doses of indinavir, 250, 350 or 500 mg/m² every eight hours. In this study, only 29 study subjects received the dose of indinavir proposed for use in HIV-infected children, 500 mg/m² every eight hours. The results of two open-label, single arm, 24-week studies were submitted by the applicant to support the safety and efficacy of indinavir 500 mg/m² every eight hours in pediatric patients. Of these two studies, Merck 068 enrolled 25 HIV-infected children and 20 completed 24 weeks of treatment, while ACTG 395 enrolled 16 children with 12 completing 24 weeks of indinavir. In each of these studies, the primary efficacy endpoint was the proportion of children with undetectable plasma HIV RNA levels at 16 weeks of treatment.

Based on the results of the initial clinical trial, Merck 041, a 48 week, Phase I/II, dose ranging study, indinavir 500 mg/m² every eight hours was further evaluated in two pediatric efficacy studies, Merck 068 and ACTG 395, both of which obtained steady state pharmacokinetic data. The plasma concentrations obtained with the pediatric indinavir dose of 500 mg/m² every eight hours were then compared to those obtained in adult historical controls who received indinavir 800 mg every eight hours. If pharmacokinetic profiles of indinavir in the pediatric population were comparable to indinavir pharmacokinetic profiles in adults, then safety and efficacy data obtained in adult trials could be extrapolated to the pediatric population. One way to compare pharmacokinetic exposure parameters in adults and children is using the ratios of each pharmacokinetic parameter in children to that in adults and the corresponding 90% confidence intervals. When comparing pediatric and adult dosages, it is not expected that each pharmacokinetic parameter in pediatric patients will be identical to that found in adults. However, in all three pediatric clinical studies the indinavir trough values for children were considerably lower than adult values. Lower trough concentrations would be acceptable if data indicate that the lower concentrations are not clinically significant. However, low indinavir troughs in children present a risk for lack of efficacy and the development of resistance; in contrast high indinavir peaks present a risk of increased adverse events such as nephrolithiasis. For these reasons, it was determined that the indinavir dose of 500 mg/m² every eight hours in pediatrics was not comparable to the indinavir adult dose of 800 mg every hours. Because of this, adult data regarding safety and efficacy could not be extrapolated to pediatrics in support of this application. Therefore, the safety and efficacy data of indinavir in children must be supported by adequate and well controlled studies.

The two clinical trials in which indinavir was used in combination with stavudine and lamivudine were multicenter, 24-week, open-label, single arm studies in 41 protease-inhibitor naïve HIV-infected children. The primary efficacy endpoint for both studies was the proportion of children with plasma HIV RNA levels less than 400 copies/ml at 16 weeks. Twenty-five children ages four to 15 years were enrolled in Merck 068 and 56% had undetectable plasma HIV RNA levels at 16 weeks of treatment. Sixteen children ages five to 13 years were enrolled in ACTG 395; 56% had undetectable plasma HIV RNA at 16 weeks of treatment. Both studies were small; only 32 of the 41 children enrolled in the two studies continued past 24 weeks. In addition, both studies were open-label trials without comparator arms. Therefore, it is difficult to state with confidence that this antiretroviral regimen containing indinavir was truly efficacious and would be as efficacious in children as regimens containing previously approved protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

Safety data were provided for the 70 HIV-infected children who received indinavir 500 mg/m² every eight hours. Although the safety profile of indinavir was similar in children to that reported in adults, the incidence of nephrolithiasis was substantially higher in children. Clinical adverse events were common and occurred in 94 of the 95 children participating in these three trials. The most frequently occurring clinical adverse events were related to the gastrointestinal tract and included abdominal pain and vomiting. Laboratory adverse events occurred less commonly and varied by study, but the laboratory adverse events seen most frequently were hematuria, pyuria, and other abnormalities noted on microscopic examination of the urine. In the FDA analyses of the safety data, more than one-half of the children in Merck 068 and ACTG 395 experienced either hematuria or pyuria while 45 of the 54 (83%) children enrolled in Merck 041 had some type of abnormality noted on at least one urinalysis. In addition, 10 children or 24% in Merck 068 and ACTG 395 had nephrolithiasis in the first 24 weeks. When 48 week data for Merck 068 was examined; four additional children developed nephrolithiasis in the second 24 weeks, so a total of 10 children or 40% of children enrolled in Merck 068 had nephrolithiasis during the first year of the study. Because different doses of indinavir were used in Merck 041, comparisons of adverse events can be made according to the indinavir dose received. In Merck 041, subjects who received indinavir at 500 mg/m² every eight hours were more likely to have nephrolithiasis than those who received indinavir 350 mg/m² with a relative risk of 4.07. In addition, two cases of interstitial nephritis, one case of hydronephrosis, and 5 abnormal ultrasound renal ultrasounds were noted in these studies. Although the types of adverse events were the same as those seen in adults, the incidence of these adverse events was much higher in HIV-infected children, particularly at the 500 mg/m² every eight hour dose, therefore, this dose of indinavir is not safe for use in pediatric patients.

This application proposed the use of indinavir capsules in combination with stavudine and lamivudine for the treatment of HIV infection in children three years of age and older, however, HIV-infected children three years of age and older already have several approved treatment options available. Other protease inhibitors such as ritonavir, nelfinavir, and amprenavir have been approved as oral solutions for use in HIV-infected

children. In addition, efavirenz is also approved for use in children three years and older. Therefore, HIV-infected children have several treatment options including antiretroviral agents that have oral formulations, and the approval of indinavir capsules would not fill an unmet medical need.

Although the proposed dose of indinavir, 500 mg/m² every eight hours, has been recommended at conferences and meetings as an appropriate dose for HIV infected children, the results of the pediatric studies submitted in this application have not been published in the scientific literature. Because the results of these studies did not provide confidence that indinavir at 500 mg/m² every eight hours is safe and effective for the treatment of HIV infection in children, the Division has recommended that the pharmacokinetic and safety results of these pediatric studies be included in the package insert to provide valuable information to clinicians about the use of the proposed dose of indinavir in HIV-infected children with few treatment options and that warnings that a safe and efficacious dose for children has not been established also be included. In order to accomplish this, the application was changed from an efficacy supplement to a labeling supplement. This decision was made at a Global Assessment Meeting with the consent of the Division director. In conclusion, this application does not support either the safety or efficacy of indinavir 500 mg/m² every eight hours in pediatric patients three years of age and older. Additional studies are needed in order to determine a dose of indinavir that is both safe and efficacious in HIV-infected children.

II. Regulatory Background

The initial IND for indinavir sulfate was submitted January 5, 1993. Phase I studies began in adults in April, 1993. The New Drug Application for Crixivan® was submitted under Accelerated Approval Regulations on January 31, 1996. Crixivan was approved for the treatment of HIV-infection in adults in March 1996. According to the applicant, more than — HIV-infected adults have been treated with Crixivan.

The original studies of indinavir in HIV-infected children began in June 1995. Phase III studies were initiated in January 1998. A summary of the applicant's pediatric development of indinavir was submitted on March 11, 1999. On December 22, 1999 the supplement NDA (20-685 S-043) for the treatment of HIV-1 infection in pediatric patients was submitted. Additional submissions regarding the supplemental NDA were submitted to the FDA on January 24, March 10, 16, and 31, April 14 and 26, May 3, August 28, 30, and 31, and September 7, 2000.

III. Pediatric Clinical Studies

A. Introduction

This supplemental NDA was submitted electronically on one CD containing 600 megabytes. In addition, paper copies consisting of one summary volume and eight volumes of clinical data were also submitted for review. All data were reviewed.

Additional safety and efficacy data were received as amendments to the NDA and reviewed.

Table 1: Pediatric Studies of Indinavir

	Merck 041	Merck 068	ACTG 395
No. of children starting study	54	25	16
No. of children reaching 24 weeks	49	20	12
Age (years)	3 – 18	4 – 15	5 - 13
Median baseline CD4 count (cells/mm ³)	153	559	808
Median Baseline RNA level (copies/ml)	50,426	8,295	6,235
Dose (mg/m ² q 8 hrs)	250, 350, and 500	500	500
Formulation	Liquid and capsule	Capsule	Capsule
Other antiretrovirals used	ZDV, 3TC	D4T, 3TC	D4T, 3TC

Source: Volume 1, December 22, 1999 submission

As shown in Table 1, three pediatric studies of indinavir were included in this submission. Merck 041 was a Phase I/II, dose-finding study of the safety and pharmacokinetics of indinavir in HIV-infected children, which was also designed to provide preliminary information about efficacy. Pharmacokinetic data from different dosages of several liquid preparations and of the indinavir sulfate capsule were collected as well as clinical and laboratory safety data and efficacy data (plasma viral RNA levels, absolute CD4 counts and CD4 percentages). Fifty-four children from 3 to 18 years of age were enrolled; 51 children completed an initial 16-week monotherapy phase and 42 completed an additional 32 weeks of combination therapy with indinavir, zidovudine, and lamivudine.

Merck 068, a Phase III study was initiated after the completion of Merck 041. Merck 068 enrolled 25 HIV-infected children from 4 to 15 years of age who received indinavir capsules at 500 mg/m² every eight hours in combination with stavudine and lamivudine. Pharmacokinetic data were obtained on day 15. Safety and efficacy data were provided for all children, however, only 20 children completed the 24-week study. Another pediatric Phase III trial, ACTG 395, was started due to slow enrollment in Merck 068. The study designs for Merck 068 and ACTG 395 were identical except for an additional day of pharmacokinetic sampling in ACTG 395. In ACTG 395, pharmacokinetic data were obtained after dosing with the indinavir capsule on day 15 and again after dosing with indinavir mixed in applesauce on day 16. Sixteen week safety and efficacy data were provided for the 16 children enrolled in ACTG 395; 12 of the 16 subjects completed

the entire 16 weeks. Additional safety and efficacy data to 24 weeks were provided in the Safety Update Report.

The results of one additional clinical trial, Merck 058, were included in this supplemental NDA. Merck 058 examined the pharmacokinetic profile of a slurry preparation of indinavir in 12 healthy adult volunteers. The slurry studied in Merck 058 was produced by mixing the contents of two indinavir capsules with two teaspoons of applesauce. Pharmacokinetic parameters of this formulation were compared to those of the capsule formulation in the same study subjects. The 12 study subjects were also asked to rate the taste of the slurry preparation. The applicant has proposed that pharmacokinetic data obtained with the slurry be included in the Crixivan package circular as an alternative formulation which would be suitable for patient unable to swallow capsules.

B. Merck 041

The first clinical trial which studied the use of indinavir in HIV-infected pediatric patients, Merck 041, "A phase I/II study of the protease inhibitor indinavir (MK-0639) in children with HIV infection," was begun July 1995 and enrolled 54 subjects.

1. Study Design

This trial was designed as a single center, open-label, dose escalation, 48-week study of the pharmacokinetics and safety of an indinavir liquid suspension as monotherapy for the first 12 weeks followed by its use in combination with zidovudine and lamivudine. The study was also designed to provide preliminary information about the antiviral activity and clinical efficacy of indinavir used as monotherapy and in combination with zidovudine and lamivudine in HIV-infected children. In Merck 041 children were entered in one of two cohorts: 6 months to 12 years of age and 13 to 18 years of age; these two cohorts proceeded with dose escalation separately. The first children in both cohorts were initially treated with 250 mg/m² every eight hours, the second with 350 mg/m², and the third with 500 mg/m². Indinavir plasma concentrations were obtained on day one and on day two. For children 6 months to 12 years of age, concentrations of indinavir liquid were compared fasted and nonfasted on days one and two; for children over 12 years of age, plasma concentrations of the capsule and liquid formulations of indinavir were compared. All subjects were then to complete the study using the liquid formulation. However, early pharmacokinetic data showed very low plasma concentrations of indinavir with the liquid preparation, and the protocol was amended several times in order to test variations in indinavir formulations so that plasma concentrations would more closely resemble those seen in adult patients.

After several amendments, the monotherapy phase was extended to from 12 to 16 weeks, and all patients who could swallow capsules and were not already receiving capsules were changed to capsules at 12 weeks.

One of the main intents of this study was to determine the optimal dose of indinavir for HIV-infected pediatric patients, and that objective was evaluated using pharmacokinetic measurements obtained as described above. Another of the primary objectives was to obtain preliminary information about the activity of indinavir when used both as monotherapy and in combination with zidovudine and lamivudine in children. Efficacy was determined by clinical response (change in weight and neurocognitive function), change in CD4 count, and change in HIV RNA levels at the end of the 16-week monotherapy phase. Safety data were collected as a tabulation of reported adverse events. Eligible patients were HIV-infected children from 6 months to 18 years of age without any current opportunistic infections. If the child was previously untreated, the percentage of CD4 cells had to be from 15 to 24% or the subject had to have moderate to severe clinical disease. A child with previous antiretroviral treatment must have failed that treatment due to toxicity or due to progression of disease as defined by the protocol. Patients who had previously received protease inhibitors were not excluded from the study but were evaluated separately. Children with hematuria, a family history of kidney stones, or with a serum creatinine greater than two times the upper limit of normal were excluded. Study subjects were evaluated at screening, daily for the first seven days of treatment, on day 14, every 2 weeks until week 16, and then every 4 weeks until week 48. Pharmacokinetic measurements were collected on days one and two and at weeks 2, 12, and 24. Study subjects were instructed to take indinavir as a liquid formulation (200mg/ml) while fasting with the exception of drinking four ounces of water after each dose. This study was initiated in June 1995 and the last patient was enrolled in August 1996; a small number of patients have continued in this study and are currently being followed prospectively.

The study report for Merck 041 was divided into three sections by the applicant: the monotherapy phase from screening to week 16, the combination phase from weeks 17 to 48, and the study extension phase from 48 to 96 weeks. However, when possible Merck 041 will be described as a single study in this review.

2. Study Population

A total of 54 HIV-infected children from three to 18 years of age were enrolled at a single study site and were included in the pharmacokinetic, safety, and efficacy analyses. The median age was 9.0 years. Study subjects were divided into two separate cohorts for dose escalation; 33 patients were included in the cohort of patients 12 years of age or younger, and 21 patients were in the cohort of patients 13 to 18 years of age. The majority of patients were male (67%) and White (63%). Thirty-five subjects or 65% had acquired HIV perinatally while 35% had acquired HIV from the transfusion of blood or blood products. At entry the median plasma viral RNA level was 50,426 copies/ml, the median absolute CD4 count was 153 cells/mm³, and the median CD4 percentage was 16%. Nineteen subjects (35%) had experienced an AIDS defining illness before study entry. Fifty-one of the 54 study subjects had received prior antiretroviral therapy. Although the majority of patients had previously received only nucleoside reverse transcriptase inhibitors, six subjects had received an experimental protease

inhibitor. One patient (AN0720) continued to receive _____ for the first 16 weeks of her participation in Merck 041.

3. Patient Accounting

A total of 54 HIV-infected children were enrolled in this study. Study subjects were enrolled at different dose levels and received different formulations of indinavir as shown in Table 2.

Table 2: Number of Study Subjects Receiving Each Dose and Formulation of Indinavir in Merck 041

Dose of Indinavir	Number of Patients	
	Suspension	Capsules
250 mg/m ² q8h	8	8
350 mg/m ² q8h	13	11
500 mg/m ² q8h	----	14

Source: Table 6, Volume 1, December 22, 1999 submission

There were five protocol violators. Study participants were instructed to stop all antiretroviral therapy for 14 days prior to beginning indinavir; all five of the protocol violators continued their previous antiretroviral therapy past this point including the subject mentioned previously who continued to take _____ an experimental protease inhibitor for the first 16 weeks of the study. The six subjects with previous protease inhibitor treatment were evaluated separately. All 54 subjects were included in the safety analysis. Ten patients did not have pharmacokinetic measurements obtained on days one, two or 14. In addition to these 10 patients, another seven study subjects had sharp increases in indinavir plasma concentrations at the end of the sampling period. This most likely represented repeated dosing with indinavir, so the indinavir trough for these patients was not included in the pharmacokinetic analyses. Five study subjects withdrew from the study during weeks 16 to 48; another three withdrew after 48 weeks. Five subjects were removed from the study after week 16 for "other" reasons including disease progression, neuropathic pain of unknown origin, and lymphoma.

4. Pharmacokinetic Analysis

Please see Dr. Kumi's review.

In the first 16 weeks of Merck 041, all 54 study subjects received indinavir as monotherapy. During this time, pharmacokinetic data for several different doses and formulations of indinavir were collected. The study investigators originally planned to treat subjects with an _____ in a dose escalating schema so that the first subjects enrolled received 250 mg/m² every eight hours, the next cohort received 350 mg/m² and the third 500 mg/m². However, early pharmacokinetic measurements comparing the solution and capsule showed such low plasma indinavir concentrations with the solution that the study protocol was modified, and a number of attempts were made to overcome the poor bioavailability noted with the suspension

including _____

_____ However, pharmacokinetic sampling revealed that plasma concentrations obtained after administration of all of the liquid formulations except for the _____ resulted in plasma concentrations that were substantially lower than those seen with the capsule. The _____ provided plasma concentrations that were roughly comparable to the capsule; the ratio of the geometric mean AUC_{0-8hr} of the _____ to the capsule was 88%. However, because of the large volume required at each dosing and the unacceptable palatability, the applicant decided not to investigate the _____ any further.

The plasma concentrations of the indinavir sulfate salt capsule at each dose level are shown in Table 3.

Table 3: Pharmacokinetic Results for Indinavir Capsules in Merck 041 (Fasted State, Week One)

Geometric Mean	250 mg/m ²	350 mg/m ²	500 mg/m ²	800 mg (adults)
AUC_{0-8hr} (nM·hr)	7,987	15,317	27,965	28,719
C_{max} (nM)	5,787	9,543	14,823	11,948
C_{8hr} (nM)	29	42	100	208

Source: Table 13, 15, Volume 1, December 22, 1999 submission

The plasma concentrations obtained after the indinavir 500 mg/m² every eight hour dose most closely resembled those seen in adult historical controls, but the peak indinavir concentration was higher in children receiving 500 mg/m² every eight hours and the trough concentration in children was only about one-half that seen in adults. In order to determine the comparability of the 500 mg/m² every 8 hours dose with the adult dose of 800 mg three times daily, individual pharmacokinetic data between the two were compared by the applicant. The results are shown in Table 4:

Table 4: Comparison of Indinavir Pharmacokinetics in Children Receiving 500 mg/m² q8h in Merck 041 and Adults Receiving 800 mg q8h as Capsules

Pharmacokinetic Parameters	Geometric Mean Ratios (90% CI) Pediatric Patients / Adult Patients
AUC_{0-8hr} (total exposure)	0.97 (0.75, 1.26)
C_{max} (peak)	1.24 (0.99, 1.56)
C_{8hr} (trough)	0.48 (0.28, 0.83)

Source: Table 15, Volume 1, December 22, 1999 submission

The applicant compared the plasma indinavir measurements obtained in pediatric patients to those in adult historical controls by calculating the ratio of each pharmacokinetic parameter in children to that parameter in adults with the corresponding 90% confidence interval. By the applicant's definition, indinavir concentrations were comparable if the 90% confidence interval of the ratios were between 0.5 and 2.0. When the pharmacokinetic data obtained from the two populations were compared, the AUC and peak concentration of the 500 mg/m² dose were comparable to those of the adult dose by the definition of comparability used by the applicant comparable (i.e. the 90% confidence

intervals were between 0.5 and 2.0). However, the trough concentration obtained in children was outside of the range for comparability and was substantially lower than the value noted in previous studies with adults.

Twenty-nine study subjects in Merck 041 also had pharmacokinetic assessments made during week 28 while receiving indinavir as a capsule in combination with zidovudine and lamivudine. Eight of these subjects were excluded from the analyses of the trough concentrations because of increased indinavir plasma concentrations at the end of the dosing interval which suggested repeat dosing with indinavir before the trough concentration was measured. The plasma concentrations obtained at week 28 during combination therapy were similar to the measurements obtained for the same subjects at week 16 during indinavir monotherapy. However, only one patient receiving 500 mg/m² every 8 hours had pharmacokinetic data collected at weeks 16 and 28, so no summary statistics for subjects receiving this dose were available. Plasma concentrations obtained during combination therapy with indinavir 250 mg/m² and 350 mg/m² every eight hours were not comparable to adult historical controls.

In summary, all of the indinavir liquid formulations studied in Merck 041 were found to have unacceptably low plasma concentrations except for the _____, but because of the _____ unacceptable taste and the large volume required, this preparation was not studied further. When three different dose levels of indinavir capsules were compared, pharmacokinetic measurements obtained after the 500 mg/m² capsule every eight hour dose most closely resembled those obtained with the adult dose of 800 mg every eight hours; however, in the applicant's analysis the indinavir trough obtained in children was lower than that obtained in adults and was not comparable to the trough obtained in adult historical controls. Finally, the AUC and peak indinavir concentrations were similar whether indinavir was used as monotherapy or in combination with zidovudine and lamivudine; but data were not available to compare indinavir 500 mg/m² every 8 hours as monotherapy with its use in combination with zidovudine and lamivudine.

5. Efficacy Analyses of Surrogate Endpoints

Monotherapy Phase (Weeks 1 - 16)

The study protocol for Merck 041 was written before the association of antiretroviral monotherapy with the rapid development of resistance was appreciated. Therefore, all study subjects received 16 weeks of indinavir monotherapy before zidovudine and lamivudine were added. In addition, study subjects received three different doses of indinavir during the monotherapy phase of this study, and as discussed above the plasma concentrations of the 250 mg/m² and 350 mg/m² were lower than those seen in adult controls. The use of indinavir monotherapy and of indinavir doses with low plasma concentrations may have contributed to a decrease in efficacy. As a result, the efficacy data obtained in Merck 041 was of limited usefulness in the determination of the antiretroviral activity of indinavir used in combination therapy, but for completeness, the efficacy results from Merck 041 will be discussed briefly.

After 16 weeks of indinavir monotherapy, no study subjects had plasma viral RNA levels that were below the limit of quantification (<400 copies/ml by AMPLICOR assay). The median decrease in plasma HIV RNA is shown in Table 5.

Table 5: Median Decrease in Plasma Viral RNA in Merck 041 (Observed Data)

Dose	Week 2	Week 16
250 mg/m ² q8h Suspension	-0.91	-0.21
350 mg/m ² q8h Suspension	-0.32	-0.07
250 mg/m ² q8h Capsule	-0.66	-0.07
350 mg/m ² q8h Capsule	-0.74	-0.07
500 mg/m ² q8h Capsule	-1.29	-0.48

Source: Table 7, Volume 1, December 22, 1999 submission

Monotherapy with indinavir resulted in an early decrease in plasma HIV RNA levels, however, this decrease was not sustained over the entire 16 week monotherapy phase. The greatest decrease in viral RNA levels was seen in the group of children receiving 500 mg/m² every 8 hours.

An increase in absolute CD4 count was also noted at weeks 2 and 16 for each treatment group. For the children receiving indinavir 500 mg/m² every eight hours, the median increase in the CD4 count at 2 weeks was 86 cells/mm³ and the median increase at week 16 was 75 cells/mm³. The percentage of CD4 cells also increased in all groups over the 16-week monotherapy phase; at week 16, there was an increase of 3% in the group of children receiving 500 mg/m². The increases in both absolute CD4 count and CD4 percentage were not dose dependent and the greatest increases were noted in the children receiving 250 mg/m² suspension every eight hours.

Data concerning changes in body weight were also collected as a means of judging the clinical efficacy of indinavir in HIV-infected children. There was a median increase in body weight for all treatment groups at 16 weeks that ranged from 0.5 kilograms in the 350 mg/m² suspension group to 2.1 kilograms in the 250 mg/m² suspension group.

Combination Phase (Weeks 17 - 48)

After 16 weeks of indinavir alone, zidovudine and lamivudine were added to the antiretroviral regimen. Three study subjects were removed from the study during the first 16 weeks, so 51 children received indinavir as part of combination antiretroviral therapy. The study subjects who received 250 mg/m² or 350 mg/m² of the indinavir suspension and the subjects who received 250 mg/m² of the indinavir capsule during the first 16 weeks received the indinavir capsule at a dose of 250 mg/m² every eight hours during weeks 17 to 48. Therefore, subjects were in one of three treatment groups during weeks 17 to 48; 250 mg/m² (26 subjects), 350 mg/m² (11 subjects), or 500 mg/m² every eight hours (14 subjects). Efficacy results after 48 weeks for these three treatment groups are shown below in Table 6.

Table 6: Effect of Indinavir in Combination with Zidovudine and Lamivudine on HIV RNA Levels at Week 48 in Merck 041

Dose Level	No. of Patients	No. of Patients with HIV RNA <400	Median Decrease in HIV RNA (log ₁₀)
250 mg/m ²	26	2	-0.3
350 mg/m ²	11	1	-0.2
500 mg/m ²	14	2	-1.0

Source: Tables 23, 24, Volume 3, December 22, 1999 submission

As seen in Table 6, five subjects or 9% of subjects enrolled in Merck 041 had undetectable plasma viral levels at 48 weeks. In addition, one-half of the subjects receiving indinavir 500 mg/m² every eight hours had at least a one-log drop in HIV RNA level after 48 weeks; a smaller proportion of subjects receiving lower doses of indinavir had a one log decrease in viral RNA levels.

Increases in the absolute CD4 count were noted for all three treatment groups. When screening CD4 counts on entry to Merck 041 were compared to CD4 counts at week 48, there was an increase of 151.5 cells/mm³ for the 250 mg/m² group, of 44.5 cells/mm³ for the 350 mg/m² group, and of 241.5 cells/mm³ for the 500 mg/m² group. As would be expected, increases in the percentage of CD4 cells were also noted in each treatment group. When compared to values obtained at screening, a median increase in the CD4 percentage of 9.5% was noted at 48 weeks in the group of subjects receiving 250 mg/m² of indinavir, an increase of 5.0% was noted in the 350 mg/m² group, and an increase of 10.5% was noted in the 500 mg/m² group. Although the increases noted in each treatment group were not dose dependent, the largest increases were seen in the group of children receiving 500 mg/m² every eight hours.

When changes in body weight were examined as a surrogate for clinical efficacy, there were increases in weight for each treatment group. When the weight at study entry was compared to the weight at week 48, the median increase was 3.0 kilograms for the 250 mg/m² group, 4.8 kilograms for the 350 mg/m² group, and 2.9 kilograms for the 500 mg/m² group.

Study Extension Phase (Weeks 49 – 96)

Forty-two study subjects continued into the study extension phase; 27 received indinavir 350 mg/m² every eight hours in combination with zidovudine and lamivudine and 15 received zidovudine, lamivudine, and indinavir 500 mg/m² every eight hours. Only safety results were reported in the study summary, but surrogate marker data was provided in datasets and revealed that two subjects (AN738 and AN740) had HIV RNA levels less than 400 copies/ml at 96 weeks. Although another three subjects had viral levels less than 400 copies/ml at 96 weeks; none of the three had two consecutive viral levels less than 400 copies/ml which are necessary to meet the FDA criteria for having undetectable plasma HIV RNA.

Since study subjects received an initial 16 weeks of indinavir monotherapy, it was difficult to evaluate the efficacy of indinavir in HIV-infected children. The efficacy evaluation was further complicated by the three indinavir doses and the different formulations used. Although only a small number of children (9%) had HIV RNA levels that were undetectable after 48 weeks of therapy, there was a slight decrease noted in viral RNA levels noted at both 16 and 48 weeks. In addition, there were increases in the absolute CD4 counts and in the percentage of CD4 cells at all dose levels at the end of the monotherapy phase and after 32 weeks of combination therapy.

6. Evaluation of Safety

Clinical Adverse Events

All 54 patients experienced at least one clinical adverse event during the first 16 weeks of the study. Fifty-two of the 54 had adverse events that were judged to be drug-related by the investigator. The more common clinical adverse events included abdominal pain, diarrhea, vomiting, headache, upper respiratory tract symptoms, rash, and dysuria. The clinical adverse events that were seen most often in the subjects receiving the highest indinavir dose (500 mg/m²) were vomiting, reflex abnormality, and dysuria. Eight subjects experienced adverse events which were described as serious; most of the serious adverse events were related to infectious processes and only one subject had a serious clinical adverse event related to indinavir (flank pain and dysuria). Although there was no statistically significant difference in the proportion of subjects with serious clinical adverse event between treatment groups, there were four serious clinical adverse events in the 500 mg/m² capsule group, two in the 350 mg/m² capsule group, and one or fewer in all other treatment groups. Only one subject was removed from the study due to a clinical adverse event (progressive encephalopathy). Clinical adverse events related to the urogenital system were more common in the group of children receiving indinavir 500 mg/m² every eight hours. Seven children (50%) in this group had urogenital clinical adverse events as compared to three (27%) children in the 350 mg/m² capsule group and 2 (25%) in the group receiving indinavir 250 mg/m² as capsules. One patient who was receiving indinavir 500 mg/m² every eight hours had urolithiasis during the first 16 weeks.

Of the 51 study subjects who entered the combination phase of Merck 041 (weeks 17 to 48), 50 experienced at least one clinical adverse event during this phase and 41 had clinical adverse events which were described as drug related. The most common clinical adverse events during the combination phase included fatigue, abdominal pain, anorexia, hepatomegaly, vomiting, and diarrhea. Ten subjects experienced serious clinical adverse events during this time period; three (11.5%) patients in the 250 mg/m² group, two (18%) in the 350 mg/m² group, and five (36%) in the 500 mg/m² group. Four of the serious clinical adverse events were judged by the investigator as drug related; these included abdominal pain, flank pain in two subjects, and hematuria. Three subjects were removed from the study during the combination therapy phase; one subject receiving 250 mg/m² was taken off study because of visual loss and two subjects who were receiving 500 mg/m² because of clinical symptoms consistent with nephrolithiasis (abdominal pain,

flank pain, and hematuria). Overall, 12 subjects had clinical adverse events related to the urogenital tract; three in the 250 mg/m² group, four in the 350 mg/m² group, and five in the 500 mg/m² group. Adverse events related to the urinary tract that were noted in the 500 mg/m² group included dysuria (three subjects), hematuria, renal insufficiency, and an echogenic foci in the kidney on ultrasonography. In the 350 mg/m² group, two subjects had dysuria, two had urinary tract infections, one had hydronephrosis related to an episode of nephrolithiasis, and one had pyelonephritis. One patient in the 250 mg/m² group had polyuria. Overall, six subjects (12%) had clinical adverse events related to an episode of nephrolithiasis; adverse events related to the urinary tract including nephrolithiasis were more common in the 500 mg/m² group than in the 250 mg/m² group at a statistically significant rate.

All of the 42 subjects who participated in the study extension (weeks 49 to 96) experienced at least one clinical adverse event. Seven patients had clinical adverse events which were described as serious, and 19 had clinical adverse events which were described as drug related; however, none of the serious clinical adverse events were judged to be drug related. Overall, the most common clinical adverse events in this phase of the study were similar to those noted in the two other phases of Merck 041 and included fever, headache, nausea, vomiting, and abdominal pain. Serious clinical adverse events seen during this phase included suicide attempt, fever, lymphoma, retinal detachment, and bone pain. The subject who attempted suicide was the only subject who was discontinued from the study because of a clinical adverse event during this phase of Merck 041. The most common drug related clinical adverse events were nausea, vomiting, and abdominal pain. In addition, clinical adverse events related to the urinary tract included one subject with dysuria, one with urolithiasis, and two with echogenic foci noted on renal ultrasonography.

In summary, all subjects in Merck 041 experienced clinical adverse events during the study. There were no deaths in any phase of this study. Certain drug related clinical adverse events such as nausea, vomiting, and abdominal pain were common in all three phases. Urological adverse events were also seen frequently and included urolithiasis, dysuria, hematuria, and renal structural abnormalities (echogenic foci and hydronephrosis) noted on ultrasonography. Clinical adverse events related to the urologic tract were more common in children receiving indinavir 500 mg/m² every eight hours, however, this finding did not achieve statistical significance. Nephrolithiasis will be discussed in a later section of this review.

Laboratory Adverse Events

Of the 54 children enrolled in Merck 041, 14 (26%) had at least one laboratory adverse event during the first 16 weeks of the study. The most common laboratory adverse events were neutropenia and hematuria. Eight subjects experienced laboratory adverse events which were described as drug related including neutropenia, increased hepatic transaminases, and abnormalities in urinalyses. The abnormalities seen on microscopic examination of urine were more common in the group of children receiving 500 mg/m², occurring in 36%, and included crystalluria, hemoglobinuria, hematuria, pyuria, and urine

occult blood. Serious laboratory adverse events were noted in two patients and both were considered to be drug related; one patient developed hematuria and hemoglobinuria and the other hematuria and crystalluria. Two study subjects discontinued the study because of laboratory adverse events; one with neutropenia and one with increased hepatic transaminases. There was no statistically significant difference in the incidence of laboratory adverse events between the treatment groups.

During the Merck 041 combination phase (weeks 17 to 48), 18 of the 51 (35%) subjects who participated in this phase experienced a laboratory adverse event. The most common adverse event was pyuria, which was noted in 6 of the 14 (43%) children in the 500 mg/m² group. Eleven children experienced laboratory adverse events that were described as drug related and these were more common in the children receiving 500 mg/m² than in the other two groups. The most frequently seen drug-related laboratory adverse events were abnormalities in urinalyses and included pyuria, hematuria, and urine occult blood. Pyuria was documented in six of the children receiving indinavir 500 mg/m² but in no children in the other two groups. Pyuria was associated with nephrolithiasis in one occasion but the etiology of the pyuria was not determined in most cases. Serious laboratory adverse events were reported in three study subjects and included hematuria (two subjects), crystalluria, and pyuria. The one serious adverse event involving pyuria was not described as drug related but the other two serious laboratory adverse events were. No subjects were removed from the study because of laboratory adverse events during this phase of the study.

Eighteen of the 41 study subjects (44%) who entered the extension phase of Merck 041 (weeks 49 to 96) experienced at least one laboratory adverse event. The only laboratory adverse events to occur in more than one subject were those noted on urinalysis. Hematuria was seen in seven subjects, crystalluria in four, hemoglobinuria in three, pyuria in three, and increased leukocyte esterase in two. All of these abnormalities were described as drug related. During this phase, the Merck 041 investigators a cluster of patients with hematuria after increasing the indinavir dose to 500 mg/m²; therefore, 350 mg/m² every 8 hours was determined to be the maximum tolerated dose. Serious laboratory adverse events were reported in two patients (anemia and neutropenia). The subject with anemia was the only subject to discontinue the study due to a laboratory adverse event during this phase.

In summary, laboratory adverse events were noted frequently in all three phases of Merck 041 and most commonly involved the urinary tract. Pyuria of unknown etiology and hematuria were especially common and were usually described as related to indinavir use. The abnormalities seen in the urinalyses were most often seen in children receiving the highest dose of indinavir (500 mg/m² every eight hours). The increased incidence of hematuria in subjects receiving 500 mg/m² of indinavir lead the investigators to determine that 350 mg/m² every 8 hours was the maximum tolerated dose of indinavir in children. Although an increased incidence of hyperbilirubinemia has been noted in adults receiving indinavir, only four children in Merck 041 developed hyperbilirubinemia that was categorized as a laboratory adverse event.

Nephrolithiasis

An adverse event associated with nephrolithiasis was defined as any episode felt by the investigator to represent nephrolithiasis clinically including but not limited to unexplained flank pain with or without hematuria. During the monotherapy phase, five children were diagnosed with nephrolithiasis, six experienced nephrolithiasis during the combination phase, and five during the extension phase. There appeared to be no relationship between nephrolithiasis and age or gender; subjects with nephrolithiasis ranged from 3 to 18 years of age and episodes of nephrolithiasis were divided equally between males and females. The most common signs and symptoms of nephrolithiasis were hematuria, abdominal pain, and flank pain; but urolithiasis, hydronephrosis, and renal echogenic foci were also reported. Onset of symptoms occurred at any time during indinavir treatment from day 9 to day 623, and symptoms lasted from one to 51 days. Although two subjects had transient increases in serum creatinine, no subject had permanent renal dysfunction following an episode of nephrolithiasis. Two subjects were removed from the study because of nephrolithiasis.

Nephrolithiasis did appear to occur more commonly in children receiving indinavir 500 mg/m² every eight hours. During the first 48 weeks of the study, there were eight episodes in subjects receiving 500 mg/m² and 3 in subjects receiving 350 mg/m² as capsules but none in any other treatment groups. The difference in incidence between treatment groups was statistically significant. The applicant also used Kaplan-Meier analyses to determine if the time to the first nephrolithiasis event varied between the 350 mg/m² and 500 mg/m² groups. Although nephrolithiasis did occur earlier in the 500 mg/m² group, it was not statistically significant. Finally, the incidence of nephrolithiasis by the time of exposure was calculated, and during the first 96 weeks, there were 2.2 episodes of nephrolithiasis per 10 patient-years in the 350 mg/m² group and 9.0 episodes per 10 patient-years for the 500 mg/m² group (relative risk = 4.07).

In summary, Merck 041 was a Phase I/II study of indinavir in 54 HIV-infected children from three to 18 years of age. One of the study's main objectives was to determine the optimal dose of indinavir in children. Initially, pharmacokinetic parameters were measured after several different liquid formulations, but no liquid formulation that was suitable for use in children was found. Ultimately, it was concluded that plasma indinavir concentrations after 500 mg/m² as capsules every eight hours most closely resembled those seen in adult historical controls. However, 350 mg/m² every eight hours was determined to be the maximum tolerated dose because of the increased incidence of hematuria noted at 500 mg/m². It was difficult to determine the efficacy of indinavir in children from the Merck 041 results because of an initial 16-week monotherapy phase and because of the different doses used. However, the use of indinavir as monotherapy and in combination with zidovudine and lamivudine did result in small decreases in HIV RNA levels and small increases in the absolute CD4 count. Safety data provided for the first 96 weeks of this study showed that all children had clinical adverse events while on indinavir with gastrointestinal symptoms such as anorexia, nausea, abdominal pain, and vomiting predominating. Laboratory adverse events were less common. Abnormalities on urinalysis such as sterile pyuria and hematuria were the most frequently seen

laboratory adverse event, and their incidence was more common in children on the highest dose of indinavir (500 mg/m² every eight hours). Finally, 16 episodes of nephrolithiasis occurred in children enrolled in Merck 041. These episodes were not generally associated with a decrease in renal function, and the subjects usually continued to receive indinavir at a reduced dose. As with laboratory adverse events involving the urologic tract, nephrolithiasis was most common in children receiving 500 mg/m² every eight hours. Overall, the results of Merck 041 raised questions about whether 500 mg/m² or 350 mg/m² every eight hours of indinavir was the correct dose in pediatric patients and raised significant concerns about the renal toxicity associated with the use of the 500 mg/m² dose in HIV-infected children.

C. FDA Analysis of Merck 041

1. FDA Pharmacokinetic Analysis

Please see Dr. Kumi's review.

Merck 041 was originally designed to study a liquid formulation of indinavir; however, the plasma concentrations were unacceptably low with every liquid tested except the _____ which was felt to have an unacceptable taste and require too large of a volume. Pharmacokinetic measurements after three separate doses (250 mg/m², 350 mg/m² and 500 mg/m² every eight hours) of indinavir sulfate salt capsules were also studied and compared to adult historical controls. The plasma concentrations after the 500 mg/m² dose most closely resembled those of the adult dose, 800 mg every eight hours, and by the applicant's analysis, the AUC and peak concentration of the 500 mg/m² dose were found to be comparable to those seen with the adult dose. After an assessment of comparability between these two populations based on the examination of geometric means (90 % confidence intervals) for the exposure measures C_{max} and C_{min} it was determined that indinavir 500 mg/m² every 8 hours in children was not comparable to indinavir 800 mg three times daily in adults. Because of this, safety or efficacy data cannot be extrapolated from adult studies to the pediatric population and results from pediatric studies alone have to support the use of this dose in HIV-infected children.

As just discussed the investigators in Merck 041 determined that 500 mg/m² was the dose that resulted in plasma indinavir concentrations most closely resembling those seen in adults so a protocol amendment was written to change all children on the study to the 500 mg/m² dose. However, after many of the children had their dose increased to 500 mg/m² every eight hours, an increase in the incidence of hematuria was noted. As a result the investigators determined that 350 mg/m² every eight hours was the maximum tolerated dose of indinavir in HIV-infected children. In conclusion, although investigators determined that indinavir 500 mg/m² every eight hours was the dose of indinavir producing plasma concentrations most closely resembling those of adult historical controls, the 500 mg/m² dose was not comparable to the adult 800 mg dose using FDA standards. In addition, the study investigators ultimately determined that 500 mg/m² every eight hours was not a safe dose for use in children.

2. FDA Analysis of Efficacy

It was difficult to determine the antiretroviral activity of indinavir in HIV-infected children from the results of Merck 041 because of the monotherapy phase and because of the number of doses and formulations studied. The applicant's analysis showed some efficacy with a decrease in plasma HIV RNA levels and an increase in absolute CD4 counts. The reviewer agrees with this assessment and there will be no further analyses of Merck 041 efficacy data.

3. FDA Analysis of Safety

The types of adverse events noted in HIV-infected children enrolled in Merck 041 were similar to those described in clinical studies of HIV-infected adult receiving indinavir, namely renal abnormalities such as hyperbilirubinemia and nephrolithiasis. According to the indinavir package insert, hyperbilirubinemia (total bilirubin of 2.5 mg/dL or greater) has been reported in 9.3% of adults receiving indinavir.¹ In Merck 041, hyperbilirubinemia was reported as a laboratory adverse event in four (7.4%) study subjects; however, 30 subjects or 56% had a total bilirubin level greater than the upper limit of normal for the laboratory during the study. Only three subjects had total bilirubin levels greater than 2.5 mg/dL; the highest total bilirubin was 6.6 mg/dL (AN0753). Although no subjects were discontinued from the study because of hyperbilirubinemia, two subjects did have to temporarily stop their antiretroviral drugs after increases in their total serum bilirubin.

Because of the high incidence of renal toxicity noted in the applicant's analysis of the safety data, the remainder of the FDA analysis will focus on adverse events relating to the urologic system with a particular focus on study subjects receiving indinavir 500 mg/m² every eight hours since this is the dose proposed for use in HIV-infected children. The applicant provided results of laboratory tests in datasets; in the FDA analyses of this data, abnormalities in the urinalyses were defined using standard criteria from pediatric textbooks; see Table 1 of the Appendix for the laboratory values used to define normal and abnormal laboratory values in this analysis. In the FDA analyses, 45 of the 54 (83%) study subjects had an abnormality noted on urinalyses. The number of abnormal values noted for each subject ranged from one to 45 and included such findings as hematuria, pyuria, proteinuria, crystalluria, and urinary casts. A comparison of the nine subjects without any urological abnormalities with the 45 children who had a clinical or laboratory abnormality related to the urinary tract are shown in Table 7.

Table 7: Comparison of Subjects with and without Urological Abnormalities in Merck 041

	Urinary Abnormality Noted (N=45)	No Urinary Abnormality (N=9)
Age (median)	9.0	11.0
Race	64% White	66.7% White
Gender	62% Male	89% Male
Weight (median)	26.4 kg	28.3 kg
Time on Indinavir (median)	673 days	674 days
Ever received Indinavir at 500 mg/m ²	58%	33.3%

Source: Merck 041 Datasets, December 22, 1999 and April 26, 2000 submission

Because of the small number of subjects who did not develop any abnormalities in an urinalysis, it is difficult to determine any significance from this comparison. Differences due to gender may be related to differences in the pharmacokinetic parameters between men and women that have not been fully explained as yet. There is a very slight trend toward an increase in urinary tract abnormalities in the younger, smaller children. Although the number of days on indinavir did not appear to affect the incidence of urinary abnormalities noted, children on the highest dose of indinavir did appear to have a greater risk of developing urologic toxicities. These findings suggest that higher indinavir peaks, as seen in children who participated in Merck 041 and discussed further in Section III.F.1. were associated with an increased incidence of renal toxicity. A comparison of the indinavir peak concentrations of the two groups is shown in Table 8.

Table 8: Indinavir Peak Plasma Concentrations in Study Subjects With and Without Urological Abnormalities

	No Urinary Abnormality (N=9)	Urinary Abnormality Noted (N=44)*
Mean C _{max}	6,308 nM	10,330 nM
Median C _{max}	6,259 nM	9,371 nM

*Pharmacokinetic results for AN719 were not included in the PK dataset for the 041 study. Peak concentrations are from day 112 if available. If not available for day 112, then day 14 peak concentrations were used.

Source: Merck 041 Datasets, December 22, 1999 and April 26, 2000 submissions

The results shown above in Table 8 suggest a relationship between peak indinavir concentration and the incidence of renal toxicity in Merck 041. However, because of the small number of subjects, the indinavir dosing changes for each subject in this study, and inpatient variability, the data presented represent one point in time and may not accurately represent indinavir levels over the entire study or at the time of urologic abnormalities. Therefore, the relationship between high indinavir concentrations in children and an increased incidence of renal adverse events can only be put forth as a hypothesis and a cause of concern.

After a protocol amendment, the dose of indinavir was increased to 500 mg/m² every eight hours; at this time, a cluster of four cases of hematuria occurred. Because of this, the investigators determined that 350 mg/m² every eight hours was the maximum tolerated dose of indinavir in children. In fact, hematuria was the most commonly seen abnormality on urinalysis in Merck 041 and occurred in 32 (59%) study subjects. Hematuria was usually noted on more than one urinalysis with a mean of 2.9 episodes per subject and occurred at any time during the study from day 14 to day 693. Fourteen of the study subjects who experienced hematuria also had hemoglobinuria. The next most common abnormality noted on examination of the urine was crystalluria that was noted in 27 (50%) study subjects. Crystal components included calcium oxalate, amorphous material, and rarely indinavir itself.² Sterile pyuria was documented in 22 (41%) subjects with up to 11 episodes per subject (mean of 3.2 episodes per subject). Proteinuria was noted in 15 (28%) study subjects but was usually mild (1+ on urine dipstick). Although abnormalities on microscopic examination were very common, only one child had a creatinine that was increased to above the laboratory upper limit of normal. Renal structural abnormalities were noted on ultrasonography in three children and were described as echogenic foci.

While the study protocol for Merck 041 did not include a definition for the diagnosis of nephrolithiasis; it did define the occurrence of kidney stones as signs and symptoms of indinavir stone formation with new hematuria (more than 15 rbc/hpf), pain apparently originating from the urinary tract, or the appearance of crystals in the urine that were not composed of calcium oxalate or uric acid. However, the study report supplied by the applicant defines nephrolithiasis as any episode felt by the investigator to represent nephrolithiasis clinically, including but not limited to unexplained flank pain with or without hematuria. Since the diagnosis of nephrolithiasis is clinical and the definition was not provided to the investigators in the original protocol; it is of concern that some episodes of nephrolithiasis may not have been documented by the investigators and that its incidence may be underestimated. Twelve patients (22%) were listed in the datasets as having had nephrolithiasis, and four of the subjects had more than one episode of nephrolithiasis. Episodes of nephrolithiasis occurred with an equal frequency between the three phases of the study: five in the monotherapy phase, six in the combination phase, and five in the study extension. For a comparison of subjects who experienced nephrolithiasis with those who did not, see Table 9.

Table 9: Comparison of Subjects With and Without Nephrolithiasis in Merck 041

	Subjects with Nephrolithiasis (N=12)	Subjects without Nephrolithiasis (N=42)
Age (median)	8.5	11.0
Gender	6 (50%) Female	12 (29%) Female
Weight (median)	24 kg	29.4 kg
Days on Indinavir (median)	674.5 days	673 days
Started on Indinavir at 500 mg/m ²	7 (58%)	7 (17%)
Ever received Indinavir at 500 mg/m ²	9 (75%)	20 (48%)

Source: Merck 041 Datasets, December 22, 1999 and April 26, 2000 submissions

As shown in Table 9, the subjects who developed nephrolithiasis were slightly younger and smaller than those who did not develop nephrolithiasis. The increase in nephrolithiasis in younger and smaller children might have been related to problems with compliance related to hydration or to differing pharmacokinetics in children with a smaller body mass. Female subjects were more likely than males to develop nephrolithiasis; this might be due to differing pharmacokinetics between males and females. Although subjects with and without nephrolithiasis had similar total exposures to indinavir, subjects with nephrolithiasis were more likely to either have started the study on 500 mg/m² or to have received 500 mg/m² at some point during the study. This supports the hypothesis that higher indinavir peak concentrations seen with the 500 mg/m² every eight hour dose resulted in an increased incidence of indinavir adverse events such as nephrolithiasis.

As discussed previously nephrolithiasis occurred at any time point in the study. By definition, nephrolithiasis was associated with flank or abdominal pain and hematuria; other abnormalities noted at the time of nephrolithiasis included urolithiasis, pyuria, proteinuria, crystalluria, and increase in serum creatinine. Several subjects also had renal structural abnormalities noted including echogenic foci on ultrasonography and hydronephrosis. Signs or symptoms associated with nephrolithiasis lasted for as long as 105 days. Two patients required hospitalization; eight subjects had their dose of indinavir reduced because of hematuria and / or nephrolithiasis; and two subjects were discontinued from the study because of nephrolithiasis.

As part of the above discussion, it was noted that subjects with any type of renal adverse event or with nephrolithiasis were more likely to have received indinavir at a dose of 500 mg/m² every eight hours. In all, 29 study subjects received 500 mg/m² at some point during the study. Of the 29 subjects, 18 (62%) experienced some type of renal adverse event while receiving the 500 mg/m² dose including hematuria, proteinuria, pyuria, and crystalluria. (See Table 2) Six subjects (21%) developed nephrolithiasis, two subjects' serum creatinine doubled, and two subjects had abnormal renal ultrasounds while on this dose. Although subjects received relatively short courses of indinavir at 500 mg/m² every eight hours (2.5 to 33 weeks, median of 15 weeks), a high incidence of renal

toxicity was noted while subjects were receiving this dose. This was most likely related to an increase in toxicity noted at higher plasma and renal concentrations of indinavir, which will be discussed further in Section III.F.1.

In conclusion, study results from Merck 041 are difficult to interpret because of the many different formulations studied, the dosage changes, and the initial 16-week monotherapy phase. One of the primary objectives of this study was to determine a safe and efficacious dose of indinavir for use in HIV-infected pediatric patients. It was concluded that of the three doses studied, the pharmacokinetic parameters obtained with 500 mg/m² most closely resembled those seen with historical adult controls. However, this dose was not felt to be a safe dose by the Merck 041 investigators because of the increased incidence of hematuria at this dose and 350 mg/m² every eight hours was determined to be the maximally tolerated dose. In addition, in the FDA analysis the 500 mg/m² dose was not comparable to the adult 800 mg three times daily dose, because the AUC, C_{max}, and C_{8hr} were all outside the 90% confidence intervals generally used by the FDA to determine comparability. Although there were early decreases in HIV RNA levels during the indinavir monotherapy phase, it is impossible to use this data to judge the efficacy of indinavir when used in combination. However, safety data from Merck 041 is evaluable. In this study, the use of indinavir was associated with the same type of adverse events that have been noted in adults but at a much higher rate. In particular, the incidence of renal adverse events was concerning especially in children receiving 500 mg/m² every eight hours. Therefore, the findings of Merck 041 did not determine an optimal dose for use in pediatrics, did not prove the efficacy of indinavir in HIV-infected children, and revealed an alarming number of adverse events particularly at the dose proposed for use in children.

D. Merck 068

“A multicenter, open-labeled, 24-week study to investigate the safety, pharmacokinetics, and efficacy of indinavir in combination with stavudine and lamivudine in pediatric patients with HIV infections”

1. Study Design

This was an open-label, single-arm, multicenter study of the safety, efficacy, and pharmacokinetics of indinavir, 500 mg/m² every 8 hours in combination with stavudine and lamivudine in HIV-infected children. The primary efficacy endpoint was defined as the proportion of patients at 16 weeks with a plasma viral RNA level below the level of quantification by the AMPLICOR assay. CD4 counts and viral resistance data were also collected as evidence of efficacy; however, results from resistance testing were not provided by the applicant. Plasma indinavir levels were collected on day 15 and were assessed by calculating the 90% confidence intervals for the geometric mean AUC, C_{max}, and C_{8hr} of indinavir. Safety data were collected as a tabulation of reported adverse events. Clinical endpoints were documented and recorded as adverse events. Eligible patients were HIV-infected children 15 years of age or younger with a CD4 count of 500 cells/mm³ or greater for children three to five years of age and 200 cells/mm³ or greater

for children six years of age or older. Children had to be protease inhibitor naïve and naïve to either lamivudine or stavudine. Children with hematuria or with a serum creatinine greater than two times the upper limit of normal were excluded. Study subjects were evaluated at screening, on day one of treatment, day 14, day 15, week 4 and every 4 weeks until week 24. Pharmacokinetic data were collected on day 15; on that day study subjects were instructed not to consume any food or liquids except water for two hours before and two hours after their morning dose of indinavir. On other days, patients were allowed to take indinavir with liquids or with a light meal. Patients were also encouraged to maintain vigorous hydration; however, no specific amount of fluid intake was recommended. This study was initiated on January 5, 1998 and was completed on March 17, 1999. Study subjects continue to be followed in an ongoing extension of Merck 068.

2. Efficacy Results

Study Population

A total of 25 HIV-infected children from four to 15 years of age were enrolled in six study centers and were included in the 24 week analysis of surrogate endpoints (CD4 cell count and serum viral RNA) and safety. The median age of patients enrolled in this study was 8.0 years with a age range from 4 to 15 years and nine children 6 years of age or younger. The majority of patients were female (68%) and Black (68%). All but one patient had acquired their HIV infection by vertical transmission from their mother. The median plasma viral RNA level at baseline was 8,295 copies/ml; the median absolute CD4 count at entry was 559 cells/mm³, and the median CD4 percentage was 25.3%. Only six of the subjects had experienced an AIDS defining illness before study entry. Twenty-three of the 25 patients had received prior antiretroviral therapy; most children had previously received zidovudine (92%), lamivudine (64%), or didanosine (52%).

Patient Accounting

Of the 25 children enrolled, one did not have baseline viral RNA level collected. Two subjects had blood for pharmacokinetic analysis collected, but the samples were lost and not analyzed. There were two protocol violators; one patient had previously received nelfinavir, and another had previously received both lamivudine and stavudine. Both patients were included in the safety and efficacy analyses. Five of the 25 (20%) children enrolled did not complete the 24-week study. Four children discontinued because of adverse events. One subject withdrew during the first 24 weeks and one at 26 weeks; one withdrew because of noncompliance, and the other because of difficulty in getting to study visits. All patients who completed the study had 24-week RNA viral load and CD4 data collected.

Pharmacokinetic Analysis

Please see Dr. Kumi's review.

Twenty-three of the 25 children enrolled in Merck 068 had plasma concentrations of indinavir measured on day 15. Three patients had increased indinavir concentrations at 8 hours that most likely reflected dosing with indinavir prior to obtaining blood for the measurement of the C_{8hr} indinavir concentration; the troughs for these subjects were not included. Results are shown in Table 10.

Table 10: Pharmacokinetic Results for Merck 068

	AUC_{0-8 hr}(nM•hr)	C_{max} (Peak) (nM)	C_{8hr} (Trough) (nM)
Median	34,811	20,238	101
Geometric Mean	30,500.3	13,921.8	108.8
Arithmetic Mean	43,230	19,279	134
Range	394 – 89,262	91 – 38,047	32 - 435
Geometric Mean for Adults (Merck 021)	28,719	11,948	208

Source: Volume 7, December 22, 1999 submission

The pharmacokinetic measurements obtained after dosing with 500 mg/m² every eight hours in children were compared with the 800 mg three times daily dose in adults by using bioequivalence criteria. If two drug regimens are found to be bioequivalent or comparable then safety and efficacy data from adult patients can be extrapolated to the pediatric population. The applicant calculated the ratio of the pharmacokinetic parameters in children to adults and the 90% confidence intervals of these ratios. When the pharmacokinetic values obtained in Merck 068 were compared to those of HIV-infected adults who participated in Merck 021, the geometric mean values for the AUC_{0-8 hr} and for C_{max} (peak) and the 90% confidence intervals were compatible by the applicant's analysis. However, the C₈ (trough) levels for the children enrolled in Merck 068 were lower than those observed in adult patients. In summary, the total exposure and peak concentration achieved in HIV infected children who received 500 mg/m² of indinavir in Merck 068 were similar to those noted in adult historical controls by the applicant's analysis, however, trough levels seen in these children were lower than those previously documented in HIV infected adults.

Efficacy Analyses of Surrogate Endpoints

The assessment of antiviral activity was based primarily on the proportion of patients with virologic success (defined as achieving suppression of viral RNA below the level of quantification) at 24 weeks. However, efficacy analyses were also provided for changes from baseline in absolute CD4 counts and CD4 percentages, serum viral RNA levels, and body weight. Three methodologies were used by the applicant to summarize data: an analysis based on the observed data, a model-based analysis based using restricted maximum likelihood (REML) methodology, and an additional analysis counting dropouts as failures. The area under the curve minus baseline (AUCMB) for plasma viral RNA, CD4 cell count, and percent CD4 count were also provided as a measure of the average change from baseline over the study period. Because of the small number of patients

enrolled in Merck 068, additional efficacy analyses by age, race, and gender were not performed.

Although none of the study subjects had undetectable viral RNA levels at baseline, 16 of the 25 patients who entered the study had viral RNA levels that were undetectable (< 400 copies/ml using the AMPLICOR assay) by week 2. At 24 weeks, 14 patients were undetectable by AMPLICOR and 11 were also undetectable by the UltraSensitive assay (viral RNA less than 50 copies/ml). When the proportion of patients with viral RNA levels below the level of detection was determined using GEE methodology where treatment related withdrawals were counted as failures, 60.4% of patients had viral RNA levels less than 400 cells/ml at week 24 and 46.2% had levels less than 50 cells/ml. The proportion of patients with viral RNA levels below the limit of quantification was also determined by counting all dropouts as failures and is shown in Table 11.

Table 11: Proportion of Children with Undetectable Serum Viral RNA Levels in Merck 068 (Dropouts as Failures)

	Amplicor Assay (<400 copies/ml)	Ultra Sensitive Assay (<50 copies/ml)
Week 2	64%	8%
Week 24	60.87%	47.83%

Source: Volume 7, December 22, 1999 submission

All but one of the 19 patients who completed the 24-week study had a decrease in plasma viral RNA levels. This decrease was seen early and maintained through 24 weeks. At week 2, the median decrease in RNA levels from baseline was 1.13 log copies/ml; at week 24, the median decrease was 1.39 log copies/ml. Using REML modeling, there was a mean decrease in viral RNA of 1.29 log₁₀ copies/ml at week 2 and a mean decrease of 1.25 log₁₀ copies/ml with 95% confidence intervals of -1.53 and -0.97 at week 24. By week 24, 72% of patients had a one log decrease or greater in plasma viral RNA level from baseline.

Finally, the efficacy of an antiretroviral regimen including indinavir was analyzed by the change in viral RNA level using the area under the curve minus the baseline value. The median AUCMB was -1.12 log₁₀ copies/ml, and this decrease was statistically significant (p<0.001).

In the pediatric population, absolute CD4 counts are age-dependent; some changes in the CD4 count may be attributable to aging and not to disease progression. Therefore, it is important to examine both the absolute CD4 count and the CD4 percentage, which is more consistent over time in HIV infected children. As shown in Table 12, both the absolute CD4 count and the CD4 percentage were increased at 24 weeks. The change as analyzed by the AUCMB was statistically significant for both the absolute CD4 count (p<0.001) and CD4 percentage (p=0.004).

Table 12: Change in Absolute CD4 count and the CD4 Percentage in Merck 068

	Change in Absolute CD4 Count (cells/mm ³)			Median Change in CD4 Percentage		
	Observed (median)	REML (mean)	AUCMB (median)	Observed (median)	REML (mean)	AUCMB (median)
Week 2	+114.5	+128.8	---	-0.7	-0.2	---
Week 24	+229.0	+241.8	+155.0	+4.5	+4.2	2.0

Source: Volume 7, December 22, 1999 submission

In the original study protocol, body weight was not included as an efficacy endpoint, however, changes in body weight were included by the applicant in the efficacy analysis. Overall, 19 of 25 children gained weight during the study, and the median increase in body weight at week 24 was 1.0 kilogram.

In conclusion, the applicant determined that 61% of HIV infected children treated with an antiretroviral regimen including indinavir had plasma viral RNA levels below the level of quantification (AMPLICOR assay). There was also a decrease in viral RNA at 24 weeks, an increase in the absolute CD4 count and CD4 percentage at 24 weeks, and an increase in body weight at 24 weeks.

3. Evaluation of Safety

All 25 patients enrolled in Merck 068 were included in the safety analysis. There were no deaths during the 24 weeks of this study.

Clinical Adverse Events

At least one clinical adverse event was reported in 24 of the 25 patients (96%); eight of 25 patients (32%) experienced a serious adverse event. Investigators described 14 of the 24 (58%) adverse events as drug related. The most commonly reported clinical adverse events included vomiting (13 patients), abdominal pain (seven patients), and flank pain (four patients). Ten serious clinical adverse events were reported in eight patients; seven of the 10 events were felt to be drug-related and included urolithiasis (five episodes in three patients), hypertension, and severe abdominal pain. Clinical adverse events related to nephrolithiasis were reported in five patients and included hematuria (three patients), urolithiasis (three patients), and flank pain (two patients). Two patients stopped indinavir treatment because of clinical adverse events (one because of recurrent urolithiasis and one because of severe vomiting); both of these adverse events were described as drug related.

Laboratory Adverse Events

Laboratory adverse events were reported in 16 of 25 children (64%), and 15 of 16 were described as drug related. Only one serious laboratory adverse event, a positive antinuclear antibody, was noted. The most frequent laboratory adverse events were pyuria (nine patients or 36%), hematuria (seven patients or 28%), and hyperbilirubinemia

(five patients or 20%). Other reported laboratory adverse events included increased indirect serum bilirubin (two patients), increased ALT (one patient), increased AST (two patients), and crystalluria (one patient). Three patients had laboratory adverse events that were associated with nephrolithiasis (hematuria, increased serum creatinine, and a positive urine leukocyte esterase). Interestingly, six of the 9 patients who developed pyuria had no evidence of either a urinary tract infection or nephrolithiasis, and three of these six patients also experienced an increase in serum creatinine. Two patients discontinued from the study due to laboratory adverse events (one with an increased serum creatinine to 1.1 mg/dL and one with a positive antinuclear antibody test); both were considered by the investigator to be drug related.

Nephrolithiasis

Additional data were reported for those patients experiencing adverse events related to nephrolithiasis, which was defined as any episode determined by the investigator to represent nephrolithiasis clinically, including but not limited to unexplained flank pain with or without hematuria. Six of the 25 (24%) children had at least one episode of nephrolithiasis during the first 24 weeks. Three of the six children had symptoms of nephrolithiasis that were graded as severe. Symptoms of nephrolithiasis lasted from two to nine days and were generally treated with interruption of study drug and aggressive hydration. Three of these patients had indinavir therapy interrupted during the acute episode then restarted at the same dose (500 mg/m²); however, one of these 3 patients was subsequently taken off study because of an increase in her serum creatinine noted during the episode of nephrolithiasis. One patient had indinavir treatment interrupted then restarted at a lower dose; this patient's indinavir dose was increased back to 500 mg/m² at a later date. Another patient was taken off indinavir at week 24 because of nephrolithiasis, and the outcome for this patient was not included in the study report. The final patient was taken off study after three episodes of nephrolithiasis. No study subject had evidence of permanent renal impairment.

In summary, although the adverse event profile was similar to that previously recognized for adult patients, the frequency of adverse events, particularly nephrolithiasis and pyuria, were much more common in children; one-fourth of children developed nephrolithiasis and more than one-third experienced pyuria. However, no study subject developed permanent renal impairment.

Summary of Merck 068

Because Merck 068 was an open-label clinical trial with only 20 subjects reaching 24 weeks, it is difficult to definitively ascertain the efficacy of the study regimen. However, it was notable that the majority of children (61%) had undetectable viral RNA levels after 24 weeks of treatment. It is also significant that every child except one enrolled in Merck 068 experienced a clinical adverse event and that one-fourth of the children were diagnosed with nephrolithiasis. Overall, Merck 068 demonstrates the therapeutic efficacy of an indinavir-containing regimen in a small number of children but also raises significant questions about the safety of such a regimen in children.

Because of the similarities in study design between Merck 069 and ACTG 395 and because of the small numbers of subjects in each study, the FDA analysis of both Merck 069 and ACTG 395 can be found in Section III.F. of this review.

E. ACTG 395

ACTG 395, “A multicenter, open-labeled, 24-week study to investigate the safety, pharmacokinetics, and efficacy of indinavir in combination with stavudine and lamivudine in pediatric patients with HIV infection,” was begun in May 1998 because of slow enrollment in Merck 068. The study design of ACTG 395 was almost identical to that of Merck 068; however, ACTG 395 included pharmacokinetic sampling after both the capsule and a slurry preparation of indinavir.

1. Study Design

Like Merck 068, ACTG 395 was an open-label, single arm, multicenter study of the safety, pharmacokinetics, and efficacy of indinavir administered as 500 mg/m² every eight hours in combination with stavudine and lamivudine. The primary endpoint was the determination of the safety and tolerability of this indinavir-containing regimen as measured by the reporting of adverse events attributed to the study drug. The secondary endpoint was the determination of the proportion of study subjects with viral RNA levels below the level of quantification (<400 copies/ml) as measured by the AMPLICOR assay after 16 weeks of treatment. Plasma indinavir concentrations were collected on both day 15 and day 16 of the study and the pharmacokinetics of indinavir were assessed by calculating the 90% confidence intervals for the AUC_{0-8hr}, C_{max}, and C_{8hr} of indinavir. On day 15, plasma indinavir levels were collected predose and after dosing with the indinavir sulfate capsule formulation. On day 16 study subjects were given a slurry of the indinavir capsule contents mixed into two teaspoons of applesauce; pharmacokinetic parameters were also measured before and after dosing with this formulation. Safety data were collected as a tabulation of reported adverse events. Eligible children were three to 15 years of age, able to swallow capsules, and had been diagnosed with HIV-1 infection categorized as CDC category 1 or 2 (CD4 count ≥ 500 cells/mm³ for children three to five years of age and CD4 count ≥ 200 for children six years of age or older). Study subjects had to be protease inhibitor naïve and naïve to either lamivudine or stavudine. Subjects with a history of hematuria, a serum creatinine of 1.7 mg/dL or greater, a bilirubin greater than 1.5 mg/dL, liver transaminases more than three times the upper limit of normal, or acute hepatitis were excluded. Study subjects were evaluated at screening, at entry, and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. On days 15 and 16, during collection of pharmacokinetic data, patients were instructed to consume nothing but water for the two hours prior to and the two hours after receiving their morning dose of indinavir. Pharmacokinetic measurements were drawn predose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours postdose. In ACTG 395, patients were encouraged to maintain vigorous hydration with recommendations for a minimum of 75 ml/kg/day of fluid for children weighing less than 20 kilograms and of 50 ml/kg/day for those weighing 20 to 40 kg. This study was initiated on May 27, 1998; although enrollment has been

completed, patients are still being followed on this study. Sixteen-week data were provided for all study subjects.

2. Efficacy Results

Study Population

Although ACTG 395 was designed to study 24 HIV infected children, the study was closed after the enrollment of 16 children in ten study centers. These 16 children were five to 13 years of age (median 8.0 years); the majority of patients were male (62.5%) and Black (62.5%). While 15 children were born to HIV-infected mothers, the mode of acquisition of one patient was unknown. The median plasma viral RNA level at entry was 6,235 copies/ml; one patient had a viral RNA level below the limit of quantification (< 400 copies/ml) by the AMPLICOR assay on entry. The median absolute CD4 count at entry was 808 cells/mm³, while the median CD4 percentage was 30.5%. Only one patient had a history of an AIDS defining illness prior to study entry. Ten of the 16 patients (62.5%) had previously received antiretroviral therapy; eight had received zidovudine, eight lamivudine, and seven didanosine. None of the patients had previously received either stavudine or a protease inhibitor.

Patient Accounting

Of the 16 patients enrolled, two subjects were taken off study during the second week. Neither pharmacokinetic data nor surrogate marker data were collected on study for these patients. A total of 11 of 16 patients had pharmacokinetic values collected on day 15, and 10 patients had pharmacokinetic parameters measured on day 16. There were no violations of the inclusion or exclusion criteria. Twelve of 16 patients (75%) completed the first 16 weeks of this study for which data were provided. Three patients discontinued the study because of clinical adverse events. One patient withdrew from the study after eight days.

Pharmacokinetic Analysis

Please see Dr. Kumi's review.

Eleven study subjects had pharmacokinetic parameters provided for the day 15 measurement. Of the five patients who did not have pharmacokinetic values provided, two had withdrawn from the study before day 15 and two had high values at 8 hours postdosing and were thought to have been redosed so were not included. Results for the pharmacokinetic analysis after dosing with the indinavir sulfate capsule are given in Table 13.

Table 13: Pharmacokinetic Results for the Capsule Formulation in ACTG 395

	AUC_{0-8hr} (nM•hr)	C_{max} (peak)(nM)	C_{8hr} (trough) (nM)
Median	30,125	12,454	127
Geometric Mean	21,926.8	9,214.6	158.5
Arithmetic Mean	29,356	12,793	343
Range	2,607 – 62,574	1,078 – 26,179	47.2 – 2,002.7
Geo. Mean for adults (Merck 021)	28,719	11,948	208

Source: January 24, 2000 submission

When geometric means for all three pharmacokinetic parameters, AUC, C_{max}, and C_{8hr}, were compared, each was lower in children participating in ACTG 395 than in adult historical controls.

When the pharmacokinetic values obtained with the indinavir capsules were compared to those noted in an adult study, Merck 021, the 90% confidence intervals of the geometric mean ratios for AUC, peak, and trough were outside the lower limits defined by the applicant as a measure of general comparability as shown in Table 14.

Table 14: Comparison of Pediatric Pharmacokinetic Parameters for Indinavir Capsules in ACTG 395 and Adult Controls

Pharmacokinetic Measurement	Indinavir Plasma Concentration	
	Geometric Mean Ratio	90% Confidence Interval
AUC _{0-8hr} (nM•hr)	0.76	0.48, 1.22
C _{max} (nM)	0.77	0.47, 1.26
C _{8hr} (nM)	0.76	0.42, 1.37

However, this may have been due in part to the wide confidence intervals resulting from a small number of patients.

Children received a slurry of indinavir on the morning of day 16 only. For preparation of the slurry, investigators were instructed to stir the contents of indinavir capsules into two teaspoons of applesauce. Children were then encouraged to eat all of the applesauce and to lick both the spoon used to eat the slurry and the utensil used to stir the mixture during its preparation. Pharmacokinetic results for ten patients after dosing with the slurry are shown in Table 15. One patient who had pharmacokinetic parameters measured on day 15 did not participate in the pharmacokinetic analysis on day 16.

Table 15: Pharmacokinetic Results for the Indinavir Slurry in ACTG 395

	AUC_{0-8hr} (nM•hr)	Cmax (peak) (nM)	C8 (trough) (nM)
Median	29,813	14,479	196.5
Geometric Mean	26,979.9	13,710.5	146.3
Arithmetic Mean	30,104	15,242	196.5
Range	10,575 – 46,045	4,518 – 23,738	41.6 – 571.5
Geo. Mean for adults (Merck 021)	28,719	11,948	208

Source: January 24, 2000 submission

When the geometric mean ratios and 90% confidence intervals for the pharmacokinetic parameters were examined, the AUC and the troughs of the slurry preparation were similar to those obtained with the capsule. However, the Cmax or peak was higher for the slurry preparation (13,710.5 nM compared to 9,214.6 nM for the capsule with a ratio of 1.6). In summary, the total exposure and trough values noted with a dose of indinavir of 500 mg/m² as a capsule are similar to those noted with the same dose when indinavir is taken as a slurry formulation; however, the peak concentration of indinavir was higher after dosing with the slurry. In addition, values for all three pharmacokinetic parameters obtained after dosing with the capsule were lower in children than those noted in historical adult controls.

Efficacy Analyses of Surrogate Endpoints

As in Merck 068, the assessment of antiretroviral activity was based primarily on the proportion of patients with virological success (defined as achieving suppression of plasma viral RNA below the limit of quantification by the AMPLICOR assay) at 16 weeks. Efficacy analyses were also provided for changes in baseline in viral RNA, absolute CD4 counts, CD4 percentages, and body weight. The identical methodologies were used in the analyses of ACTG 395 as were used in Merck 068 (see Section III.D.E.). As in Merck 068, additional analyses by age, race, and gender were not performed because of the small number of patients enrolled in ACTG 395.

By week 2, nine of 16 children had RNA viral levels that were below the limit of quantification by the AMPLICOR assay; in addition, two of these 16 had levels below 50 copies/ml. At week 16, eight study subjects had plasma viral RNA levels below 400 copies/ml and five subjects had levels below 50 copies/ml. When the proportion undetectable was analyzed using GEE methodology where treatment related withdrawals are counted as failures, 67% of patients were undetectable at week 2 and 59% were undetectable (less than 400 copies/ml) at week 16. However, the 95% confidence intervals were wide and for the proportion undetectable at week 16 ranged from 33.5% to 80.1%. When dropouts were counted as failures, 53% were below 400 copies/ml at 16 weeks. The proportion of patients with viral levels below the limit of quantification with dropouts counted as failures is shown in Table 16.

Table 16: Proportion of Subjects in ACTG 395 with Undetectable Viral RNA Levels

	<400 copies/ml	<50 copies/ml
Week 2	60%	12.5%
Week 16	53%	33%

Source: January 24, 2000 submission

When viral RNA levels were analyzed by the change from baseline, there was a median decrease of 1.39 log₁₀ copies/ml at week 2 and a median decrease of 1.27 log₁₀ copies/ml at week 16. Similar results were described after REML modeling with a mean decrease of 1.19 log₁₀ copies/ml at week 2 and of 1.23 at week 16 (95% confidence intervals of -1.46 and -1.0). By week 16, 64% of patients had a decrease in viral RNA level of one log or greater from baseline. The efficacy was also analyzed by the change in viral RNA under the curve minus the baseline value. The median change in AUCMB was -1.17 log₁₀ copies/ml and was statistically significant as compared to zero (p<0.001).

As explained earlier, the absolute CD4 count is age-dependent, so changes in CD4 counts may be normal changes that come with aging and not due to disease progression or to immune reconstitution. Therefore, in Table 17, both changes in the absolute CD4 count and the CD4 percentage are shown for patients enrolled in ACTG 395.

Table 17: Change in Absolute CD4 count and the CD4 Percentage in ACTG 395

	Change in Absolute CD4 Count (cells/mm ³)			Median Change in CD4 Percentage		
	Observed (median)	REML (mean)	AUCMB (median)	Observed (median)	REML (mean)	AUCMB (median)
Week 2	+5	-46	--	-0.5	-0.6	--
Week 16	+75.5	+72.7	-8.7	+1.0	+1.2	+1.5

Source: January 24, 2000 submission

The median CD4 count increased by 75.5 cells over the 16-week study. However, the 95% confidence intervals by the REML were wide with a lower limit of -21.1. In addition, the AUCMB was -8.7 cells but was not statistically significantly different from zero. The magnitude of change in CD4 cells was related to baseline CD4 values; those patients with a higher CD4 count at baseline tended to have decreases in CD4 counts while those with lower CD4 counts at baseline had increases in absolute CD4 counts. Although the observed change in CD4 percentage, the change in CD4 percentage by REML methodology, and the AUCMB for the CD4 percentage all showed a small increase at 16 weeks, the 95% confidence intervals by REML modeling were again wide with a lower limit of -0.9. There was no association of the change in viral RNA level from baseline to week 16 and the change in CD4 count or percentage.

Although body weight was not included in the study protocol as an endpoint, it was included in the study report as a measure of efficacy. At week 16, there was a median increase in body weight of 2.2 kg.

The primary method used by the applicant to measure the efficacy of an indinavir containing regimen was the proportion of subjects achieving a plasma RNA level less

than 400 cells/mm³ at 16 weeks. When study dropouts are counted as failures, 53% of children had undetectable plasma viral RNA by the AMPLICOR assay. The viral load decreased by a mean of 1.27 log₁₀ copies/ml, and the majority of patients had more than one log decrease in viral RNA. Although this regimen was a virologic success in a very small number of HIV-infected children, there was very little change in the absolute CD4 count or CD4 percentage.

3. Evaluation of Safety

All 16 patients enrolled in ACTG 395 were included in the safety analysis. There were no deaths during the initial 16 weeks of this study.

Clinical Adverse Events

All 16 study subjects reported at least one clinical adverse event. Seven of the 16 patients (44%) experienced a clinical adverse event that was judged as drug related by the investigator. The most commonly reported clinical adverse events were abdominal pain (three patients) and vomiting (four patients). Serious clinical adverse events were reported by two patients (12.5%); one patient with Grade 3 vomiting and one with nephrolithiasis, increased serum creatinine, and interstitial nephritis. Three patients (18.8%) experienced adverse events related to the urogenital system including flank pain (one patient), hematuria (one patient), and urolithiasis (two patients). Three patients stopped indinavir and were taken off study because of clinical adverse events; these included the previously mentioned patient with nephrolithiasis, increased serum creatinine, and interstitial nephritis, one patient with persistent nausea and vomiting, and one patient with urolithiasis, abdominal pain, and hematuria. All three of these adverse events were described as drug related.

Laboratory Adverse Events

Of the 16 patients in ACTG 395, 14 (87.5%) reported laboratory adverse events. One-half of these adverse events were described as drug related. No serious laboratory adverse events were reported. No patients discontinued indinavir due to a laboratory adverse event. The most common laboratory adverse events were increased cholesterol (nine patients), increased triglycerides (six patients), and decreased hemoglobin (five patients). Other frequently reported laboratory events included increased creatinine (four patients) and increased total serum bilirubin (four patients). Crystalluria, hematuria, proteinuria, and pyuria were each reported in one patient.

Nephrolithiasis

Additional data were reported for those patients experiencing adverse events associated with nephrolithiasis. Three of 16 (19%) study subjects were diagnosed with nephrolithiasis. Onset of symptoms occurred on days 1, 13, and 75 and included abdominal pain, hematuria, and flank pain. Two of the three patients also had increases in serum creatinine during the episode of nephrolithiasis. Nephrolithiasis was only

judged to be of a severe intensity in one patient; this patient required hospitalization and had interstitial nephritis diagnosed by renal ultrasound. Two subjects were taken off indinavir and removed from the study; the third continued on study with a reduced dose of indinavir.

In summary, the adverse event profile noted in HIV-infected children enrolled in ACTG 395 was similar to that seen in adults receiving indinavir. However, the frequency with which these adverse events were noted was greater in children. All 16 patients experienced clinical laboratory events and 14 experienced laboratory adverse events. The most common adverse events were related to the gastrointestinal system (vomiting and abdominal pain) and to lipid metabolism (increased cholesterol and triglycerides). However, signs and symptoms associated with renal toxicity were also noted frequently including increased serum creatinine, urolithiasis, and nephrolithiasis. In addition, one patient developed interstitial nephritis during this 16-week study.

Summary of ACTG 395

Like Merck 068, ACTG 395 was a small, open-label, single-arm study of an indinavir-containing antiretroviral regimen in HIV infected children. In ACTG 395, the majority of children (53%) had undetectable viral RNA levels at 16 weeks. However, this type of benefit was not noted in measures of the immunologic response. In addition, every child participating in this study experienced some type of adverse event. In conclusion, although this indinavir-containing regimen did result in virologic success for the majority of children, the small number of children studied decreases the significance of the finding. In addition, the lack of an immunologic response and the high rate of adverse events are of concern.

F. FDA Analysis of Merck 068 and ACTG 395

The study designs of Merck 068 and ACTG 395 were very similar; the main difference between the two studies was the collection of pharmacokinetic data after the administration of indinavir as a slurry preparation on day 16 in ACTG 395. The study populations of Merck 068 and ACTG 395 were also comparable. There were few differences between the study subjects in age, race, method of HIV acquisition, or baseline virologic and immunologic values (see Table 1). Because of the similarities of Merck 068 and ACTG 395 in study design and populations and because of the small numbers of study participants in both studies, the FDA analyses of both studies are described together in the following sections.

1. FDA Pharmacokinetic Analysis

Please see Dr. Kumi's review

In both Merck 068 and ACTG 395, plasma concentrations of indinavir after the administration of the capsule formulation were measured on day 15 and compared to adult historical controls. See Tables 18 and 19.

Table 18: Comparison of Pharmacokinetic Parameters for Pediatric Patients in Merck 068 with Adult Historical Controls

Pharmacokinetic Measurement	Indinavir Plasma Concentrations	
	Geometric Mean Ratio	90% Confidence Interval
AUC _{0-8hr} (nM•hr)	1.06	(0.63, 1.78)
C _{max} (nM)	1.17	(0.68, 2.00)
C _{8hr} (nM)	0.52	(0.37, 0.75)

Source: Volume 7, Table 14, December 22, 1999 submission

Table 19: Comparison of Pharmacokinetic Parameters for Pediatric Patients Receiving Indinavir Capsules in ACTG 395 with Adult Historical Controls

Pharmacokinetic Measurement	Indinavir Plasma Concentrations	
	Geometric Mean Ratio	90% Confidence Interval
AUC _{0-8hr} (nM•hr)	0.76	(0.48, 1.22)
C _{max} (nM)	0.77	(0.47, 1.26)
C _{8hr} (nM)	0.76	(0.42, 1.37)

Source: Table 16, January 24, 2000 submission

In Merck 068, the geometric mean ratios (GMR) for the AUC_{0-8hr} and the peak (C_{max}) were higher in the children than those reported for adult historical controls, but the GMR for the troughs in children (C_{8hr}) were lower. When the applicant compared pharmacokinetic parameters, the AUC and C_{max} were within the limits of comparability using the applicant's definition of comparability with 90% confidence intervals between 0.5 and 2.0. The applicant noted that the trough value or C_{8hr} was below this defined limit of comparability. However, the Division does not agree with the applicant's definition of comparability, and reviewers from the Division have determined that the indinavir dose of 500 mg/m² every eight hours in pediatric patients was not comparable to the indinavir adult dose of 800 mg every eight hours. See Dr. Kumi's review for further discussion. Because the dose proposed for use in pediatrics was not comparable to the adult dose and because this lack of comparability could have clinical consequences, safety and efficacy data from adult studies cannot be used to support the approval of the 500 mg/m² dose in children, and approval must be based on the results of pediatric clinical trials only.

In ACTG 395 pharmacokinetic parameters were also measured after the administration of a slurry formulation which was made by emptying the contents of indinavir capsules into two teaspoons of applesauce. With the slurry preparation, the peak plasma concentration was higher than seen in adults, but both the AUC_{0-8hr} and the C_{8hr} were lower. Because of this low total exposure and low trough, the indinavir slurry is not interchangeable with the capsule.

Because of the differences in pharmacokinetic measurements that were noted in pediatric subjects participating in both Merck 068 and ACTG 395 as compared to adult historical controls, potential problems arising from these differences must be considered. In both studies the trough or C_{8hr} was much lower than the trough noted in adult historical controls; the geometric mean trough for patients in Merck 068 was 108.8 nM, in ACTG 395 it was 158.5 nM, and in adults participating in Merck 021 it was 208 nM. Since the 95% inhibitory concentration of indinavir in vitro is 100 nM, some investigators have stated that indinavir troughs should be greater than 100nM.^{3,4} The average trough in both Merck 068 and ACTG 395 was just slightly above 100 nM; however, ten of 20 patients in Merck 068 and four of eight in ACTG 395 with trough values measured had trough values which were lower than 100nM. (One patient in ACTG 395 with a C_{8hr} over 2,000 nM was omitted from the FDA analysis, because this high trough level suggests redosing with indinavir prior to trough sampling). Overall, nine of the 24 children with measurable C_{8hr} values had troughs that were below the IC_{95} for indinavir; the potential effect that this may have on the efficacy of indinavir in children is concerning.

Although the specific indinavir trough value needed for efficacy has not been identified, multiple studies in the scientific literature assert that trough correlates with efficacy for indinavir.³⁻¹⁰ Drs. Kline and Fletcher studied 18 HIV-infected children receiving indinavir, stavudine, and didanosine.^{3,4} Children initially received indinavir at 500 mg/m² every 8 hours then doses were adjusted to maintain trough values of 0.1 mg/L (162.9 nM). Nine of the 18 patients required doses of 500 mg/m² every 6 hours in order to maintain this trough. The pharmacodynamic relationship between indinavir plasma concentrations and efficacy was explored for a subgroup of nine children. The investigators found that the log₁₀ change in plasma viral RNA level from baseline to 24 weeks inversely correlated with the indinavir trough ($r^2=0.73$) for these nine patients. Seven of the nine patients had more than a log₁₀ decrease in plasma viral RNA; all seven had a trough greater than 0.1 mg/L, while the two patients without a log₁₀ decrease in viral RNA had troughs of 0.1 mg/L and <0.02 mg/L. Using pharmacokinetic modeling, the authors concluded that only 28% of patients receiving 500 mg/m² every 8 hours would maintain a trough of 0.1 mg/L and that this dose may not be adequate to “maintain a sustained anti-HIV response.”³ Of the 28 patients from Merck 068 and ACTG 395 who had evaluable trough levels, only 7 (25%) reached the trough values proposed by Fletcher et al. as needed for sustained efficacy.³ In a separate study, Gatti and colleagues showed an inverse correlation between indinavir troughs and change in CD4 percentage from baseline in HIV-infected children on indinavir, stavudine, and lamivudine.¹⁰ However, this finding was not statistically significant.

Other authors have reported similar results in studies of adult patients receiving indinavir.⁵⁻⁹ Burger et al studied 65 HIV-infected adults receiving 800 mg of indinavir three times daily and reported that a low plasma concentration of indinavir (less than 0.1 mg/L) correlated with virologic treatment failure defined as a plasma viral level greater than 200 copies/ml at 24 weeks (odds ratio 0.1).⁵ Acosta et al. described pharmacokinetic measurements obtained from 43 HIV-infected adults receiving indinavir 800 mg three times daily in combination with nucleoside reverse transcriptase inhibitors.⁶ When pharmacokinetic parameters of patients who had undetectable viral RNA levels

(<500 copies/ml) were compared with patients with viral RNA levels of 500 copies/ml or greater, trough values were significantly higher for patients with undetectable serum viral RNA than for patients with detectable virus. Finally, Stein et al. also reported a significant correlation of indinavir trough with change in log₁₀ HIV RNA copies/ml (p<0.0001).⁷ However, for study subjects in Merck 068 and ACTG 395, trough values did not appear to correlate with efficacy. As shown in Table 20, 77% of patients with trough values less than 100 nM had undetectable plasma viral RNA at study end as compared to 70% of patients who reached 24 weeks and had trough values greater than 100 nM. This may be due to the small percentage of patients with evaluable troughs (18/41, 44%), the 25% dropout rate, or the small number of patients in these studies.

Table 20: Relationship of Indinavir Trough and Plasma Viral RNA Level

	Indinavir Trough < 100 nM		Indinavir Trough > 100 nM	
	Undetectable (<400 cells/ml)	Detectable (>400 cells/ml)	Undetectable (<400 cells/ml)	Detectable (>400 cells/ml)
Merck 068	7	2	5	2
ACTG 395	3	1	2	1
Total	10	3	7	3

Source: Electronic submission December 22, 1999 Tables 4.9.2 and 4.1.8; Electronic submission January 24, 2000 Tables 4.9.2 and 4.1.8

The higher C_{max} or peak concentration of indinavir noted in children participating in Merck 068 is also of concern because of the reports in the scientific literature that high indinavir concentrations are associated with an increased risk of nephrolithiasis.⁹⁻¹¹ When the indinavir dose for all of the study subjects in Merck 041 was increased to 500 mg/m² every eighth hours, four children developed hematuria (more than 15 rbc/hpf on urinalysis). By study criteria, this was a dose limiting toxicity, so all patients were then down dosed to 350 mg/m². In their journal article reporting the findings of Merck 041, the investigators hypothesized that the higher indinavir peak noted in patients participating in Merck 041 might have been the cause of the increased incidence of hematuria and of nephrolithiasis in that study.² Gatti and colleagues studied the relationship between indinavir plasma concentrations and urologic adverse events in 11 HIV-infected children.¹⁰ There was a trend toward a higher AUC_{0-8hr} and C_{max} in the children who experienced renal toxicity. Interestingly, the child with the highest indinavir peak was also the only child with a kidney stone. Dielman and colleagues described the relationship between plasma indinavir concentration and urological complaints in 15 HIV-infected patients.¹¹ Urological complaints such as renal colic, flank pain, and hematuria were associated with an elevated indinavir plasma concentration in 80% of patients studied. One-fourth of the HIV-infected children enrolled in Merck 068 developed nephrolithiasis. Although the relationship between increased indinavir peak concentrations and an increased risk of nephrolithiasis is only theoretical, the results in Merck 068 support this theory.

In general, the dosage regimen of a drug to be used in children is estimated with the goal of achieving pharmacokinetic parameters of drug exposure comparable to those of adults with the assumption that similar drug exposure will result in comparable efficacy and toxicity. The dose of indinavir proposed for use in HIV-infected pediatric patients and

studied in both Merck 068 and ACTG 395, 500 mg/m² every 8 hours, was chosen by the applicant after the Merck 041 study, because of the regimens studied the pharmacokinetics of this dose most closely resembled the pharmacokinetics of the adult dose, 800 mg three times daily. However, the use of 500 mg/m² dose resulted in troughs that were significantly lower in children than those seen in adults. Although the consequences of this lower trough are not known, the possibility that the lower troughs may be associated with decreased efficacy and the inability to maintain viral suppression is concerning. In addition, the geometric mean of the indinavir peak concentrations for patients in Merck 068 was higher than noted with adult controls. The significance of this difference is uncertain, but the higher peak indinavir concentrations seen in children may explain the increased incidence in urological adverse events which was noted in Merck 068 and ACTG 395 (See Section III.F.3). Finally, when the geometric mean ratios of AUC_{0-8hr}, C_{max}, and C_{8hr} observed in children after the 500 mg/m² dose were compared with those from historical adult controls, the values fell outside of the 95% confidence intervals. For this reason, the dose of indinavir proposed for use in children is not comparable to the adult dose, and safety and efficacy data from adults cannot be extrapolated to children. In conclusion, more studies are needed to determine the appropriate dose of indinavir in order to assure its safe and effective use in HIV-infected children.

2. FDA Analysis of Efficacy

The primary efficacy endpoint in both Merck 068 and ACTG 395 was the proportion of subjects with virologic success at study end; virologic success was defined as suppression of plasma viral RNA below the level of quantification by the AMPLICOR assay (<400 copies/ml). The proportion of children in both studies with undetectable HIV RNA levels after discontinuations were counted as failures is shown in Table 21.

Table 21: Proportion of Study Subjects with Undetectable HIV RNA Levels at Study Endpoint

Study	Proportion Undetectable
Merck 068	14/25 (56%) at 24 weeks
ACTG 395	9/16 (56%) at 16 weeks

Source: December 22, 1999 submission Table 4.9.2, January 24, 2000 submission Table 4.9.2

As shown in Table 21, the proportions of study subjects with undetectable viral RNA levels at study endpoint were identical in Merck 068 and ACTG 395. This was most likely due to the similarities between the two study populations: the baseline viral RNA level were 8,295 copies/ml in Merck 068 and 6,235 copies/ml in ACTG 395, the baseline CD4 counts were 559 cells/mm³ in Merck 068 and 808 in ACTG 395, and neither study allowed protease inhibitor experienced patients to participate.

These results are consistent with Study 028 and ACTG 320 results, which are included in the package circular for indinavir.¹ The results of Merck 068 and ACTG 395 are also similar to those of other studies of the use of indinavir in children such as Vignano et al and Van Rossum.^{13,14} The positive treatment effect of an antiretroviral regimen

containing indinavir is also supported by the decrease in plasma viral RNA levels which was seen in both Merck 068 and ACTG 395. The majority of patients in these two studies had a change in HIV RNA level from baseline to study end of greater than one log. In addition, most patients also had an increase in both absolute CD4 counts and CD4 percentage over time; however, the increase in CD4 cells and CD4 percentage in ACTG 395 was minimal. Body weight was not defined in either study protocol as an efficacy endpoint but was included in analyses by the applicant; a small increase in median body weight was noted in each study. But these efficacy results must be confirmed, because both studies were small (only 32 subjects reached 24 weeks), open-label, and lacked a comparator arm.

In conclusion, results from both Merck 068 and ACTG 395 show that treatment of a small number of protease-inhibitor naïve HIV-infected children with indinavir, stavudine, and lamivudine can result in a short-term decrease in plasma viral levels and many HIV-infected children treated had undetectable (<400 copies/ml) HIV RNA levels at 16 to 24 weeks. A concomitant increase in CD4 cells and percentage was also observed. However, these results must be verified because of the small number of children studied; only 20 children in Merck 068 reached 24 weeks and only 12 children in ACTG 395 reached 24 weeks. In addition, data was only reported for a short period of time (16 and 24 weeks), and it is not known if viral suppression will be maintained over longer periods of time. We cannot say with confidence that this regimen is compatible to the adult regimen and will result in the same effect on viral RNA levels and CD4 counts in a larger patient population. Controlled clinical trials over longer periods of time are needed to confirm the efficacy of an antiretroviral regimen that includes indinavir 500 mg/m² every eight hours and two nucleoside reverse transcriptase inhibitors in HIV-infected children.

3. FDA Safety Analysis

Twenty-four week safety data was reviewed for all 25 patients enrolled in Merck 068; 16-week safety data was reviewed for the 16 patients enrolled in ACTG 395.

FDA Analysis of Clinical Adverse Events

There were no deaths in either Merck 068 or ACTG 395. The incidence of clinical adverse events, serious clinical adverse events, and drug-related clinical adverse events are shown in Table 22.

Table 22: Frequency of Adverse Clinical Events in Merck 068 and ACTG 395

	Merck 068 (N=25)	ACTG 395 (N=16)	Total (N=41)
Overall			
Any Clinical AE	24	16	40 (98%)
Serious AE	8	2	10 (24%)
Drug-Related AE	14	7	21 (51%)
Drug-Related Serious AE	5	2	7 (17%)
Most Common Adverse Events (10% or more of patients in one of the studies)			
Vomiting	13	4	17 (41%)
Upper Respiratory Infection	12	0	12 (29%)
Abdominal Pain	7	3	10 (24%)
Cough	6	2	8 (19.5%)
Flank Pain	4	1	5 (12%)
Fever	4	1	5 (12%)
Urolithiasis/Nephrolithiasis	3	2	5 (12%)
Gastroenteritis	2	2	4 (10%)
Impetigo	2	2	4 (10%)
Ear Pain	0	2	2 (5%)
All Serious Adverse Events			
Urolithiasis/Nephrolithiasis	3	1	4 (10%)
Vomiting	0	1	1 (2%)
Abdominal Pain	1	0	1 (2%)
Hypertension	1	0	1 (2%)
Dehydration	1	0	1 (2%)
Pneumonia	1	0	1 (2%)
Sepsis	1	0	1 (2%)

Source: December 22, 1999 submission Tables 31, 32. January 24, 2000 submission Tables 33, 34

The most frequently reported clinical toxicities are shown in Table 22. Almost all patients experienced some type of clinical adverse event; gastrointestinal complaints including vomiting and abdominal pain were commonly seen. It is important to note both the frequency and seriousness of renal toxicity. Clinically apparent nephrolithiasis was reported in five or 12% of patients and was described as serious in four of these patients. In addition, one patient had three episodes of nephrolithiasis before being taken off indinavir. A total of five (12%) of patients in the two studies were taken off indinavir because of clinical adverse events including three patients with nephrolithiasis. Nephrolithiasis will be discussed further later in this section of the review. In conclusion, clinical adverse events were extremely common in patients receiving an antiretroviral regimen that included indinavir, and the frequency and seriousness of the gastrointestinal and urological complaints present a serious concern.

FDA Analysis of Laboratory Adverse Events

In the applicant's analysis of Merck 068 and ACTG 395, laboratory adverse events were reported in 16 of 25 (64%) and 14 of 16 (87%) patients respectively. The frequency of laboratory adverse events and the types of laboratory adverse events noted in these two studies are shown in Table 23.

Table 23: Frequency of Adverse Laboratory Events in Merck 068 and ACTG 395

	Merck 068 (N=25)	ACTG 395 (N=16)	Total (N=41)
Overall			
Any Laboratory AE	16	14	30 (73%)
Serious AE	1	0	1 (2%)
Drug-Related AE	15	7	22 (54%)
Drug-Related Serious AE	1	0	1 (2%)
Most Common Adverse Events (10% or more of patients in one of the studies)			
Pyuria	9	1	10 (24%)
Hematuria	7	1	8 (20%)
↑ total bilirubin	5	4	9 (22%)
↑ cholesterol	0	9	9 (22%)
↑ triglycerides	1	6	7 (17%)
↓ hemoglobin	0	5	5 (12%)
↑ serum creatinine	2	4	6 (15%)
↑ amylase	0	4	4 (10%)
↓ sodium	0	3	3 (7%)
↑ AST	2	2	4 (10%)
↓ neutrophils	0	2	2 (5%)
↓ glucose	0	2	2 (5%)
All Serious Adverse Events			
Hematuria	1	0	1 (2%)

Source: December 22, 1999 submission Tables 34, 35. January 24, 2000 submission Tables 36, 37

As shown in Table 23, study subjects in Merck 068 and ACTG 395 commonly experienced a laboratory adverse event, and these laboratory adverse events were often described as drug related. However, laboratory toxicities were rarely described as serious.

While hyperbilirubinemia was reported as an adverse event in nine or 22% of children, 22 children or 54% had total bilirubin values over the upper limit of normal for the laboratory. However, only four children had total bilirubins of 2.5 mg/dL or more. As noted with adults receiving indinavir, increases in hepatic transaminases in children were uncommon; four children had an increased AST value recorded as a laboratory adverse event and 2 had an increased ALT reported as an adverse event.

Disturbances in lipid metabolism are commonly reported in HIV-infected adults treated with protease inhibitors including indinavir. Increases in both cholesterol and triglycerides have been described in adults receiving indinavir.² Although nine children in ACTG 395 had an increased total serum cholesterol reported as a laboratory adverse event, no children in Merck 068 had hypercholesteremia reported as an adverse event. This was largely due to how normal cholesterol levels were defined in each study. The upper limit of normal for cholesterol varied by center in ACTG 395 but was as low as 169 mg/dL, while the upper limit of normal in Merck 068 was 217 mg/dL. Using the definition of normal total cholesterol that was used in ACTG 395, there were nine subjects with increased cholesterol levels described as an adverse event. But if the upper limit of normal for cholesterol were defined as 217 mg/dL for all patients in ACTG 395 as it was for Merck 068, then only three patients would have had cholesterol levels described as increased. The definition of normal triglyceride levels also differed between Merck 068 and ACTG 395 and lead to different rates of hypertriglyceridemia in each study. Although increased triglyceride levels were reported as laboratory adverse events in one patient in Merck 068 and in six patients in ACTG 395, triglyceride levels were actually slightly higher in Merck 068. At closer inspection, six subjects in Merck 068 had triglyceride values greater than 200 mg/dL but no patient in ACTG 395 had a level of 200 or greater. The average triglyceride levels before treatment for children in Merck 068 and in ACTG 395 were similar (118.3 and 103.5 mg/dL respectively), but children in Merck 068 had higher mean triglyceride levels during treatment than children enrolled in ACTG 395 (183.3 compared to 125.6 mg/dL). The reason for higher triglyceride levels in Merck 068 is unknown but may be related to a longer exposure to combination antiretroviral therapy; values from Merck 068 were from the first 24 weeks of treatment, while values in ACTG 395 were from the first 16 weeks of treatment.

While nephrolithiasis and urolithiasis are known toxicities of indinavir in adults, other renal abnormalities also described with the use of indinavir include acute renal failure, renal insufficiency, interstitial nephritis, hydronephrosis, and hematuria.¹ Reports of the use of indinavir in HIV-infected children have described additional abnormalities on examination of the urine such as hematuria, crystalluria, and sterile pyuria.^{2,4,10,13,14} Different laboratory values were used to define abnormalities on urinalyses in Merck 068 and in ACTG 395. In our analyses of the data, urinary abnormalities were defined using standard criteria from pediatric textbooks; see Table 1 in the appendix for the laboratory values used to define normal in this analysis and Table 3 and 4 in the appendix for laboratory abnormalities noted in subjects enrolled in Merck 068 and ACTG 395 when these criteria were used. The applicant described 5 subjects with hematuria, four with blood in their urine, and ten with pyuria. However, after using our laboratory criteria to define hematuria and pyuria, more than one-half of children experienced either hematuria or pyuria while receiving indinavir and 18 subjects (44%) had both hematuria and proteinuria during indinavir treatment. In addition, 8 subjects had occult blood in their urine. Furthermore, in our analyses, 10 subjects (24%) experienced proteinuria, 12 (29%) had crystalluria, and 2 (5%) had urine casts. Overall, 13 of the 16 (81%) children in ACTG 395 experienced some type of abnormality noted on microscopic examination of their urine during the 16 week study, and 19 of 25 (76%) children in Merck 068 had abnormal urine microscopic examinations during that 24 week study. (See tables 3 and 4

in the appendix). Although 30 children were described by the applicant as having some type of laboratory abnormality and 22 children had a drug-related laboratory abnormality, in our analyses it appears that the majority of children had abnormalities noted on their urinalyses that were almost certainly related to indinavir use.

Nephrolithiasis

While the majority of children experienced laboratory abnormalities related to the urinary tract, some children also developed nephrolithiasis, an adverse event that is usually diagnosed using both laboratory and clinical criteria. Nephrolithiasis was defined as any episode determined by the investigator to represent nephrolithiasis clinically, including but not limited to unexplained flank pain with or without hematuria. Six of 24 (25%) of subjects in Merck 068 developed nephrolithiasis during that 24 week study, while 3 of 16 (19%) of subjects in ACTG 395 developed nephrolithiasis during the 16 week study. In contrast, nephrolithiasis has been reported in 9.3% of HIV-infected adults receiving indinavir during blinded and controlled clinical trials.¹

The onset of nephrolithiasis occurred at any time during the study and was reported both in the first and the last week of treatment. Eight of the nine patients with nephrolithiasis had multiple other signs and symptoms in addition to flank pain and hematuria including pyuria (eight subjects), positive urine leukocyte esterase (four subjects), increased serum creatinine (three subjects), proteinuria (two subjects), crystalluria (two subjects), and hypertension (one subject). The signs and symptoms of nephrolithiasis lasted from two to 39 days. Typically, subjects had their antiretroviral drugs temporarily stopped and were treated with aggressive hydration. Four patients required hospitalization. Two subjects had their dose of indinavir reduced to 350 mg/m² every 8 hours. Four children were taken off study permanently because of nephrolithiasis. One patient (AN0613) was dose reduced but symptoms and signs of nephrolithiasis returned, and she was removed from the study after her third episode of nephrolithiasis. One patient (AN0173) with nephrolithiasis diagnosed during week two of ACTG 395 was subsequently diagnosed with interstitial nephritis. However, no study subjects required surgery for stent placement or lithotripsy, and none had a permanent decrease in renal function as documented by serum creatinine.

There was no clear association of age, race or sex with risk of developing nephrolithiasis; however, the small number of patients makes this determination difficult. The correlation of peak plasma indinavir concentration and indinavir exposure or AUC with nephrolithiasis is shown in Table 24.

Table 24: The Relationship of Peak Indinavir Concentration and Indinavir Exposure with Nephrolithiasis

Pharmacokinetic Parameter	Mean Value in Patients with Nephrolithiasis	Mean Value in Patients without Nephrolithiasis
<i>Merck 068</i>		
AUC (nM•hr)	63,849.92	37,502.46
C _{max} (peak) (nM)	24,688.26	17,776.38
<i>ACTG 395</i>		
AUC (nM•hr)	3,952.7	31,896.59
C _{max} (peak) (nM)	1,078	13,964.47

Source: December 22, 1999 submission, Tables

There appeared to be a relationship between both higher exposure to indinavir (AUC) and higher indinavir peak concentrations (C_{max}) with nephrolithiasis in Merck 068 but not in ACTG 395. However, only one of the three patients in ACTG 395 with nephrolithiasis had pharmacokinetic measurements provided in this submission and the plasma concentrations for this one patient (AN3399) were unusually low. The possible association of high indinavir peaks with an increased incidence of renal abnormalities, particularly nephrolithiasis, has been reported in the scientific literature.^{2,11} One recent report has suggested that a higher total exposure or AUC correlates with an increased incidence of nephrolithiasis; in this study, subjects who received indinavir in combination with ritonavir as a twice daily regimen had a higher incidence of nephrolithiasis (10%) than those who received indinavir three times daily (4%).¹² There was clearly a substantial increase in the incidence of nephrolithiasis and urologic abnormalities in the small number of children enrolled in Merck 068 and ACTG 395, compared to adult historical controls.

Safety data was provided for the 41 pediatric subjects who received indinavir during the first 24 weeks of Merck 068 and the first 16 weeks of ACTG 395. The toxicity profile in these children resembled that of adults which is described in the package circular; however, adverse events were much more common in pediatric patients. Forty of 41 patients experienced clinical laboratory events while 30 of 41 experienced laboratory adverse events. The frequency of adverse events related to the urinary tract was particularly concerning. While nine subjects experienced at least one episode of nephrolithiasis, 88% had some type of renal toxicity noted by an abnormality in either serum creatinine or urinalysis. The reason for this increased renal toxicity in children is unknown but may have been related to increased plasma indinavir concentration. In conclusion, there was an alarmingly high rate of toxicity noted in both Merck 068 and ACTG 395, and the renal toxicity was of particular concern.

G. Merck 058

“An open-label, 3-period, crossover study to compare the tolerability and pharmacokinetics of single 800-mg doses of indinavir sulfate salt capsule administered fasted versus with applesauce versus after a heavy meal”

1. Study Design

This was an open-label, single-center study of the pharmacokinetics and tolerability of a single dose of indinavir 800 mg administered three different ways: as two 400 mg capsules after fasting, as two 400 mg capsules after a heavy meal, and as a slurry of two 400 mg capsules in applesauce. Twelve healthy adult volunteers were enrolled, and each subject received three single doses of indinavir as described above with at least six days between each dose. Plasma concentrations of indinavir were collected at specific timepoints after each indinavir dose. Pharmacokinetic measurements obtained included $AUC_{0-24hrs}$, C_{max} , C_{8hr} , and T_{max} . Indinavir safety and tolerability was evaluated by the tabulation of adverse experiences and the collection of laboratory data. Taste was assessed by questionnaires utilizing a scoring system.

2. Study Results

Study Population

Twelve healthy adult volunteers, six males and six females, between the ages of 19 and 43 years were enrolled in and completed the study. Data from all 12 study subjects were included in the pharmacokinetic and safety analyses.

Study Analysis

Please see Dr. Kumi's review.

A summary of the geometric means of the different pharmacokinetic parameters measured and a comparison of indinavir administered as a slurry with indinavir capsules taken after fasting are shown in Table 25.

Table 25: Pharmacokinetic Results after a Single Dose of Indinavir 800 mg in Merck 058

Indinavir Pharmacokinetic Measurement	Geometric Mean		Geometric Mean Ratio (Applesauce/Fasted)	90% Confidence Intervals
	Slurry in Applesauce	Capsules After Fasting		
AUC_{0-24} (nM•hr)	29,688.71	26,668.2	1.11	0.75, 1.65
C_{max} (nM)	13,562.5	12,225.76	1.11	0.70, 1.75
C_{8hr} (nM)	136.02	156.59	0.87	0.59, 1.29

Source: December 23, 1999 Submission, Merck 058 Study Report, Table 3

In this study, the applicant compared plasma indinavir levels obtained with the slurry preparation and those obtained with indinavir capsules. According to the applicant, the slurry preparation and the capsule were comparable because the 90% confidence intervals obtained when comparing plasma levels of indinavir with the slurry and the capsule fell

between 0.5 and 2.0. When the T_{max} or the time to peak concentration was compared between the slurry and capsules given after fasting, the T_{max} for the slurry was shorter, 0.6 hours as compared to 1.2 hours for the capsule.

Pharmacokinetic parameters were also compared between indinavir capsules given after fasting and indinavir capsules given after a heavy meal. In this comparison, the geometric mean AUC_{0-24hr} after indinavir administered with a heavy meal was considerably lower than that of indinavir given after fasting (18,437.9 versus 26,668.2 $nM \cdot hr$). This value fell outside of the 90% confidence intervals used by the sponsor to define comparability. In addition, the C_{max} and the C_{8hr} were also substantially lower when indinavir was administered with food; however the C_{8hr} value did fall within the 90% confidence interval. The T_{max} value for indinavir taken with food was 2.0 hours as compared to 1.2 hours with fasting; suggesting that taking indinavir with food delays its absorption.

The taste of indinavir was evaluated using a questionnaire. Eleven of the 12 study subjects rated indinavir administered in applesauce as worse than average taste for medicine (2 subjects), awful taste (3 subjects), or the worst taste for any medication ever taken (6 subjects). In contrast, all 12 subjects rated indinavir with a heavy meal as having no taste. Ten subjects described indinavir taken when fasting as having no taste and two rated it as having a better than average taste.

All 12 study subjects were included in the safety analysis. Two subjects had clinical adverse experiences which were described as mild; one subject had two episodes of headache and one subject experienced dizziness, fatigue, and somnolence after taking indinavir while fasting. There were no laboratory adverse events. No study subjects developed abnormalities on physical examination, vital signs, or electrocardiogram.

In summary, when the comparability of two indinavir preparations was defined by 90% confidence intervals of 0.5 and 2.0, pharmacokinetic measurements of indinavir administered as a slurry in applesauce was comparable to indinavir taken as a capsule while fasting. The peak concentration of indinavir was earlier when indinavir was administered as a slurry; however, the clinical significance of this is uncertain. In addition, the taste of this indinavir slurry preparation was rated as worse than other medication or the worst medication ever taken by the study subject raising questions about its palatability for children. Finally, indinavir plasma concentrations are notably lower when indinavir was taken with a heavy meal than when indinavir is taken after fasting.

3. FDA Analysis

Please see Dr. Kumi's review.

In Merck 058, two hypotheses were tested. First, the sponsor hypothesized that the AUC_{0-24hr} or exposure to indinavir would be the same when the contents of indinavir were mixed with applesauce as it was when indinavir capsules are taken while fasting.

To test this hypothesis, 12 healthy adult volunteers had plasma concentrations of indinavir measured after ingestion of indinavir as a slurry and after indinavir capsules taken while fasting. By the applicant's definition of comparability, the slurry and capsule regimens were comparable. However, both the AUC and C_{max} were higher with the slurry preparation as compared to the capsule formulation, and the C_{min} was considerably lower with the indinavir slurry. In the opinion of FDA pharmacokinetic reviewers, results in Merck 058 did not show comparability between indinavir administered as a slurry in applesauce and indinavir taken as a capsule.

The second hypothesis tested in Merck 058 was that 800 mg indinavir capsules taken after a heavy meal would result in a similar exposure or AUC_{0-24hr} as 800 mg taken while fasting. The sponsor found that the AUC_{0-24hr} , C_{max} , and the C_{8hr} were considerably lower when indinavir was taken with food and that the exposure was substantially different.

In summary, both hypotheses of Merck 058 were disproved. The exposure to indinavir after its administration as a slurry in applesauce was not comparable to the exposure after administration of the indinavir capsule, and the slurry preparation of indinavir was not appropriate for use in HIV-infected patients. In addition, the current recommendations to take indinavir on an empty stomach or after a light meal should be continued.

H. Summary of Clinical Studies

In each of the pediatric clinical trials, pharmacokinetic parameters of indinavir were measured, and the results failed to show that the 500 mg/m² every eight hour dose proposed for use in HIV-infected children was comparable to the adult dose of 800 mg three times daily. Because the dose proposed for use in pediatrics is not comparable to the dose used in adults, safety and efficacy data from adult clinical trials cannot be extrapolated to the pediatric population; and approval of the use of this dose in children must be based on studies of this dose in children.

The applicant submitted two studies, Merck 068 and ACTG 395, to support the efficacy of indinavir at a dose of 500 mg/m² every eight hours in HIV-infected children three years of age and older. These two studies only enrolled a total of 41 subjects and only 32 of the enrolled subjects completed 24 weeks. Although some efficacy was shown, with more than one-half of the subjects in each clinical trial achieving plasma HIV RNA levels less than 400 copies/ml at the study end, there were not enough patients studied over an adequate period of time to support the efficacy of indinavir in pediatrics.

The safety profile of indinavir in children closely resembled that of adults, however, adverse events were much more common in pediatric patients. A total of 70 study subjects in three clinical trials were exposed to the proposed indinavir dose. The majority of these subjects developed abnormalities on microscopic examination of the urine. A smaller but significant number experienced nephrolithiasis. Therefore, the results of these three clinical trials studying indinavir in children, do not show that indinavir at 500 mg/m² every eight hours can be used safely in HIV-infected children.

IV. Worldwide Clinical Summary

The Worldwide Clinical Summary provided a summary of the safety and efficacy results of the three pediatric clinical trials, rationale for the pediatric development program and the dose selection, and a risk benefit analysis for the use of indinavir in HIV-infected children. For a description of the results of these pediatric trials, please see Section III of this review.

Children who are infected with the human immunodeficiency virus have a high level of HIV RNA present in their blood. Studies have shown that lowering the level of plasma HIV RNA and inhibition of HIV replication provide clinical benefits to HIV-infected patients; the most effective method of lowering the plasma viral level and of preventing HIV RNA levels is combination antiretroviral therapy. In addition, successful antiretroviral treatment after the failure of an existing therapy is difficult to achieve. Approval of indinavir for use in children would provide health care professionals with another option for the treatment of HIV-infected children.

Indinavir was first studied in children in Merck 041, a dose finding study of 54 HIV-children from three to 18 years of age. The results of Merck 041 showed that a similar overall drug exposure was obtained with indinavir 500 mg/m² every eight hours in children as with 800 mg every eight hours in adults. In the limited information on efficacy obtained in this study, the 500 mg/m² dose appeared to be more efficacious than the 250 or 350 mg/m² every eight hour doses. However, there was also dose related toxicity; children receiving 500 mg/m² every eight hours had the highest incidence of nephrolithiasis. Two subsequent pediatric efficacy trials, Merck 068 and ACTG 395, were then initiated to determine if indinavir 500 mg/m² every eight hours used in combination with stavudine and lamivudine would result in antiretroviral suppression. Thus two trials, Merck 068 and ACTG 395, provided efficacy data for 41 children who received indinavir 500 mg/m² every eight hours. With noncompleters counted as failures, 66% of subjects had plasma HIV RNA levels less than 400 copies/ml and subjects had a mean increase in CD4 count of 149 cells/mm³ at 16 weeks.

All three pediatric trials, Merck 041, Merck 068, and ACTG 395, provided safety data for 95 children who received indinavir including 70 subjects who received indinavir 500 mg/m² every eight hours and 25 children who received lower doses of indinavir. Overall, the safety profile in indinavir treated pediatric patients appeared to be similar to that experienced in adults. The use of indinavir was associated with abdominal pain, vomiting, hyperbilirubinemia, hematuria, and pyuria, but these adverse events usually did not limit treatment with indinavir. The use of indinavir in children was also associated with a high incidence of nephrolithiasis. The clinical picture of nephrolithiasis in children is similar to that in adults; in general the signs and symptoms resolve with hydration and did not result in permanent renal dysfunction. According to the applicant, these adverse events were all consistent with the current labeling for indinavir.

In addition, the applicant performed a review of the scientific literature; 20 articles, 22 abstracts, four letters, and one case report describing the use of indinavir in HIV-infected children were summarized. Indinavir, 500 mg/m² every eight hours, used in combination with other antiretroviral agents resulted in sustained decreases in plasma HIV RNA levels, increases in CD4 cells, and weight gain in these reports. Adverse events associated with the use of indinavir were also reported and again mirrored those adverse events noted in adults receiving indinavir. Nephrolithiasis was commonly noted and was reported in as many as 80% (4/5) of children in one patient series. Descriptions of interstitial nephritis with increases in serum creatinine were also reported. Overall, data from this literature review were generally consistent with data included in the submission.

Finally, the applicant provided a rationale for the use of indinavir at 500 mg/m² every eight hours in HIV-infected children three years of age and older. When this dose of indinavir was used in children, the overall exposure was similar to that noted in adult historical controls. Although the trough was considerably lower in children, there is no definitive evidence that the indinavir trough correlates with efficacy. In addition, there was no correlation between indinavir trough levels and efficacy in the two pediatric efficacy trials. Since the majority of children in Merck 068 and ACTG 395 had suppression of plasma HIV RNA levels, these two trials further supported the use of indinavir 500 mg/m² every eight hours in children. Safety data revealed an adverse event profile that was similar to that seen in adults; and although adverse events were noted more frequently in children, they generally did not result in discontinuation of indinavir or in long-term sequelae. Thus according to the applicant, indinavir 500 mg/m² every eight hours used in combination with other antiretroviral agents demonstrates substantial antiretroviral effect and an acceptable adverse event profile. The risks of nephrolithiasis and renal dysfunction are outweighed by the need for potent antiretroviral agents in HIV-infected pediatric patients.

V. Safety Update Report

Updated safety information through January 10, 2000 was submitted as a Safety Update Report addendum to the supplemental NDA (20,685 S-043) on March 31, 2000. This SUR contained additional safety information for patients continuing on Merck 041 after 96 weeks and on Merck 068 past 24 weeks, a revised study report with 24-week efficacy and safety data for subjects on ACTG 395, additional safety information from the Worldwide Adverse Experience Database and from postmarketing surveillance, and safety information from one additional clinical trial, Merck 065. Although the safety information presented in this update did not include any important new adverse experiences, it did further clarify the frequency of adverse events such as nephrolithiasis in HIV-infected children receiving indinavir. Each study was reported separately by the applicant and will be discussed separately in this review.

A. Merck 041

Safety data for 16 study subjects who were receiving indinavir 350 mg/m² every eight hours with zidovudine and lamivudine after 96 weeks were provided in the Safety Update Report. There were no deaths in this study and no study subjects were discontinued from the study because of adverse events. Only two study subjects experienced clinical adverse events during this time (vaginal fistula and fever); neither was judged to be drug related. Three study subjects developed laboratory adverse events after 96 weeks. However when datasets were examined, the results of only one serum creatinine and two urinalyses were reported. Both urinalyses were abnormal; one subject had 1+ protein and the other had 10 red blood cells noted on each high power field. In addition, another study subject had a renal ultrasound done, however neither the reasons for obtaining the renal ultrasound or the results were provided. Because of the limited data provided for subjects participating in Merck 041 after 96 weeks, it is impossible to reach any conclusions about the safety of indinavir during this time period.

B. Merck 068

Twenty subjects completed the first 24 weeks of Merck 068, a study of indinavir 500 mg/m² every eight hours in combination with stavudine and lamivudine in HIV-infected children. There were no deaths in this study. Three subjects were discontinued from Merck 068 after 24 weeks; one subject withdrew from the study and two were removed because of adverse events (one with pyuria, increased creatinine, and hypertension and one with increased creatinine and nephrolithiasis). The Safety Update Report did not include information on one subject (AN0206) who withdrew from Merck 068 on day 183 (week 26). All 19 of the remaining 19 subjects experienced some type of clinical adverse event during weeks 25 to 48. Clinical adverse events were described as drug related in 12 subjects. The clinical adverse event noted most commonly was vomiting (4/19 or 21%); clinical adverse events occurring in two or more patients (i.e., more than 10%) were abdominal pain, dysuria, urinary tract infection, and urolithiasis. Two subjects experienced serious clinical adverse events: one with vomiting, diarrhea, and urolithiasis and one with herpes simplex virus infection. Only one subject was removed from the study because of an adverse clinical event; this subject was discontinued because of hypertension that was associated with pyuria and an increase in serum creatinine.

Twelve of 19 subjects or 63% experienced a laboratory adverse event; all were determined to be drug-related but none were judged as serious. Laboratory adverse events included increased total serum bilirubin (six subjects), increased indirect serum bilirubin (four subjects), and increased serum creatinine (four subjects). In addition, nine of the 19 subjects (47%) had at least one abnormality on urinalysis including eight with pyuria, two with hematuria, one with bacteriuria, and one with crystalluria. Of the eight subjects with pyuria, four had sterile pyuria of unknown etiology. Pyuria in these four patients was not associated with nephrolithiasis but all four had an increase in serum creatinine. Only one subject was discontinued from the study because of a laboratory adverse event. This patient, a five year old female, developed an increase in serum

creatinine starting on study day 225 and was removed from the study on day 285 with a continued increase in serum creatinine and the onset of urolithiasis.

Datasets containing individual study subject laboratory values were supplied by the applicant and were analyzed further. In the reviewer's analysis, ten subjects were noted to have total serum bilirubin values greater than the upper limit of normal for the laboratory. Five of these subjects had values of 2.5 mg/dL or greater, and the highest total bilirubin was 3.6 mg/dL. Nine study subjects (47%) had serum creatinine values that were greater than the upper limit of normal for the laboratory; however, the increases in creatinine were mild or moderate and the highest creatinine noted was 1.5 mg/dL. Urinalyses were further reviewed using the laboratory values defined in Table 1 of the appendix. When using these standard definitions for normal urinalyses values, ten (53%) subjects had hematuria, eleven (58%) had pyuria, two (10%) proteinuria, and four (21%) crystalluria including one subject with indinavir crystals identified in his urine.

Four subjects who had not had nephrolithiasis in the first 24 weeks of Merck 068 developed nephrolithiasis after 24 weeks. Symptoms associated with nephrolithiasis included back pain, vomiting, hypertension, and urolithiasis. Although all four subjects with nephrolithiasis had a serum creatinine greater than the upper limit of normal for the laboratory at some time during the study, only one study subject developed an increase in serum creatinine at the time of her episode of nephrolithiasis. Nephrolithiasis occurred any time from study day 193 to day 539 and symptoms lasted from three to 29 days. Only one subject required hospitalization, and only one subject was taken off the study after the development of nephrolithiasis.

Although this additional safety data from Merck 068 did not reveal any new or unexpected types of adverse events, the safety data did confirm the high incidence of adverse events in HIV-infected children receiving indinavir. In addition to the six subjects who experienced nephrolithiasis during the first 24 weeks of the study, another four subjects had nephrolithiasis during the second 24 weeks of the study for an overall incidence of 40% during the first 48 weeks of the study. Increases in serum creatinine were also common and were noted in almost half of the study subjects. More than half of the subjects developed hematuria or pyuria. In conclusion, the Safety Update Report again showed that HIV-infected children experienced an unacceptably high rate of adverse events while receiving indinavir; these results only reinforce the need for further safety information concerning the use of indinavir 500 mg/m² in pediatric patients.

C. ACTG 395

A complete study report for the first 24 weeks of ACTG 395 was submitted in the Safety Update Report. A study report for the first 16 weeks of ACTG 395 had been previously submitted and was described in Sections III. E and F of this review. Because the first 16 of the 24 weeks have been reviewed in detail in these sections, the results of the entire 24 weeks will only be summarized.

Three study subjects were removed from ACTG 395 because of adverse events during the first 16 weeks of the study; another subject withdrew from the study. No subjects were either removed from the study or withdrew during weeks 17 to 24. There were no deaths during the study.

Efficacy results using surrogate marker endpoints are shown in Table 26.

Table 26: Number of Subjects with Undetectable HIV RNA Levels in ACTG 395 (Dropouts as Failures)

	HIV RNA < 400 copies/ml
At 16 Weeks	9/16 (56%)
At 24 Weeks	8/16 (50%)

Source: Datasets, Safety Update Report

As shown in the table above, one-half of the subjects enrolled in ACTG 395 had undetectable plasma viral levels at 24 weeks. However, only 12 subjects completed the first 24 weeks of this study, and it is hard to reach any conclusions about the efficacy of indinavir in HIV-infected children because of the small number of subjects studied and the lack of a comparator arm.

All study subjects in ACTG 395 experienced adverse events while on study. All 16 reported clinical adverse events, which was unchanged from the findings at 16 weeks. Nine subjects (56%) had clinical adverse events that were described as drug-related. Only two subjects had serious clinical adverse events and both were felt to be drug-related (vomiting and urolithiasis). Three subjects were withdrawn from the study because of clinical adverse events including nausea and vomiting, nephrolithiasis and interstitial nephritis, and nephrolithiasis. The clinical adverse events seen most frequently were abdominal pain (four subjects), flank pain (two subjects), and vomiting (five subjects). Urogenital abnormalities were noted in five or 31% of subjects and included two subjects with interstitial nephritis and three with nephrolithiasis.

According to the ACTG 395 study report, 15 of the 16 subjects experienced laboratory adverse events. None were reported as serious, and no subjects were removed from the study because of laboratory adverse events. Nine study subjects had laboratory adverse events that were described as drug-related. The most commonly seen laboratory adverse events included increased serum cholesterol (10 subjects), increased triglycerides (seven subjects), increased total bilirubin (five subjects), and increased serum creatinine (five subjects). Three study subjects had abnormalities on urinalysis including hematuria, pyuria, proteinuria, crystalluria, and increased leukocyte esterase. Of the three subjects with pyuria, two had nephrolithiasis, two had interstitial nephritis, and all three had mild increases in serum creatinine.

Laboratory data for individual study subjects were reexamined to identify the incidence of certain laboratory abnormalities that have been seen commonly in adults receiving indinavir. According to the Crixivan package circular, asymptomatic hyperbilirubinemia (total bilirubin \geq 2.5 mg/dL) has been reported in 10% of adult subjects.¹ In ACTG 395,

five children had increased bilirubin values which were reported as adverse events and nine had bilirubin levels greater than the upper limit of normal for the laboratory; however, the none of the total bilirubin levels were greater than 2.5 mg/dL. While increases in serum creatinine are uncommon in adults receiving indinavir, five subjects (31%) in ACTG 395 had increased creatinine levels reported as adverse events. Because of the concern about the renal toxicity of indinavir in pediatric patients, results from urinalyses obtained during ACTG 395 were reviewed using standard laboratory criteria described in Table 1 of the appendix. Using these criteria, four subjects or 25% had nephrolithiasis, 12 (75%) had either hematuria or occult blood in their urine, 10 (63%) had pyuria, 7 (44%) had crystalluria, and 7 (44%) had proteinuria. On comparison of the 16 and 24 week data, one additional subject developed nephrolithiasis, three hematuria, three pyuria, and one proteinuria after 16 weeks but before 24 weeks. Although no subjects had irreversible decreases in renal function, two subjects had serum creatinine levels which were greater than the upper limit of normal for laboratory and five had increases in creatinine which were listed as adverse events in the study. See Table 5 in the appendix for a summary of individual study subject laboratory findings related to the urinary tract.

In summary, the review of the efficacy and safety data for the entire 24 weeks of ACTG 395 did not change the conclusions reached after the review of the 16-week data (See Section III.F.). Some efficacy of an antiretroviral regimen containing indinavir, stavudine, and lamivudine was demonstrated in these study subjects, but there were so few subjects enrolled in this study and there was no comparator arm, so no definitive conclusions about efficacy can be made. The safety concerns that were described in the review of the 16-week data were unchanged after the review of the entire 24-week datasets. During ACTG 395, a large number of children developed urinary tract abnormalities including hematuria and pyuria. In addition, it is of particular concern that four subjects developed nephrolithiasis and two interstitial nephritis. Therefore, the results of this small study did not support either the safety or efficacy of the use of indinavir 500 mg/m² in HIV-infected children.

D. Evaluation of Nephrolithiasis

A separate description of nephrolithiasis-associated adverse events occurring in all three pediatric clinical trials was included in the Safety Update Report. An adverse experience associated with nephrolithiasis was defined as any episode determined by the investigator to represent nephrolithiasis clinically, including, but not limited to, unexplained flank pain with or without hematuria, including microscopic hematuria. In order to more accurately assess the frequency and incidence of nephrolithiasis in HIV-infected children receiving indinavir in these studies, all data from the initiation of each study were included in this summary.

The clinical picture of nephrolithiasis in children was similar to that previously described in adults. Many children had nephrolithiasis described as mild or moderate but nine of 20 episodes were described as serious. Although increases in serum creatinines were reported, no study subjects had a permanent decline in renal function. Other signs and

symptoms associated with nephrolithiasis included hypertension, hydronephrosis, and changes in renal structure on ultrasound. Although most subjects continued to receive indinavir, five subjects were removed from the study because of nephrolithiasis. In addition, five of the 15 subjects remaining on indinavir experienced a second episode of nephrolithiasis.

Three different tools were used by the sponsor to measure the occurrence of nephrolithiasis in the three pediatric clinical trials included in this supplemental New Drug Application. The frequency of nephrolithiasis was determined by analyzing the proportion of subjects who developed nephrolithiasis. Overall, 20 of 70 (29%) subjects receiving indinavir 500 mg/m² every eight hours developed nephrolithiasis. The frequency varied between clinical trials with 10/25 (40%) experiencing nephrolithiasis in Merck 068, 4/16 (25%) in ACTG 395, and 6/29 (21%) of subjects on 500 mg/m² in Merck 041. The incidence of nephrolithiasis was calculated to provide information about the frequency of nephrolithiasis over time. The incidence of nephrolithiasis for all three clinical trials was 5.9 nephrolithiasis events per 10 patient-years. The incidence rates were not statistically significantly different between the studies; the incidence of nephrolithiasis in Merck 068 was 4.6 events per 10 patient-years and in ACTG 395 was 7.3 events per 10 patient-years. The incidence rates of nephrolithiasis were calculated for both the 350 mg/m² and the 500 mg/m² dose in Merck 041 and the incidence was higher for the group of subjects receiving 500 mg/m² (9 events per 10 patient-years) compared to those receiving 350 mg/m² (2.1 events per patient-years). Finally, Kaplan-Meier analyses were performed to assess the time to first nephrolithiasis event. In these analyses, there was no statistically significant difference between Merck 068 and ACTG 395. Nephrolithiasis did appear to occur earlier in subjects receiving 500 mg/m² in Merck 041 than in those receiving 350 mg/m².

E. Other Sources

Safety information from sources other than the case report forms of Merck 041, Merck 068, and ACTG 395 were also included in the Safety Update Report. Investigators in these three studies were required to report all serious adverse events to the applicant within 24 hours; reports for adverse events in four subjects were received after the cutoff date for final case report forms to be included in the Safety Update Report. These four subjects experienced nine adverse events including fever, pneumonia, varicella, and mastoiditis; none were judged to be related to indinavir. Reports from the Worldwide Adverse Experience System (WAES) database were also included. This is a voluntary spontaneous reporting system and receives reports from clinical trials, expanded access programs, marketed use, and the medical literature. During a six month time period (August 15, 1999 to January 10, 2000), there were nine reports of adverse events occurring in children receiving indinavir. These included five subjects with flank pain, two with urolithiasis, two with increased serum creatinine, and one with jaundice.

Finally, five adverse event reports from Merck 065, a pilot study of the effect of antiretroviral therapy on coagulation factors in hemophiliacs, post marketing surveillance studies and temporary authorization for use programs were also included in the Safety

Update Report. Two of the subjects experienced *nephrolithiasis*, *one pyuria* and hyperuricemia, one urinary retention due to a urethral valve, and one pancreatitis. Only the nephrolithiasis was felt to be definitely related to indinavir use. The patient with hyperuricemia and pyuria had preexisting renal disease, and it was unclear whether the preexisting renal disease was the cause of his signs and symptoms. There were no deaths in any of these reports. The safety data from sources other than the case report forms of the three pediatric studies included in the sNDA application confirm the renal toxicity noted during the three pediatric clinical studies.

VI. August 31, 2000 Addendum

This addendum to the supplemental NDA was made in response to a telephone facsimile in which the Division requested any additional information to support the approval of this application. In this addendum, the applicant agreed with the Division that indinavir troughs were lower in children than in adults but stated that approval of the proposed pediatric dosing regimen could be based on pediatric efficacy and safety data. In order to support the efficacy and the durability of response of indinavir 500 mg/m² every eight hours in HIV-infected children, 60-week results from Merck 068 were submitted. In the applicant's analysis, 56% of the 25 children in Merck 068 had plasma HIV RNA levels less than 400 copies/ml at 60 weeks. In addition, the applicant combined the 24 week efficacy data from Merck 068 and ACTG 395 to summarize the efficacy results of indinavir in children; in this analysis 59% of subjects had HIV RNA levels less than 400 copies/ml at 24 weeks. Finally, a summary of indinavir pharmacokinetic and pharmacodynamic relationships in pediatric patients from the applicant's data and from the literature was also included. This summary was provided to support the applicant's position that there is no relationship between indinavir trough and efficacy.

VII. Other Data, Use and Interpretation Issues

A. Financial disclosure

There were 144 investigators listed on the 3454 financial disclosure form provided by the applicant. Nineteen investigators did not provide financial information to the applicant and eight investigators were no longer with the institution that was involved with the studies. The applicant certified that none of these investigators received significant payments or entered into any financial arrangement with the applicant during the reporting period. The Division acknowledges that steps have been taken to minimize the potential for bias.

VIII. Labeling Issues

It was considered important that the Crixivan package circular reflect the high incidence of adverse events noted in HIV-infected children receiving indinavir 500 mg/m² every eight hours. In order to bring about changes in the package insert to support these safety concerns, it was decided to change the supplement from a pediatric efficacy supplement to a labeling supplement with the consent of the Division Director. In addition,

recommendations for labeling changes were made by the Division and discussions and negotiations about these changes were held with the applicant. It was decided that safety information concerning the use of indinavir in pediatrics would be appropriate for the Clinical Pharmacology section, the Warnings section, and the Precautions, Pediatric Use section with limited information on efficacy included in the Precautions, Pediatric Use section.

IX. Recommendation for Regulatory Action

After review of the information made available by the applicant, the relevant scientific literature, and the transcript of the July 2000 Division of Antiviral Drug Products Advisory Committee; it was decided that a safe and efficacious dose of indinavir for use in HIV-infected children had not been determined. On review of the pharmacokinetic data submitted, it was determined that the indinavir dose proposed for use in children, 500 mg/m² every eight hours, was not comparable to the adult 800 mg every eight hour dose. Therefore, safety and efficacy information for children could not be extrapolated from safety and efficacy data obtained in studies of HIV-infected adults and the use of indinavir at this dose in children had to be supported by the results of pediatric clinical studies alone. Two clinical trials did show that more than one-half of HIV-infected children had plasma HIV RNA levels less than 400 copies/ml after 24 weeks of treatment with an antiretroviral regimen including indinavir, stavudine, and lamivudine. However, both of these studies were small, open-label, and had no comparator arms; only 31 children reached 24 weeks of treatment in these studies. There were simply not enough patients in these uncontrolled studies to be able to confidently determine the efficacy of indinavir in pediatrics. In addition, significant safety concerns were raised in the pediatric clinical trials. The safety profile of indinavir in children resembled that seen in adult studies; however, the incidence of adverse events, particularly renal toxicities, was much higher in children. Of the 41 children enrolled in the two clinical efficacy studies, more than 80% had some type of abnormality noted on urinalysis, 10 developed nephrolithiasis, and two developed interstitial nephritis.

It was decided to change this supplement from a pediatric efficacy supplement to a labeling supplement so that the Crixivan package circular would accurately reflect the Division's concerns about the lack of a safe and effective dose for children. This would also allow for a description of the pediatric safety concerns in the package circular. Information concerning the increased incidence of adverse events in the pediatric population should be available to physicians who are considering "off-label" use of indinavir in children. Therefore, the Division's concerns were discussed with the applicant and the Crixivan package circular was amended to reflect these conclusions.

X. References

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efficacy and safety trial (BEST). Program and abstracts of the XIII International AIDS Conference; July 9-14, 2000; Durban, South Africa. Abstract WeOrB484.

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XII. Appendix

Table 1: Urinalysis Abnormality Definitions: Limits for Normal Values¹

	Merck 068	ACTG 395	FDA Review²
Test	Range	Range³	Range
Urine wbc's	0 - 2, 0 - 5, or 0 - 12 wbc/hpf	None or 0 - 0.5	M: 0 - 3 F: 0 - 5
Urine rbc's	0 - 2, 0 - 3, or 0 - 8 rbc/hpf	None	0 - 2
Urine blood	None	None	None
Urine protein	None	None or 0 - 0.5	None
Urine crystals	None	None	None
Urine casts	None	None or 0 - 0.5	None
Urine leukocyte esterase	None	None	None

Source: December 23, 1999 submission Tables ----, January 24, 2000 submission Tables ---

1. This table does not include all laboratory tests that were evaluated during these studies.
2. Normal limits for laboratory values were obtained from Nelson Textbook of Pediatrics - 15th Edition (RE Behrman, RM Kliegman, AM Arvin eds. W.B. Saunders Company, Philadelphia, PA, 1996; Interpretation of Pediatric Tests. J Wallach Boston: Little, Brown, and Company. 1983; Principles and Practice of Pediatrics - 2nd Edition. CD DeAngelis, RD Feigin, JA McMillan, JB Warshaw eds. Philadelphia: J.B. Lippincott Company, 1994.
3. Values reported for patients participating in ACTG 395 are provided on a numeric scale from 1 to 9 in which one is negative, two is rare, three is mild (6-10), etc. The exact values from microscopic examination of the urine were not provided for ACTG 395.

Table 2: Merck 041: Safety Summary for Study Subjects Receiving Indinavir 500 mg/m²

Patient Number	Nephrolithiasis	Hematuria or Occult Blood	Pyuria	Crystalluria	Proteinuria	Maximum Cr (Abnormal)
0712	N	N	N	N	N	0.4 (N)
0754	N	N	N	N	N	0.6 (N)
0707	Y	Y	Y	N	Y	0.8 (N)
0716	Y	Y	Y	N	Y	0.8 (N)
0706	N	Y	Y	Y	Y	1.3 (N)
0709	N	N	N	N	N	1.1 (N)
0710	N	N	N	N	N	0.8 (N)
0753	N	Y	Y	N	N	0.9 (N)
0717	N	N	N	N	N	0.9 (N)
0718	N	N	N	Y	N	0.6 (N)
0714	N	N	N	N	N	0.8 (N)
0708	N	N	N	N	N	0.8 (N)
0749	Y	Y	N	Y	Y	0.8 (N)
0747	Y	Y	N	N	N	0.8 (N)
0704	N	N	N	N	N	0.8 (N)
0748	N	Y	Y	N	Y	0.9 (N)
0701	N	N	N	N	N	1.0 (N)
0705	N	N	N	Y	N	0.6 (N)
0750	N	N	N	N	N	0.6 (N)
0752	N	Y	N	N	N	0.9 (N)
0711	N	N	N	Y	N	0.9 (N)
0746	N	Y	Y	N	Y	0.6 (N)
0735	Y	Y	Y	Y	Y	0.6 (N)
0703	N	N	N	N	N	0.8 (N)
0751	Y	Y	Y	N	Y	0.8 (N)
0742	N	N	N	Y	N	0.8 (N)
0739	N	Y	Y	N	N	1.1 (N)
0740	N	N	N	Y	Y	0.8 (N)
0733	N	Y	Y	Y	N	0.8 (N)

Table 3: Merck 068: Safety Summary

Patient Number	Nephrolithiasis	Hematuria or Occult Blood	Pyuria	Crystalluria	Proteinuria	Maximum Cr (Abnormal)	Peak on Day 14
101	Y	Y	Y	N	N	1.2 (Y)	20490.2
102	N	Y	Y	N	N	0.7 (N)	4422.9
201	N	N	N	N	N	0.8 (N)	31275.3
202	N	Y	Y	N	N	1.3 (Y)	24693.6
204	N	Y	N	Y	Y	0.7 (N)	22943.5
206	N	N	N	Y	N	0.8 (N)	21722.4
304	N*	Y	Y	N	Y	1.2 (Y)	4711.6
401	N*	N	N	N	N	0.8 (N)	13610.9
501	Y	Y	Y	N	N	2.1 (Y)	---
502	N	Y	Y	N	N	1.3 (Y)	---
601	N	N	N	N	N	0.8 (N)	20198.2
602	N*	Y	N	N	N	0.7 (N)	33704.0
603	N*	N	N	N	N	0.9 (Y)	17367.6
604	N	Y	Y	N	N	0.8 (Y)	12771.6
605	N	Y	N	N	N	1.0 (N)	20237.5
606	Y	N	Y	N	N	0.7 (N)	10847.1
607	Y	Y	Y	N	N	1.1 (Y)	21501.8
608	Y	Y	Y	Y	N	0.8 (N)	38047.2
609	N	Y	Y	N	Y	0.9 (Y)	90.7
610	N	N	N	N	N	0.8 (N)	14319.8
611	N	N	N	Y	N	0.6 (N)	33940.4
613	Y	N	Y	N	Y	0.8 (N)	32555.0
614	N	Y	Y	Y	N	1.0 (N)	6873.0
615	N	N	N	N	N	0.7 (N)	21123.3
616	N	Y	Y	N	N	0.9 (Y)	15968.5

*Developed nephrolithiasis after 24 weeks

Table 4: ACTG 395: Safety Summary – 16 Week Results

Patient Number	Nephrolithiasis	Hematuria or Occult Blood	Pyuria	Crystalluria	Proteinuria	Maximum Cr (Abnormal)	Peak on Day 14
0065	N	N	N	N	Y	0.6 (N)	?
0423	N	Y	Y	Y	N	0.5 (N)	15456.1
0116	N	Y	Y	N	Y	0.6 (N)	18842
0354	N	Y	Y	Y	N	0.7 (N)	26178.9
0371	N	Y	Y	N	N	0.6 (N)	13501.1
0551	N	N	Y	N	N	0.5 (N)	12453.6
0530	N	N	N	N	N	0.8 (N)	?
1357	N	N	N	N	Y	0.8 (N)	12346.9
3399	Y	Y	Y	N	N	0.8 (N)	1078
4667	N*	N	N	N	N	0.5 (N)	1258.4
4668	N	Y	N	Y	Y	0.7 (N)	19929.6
0025	N	Y	N	Y	Y	0.6 (N)	8507.4
0049	Y	N	N	N	N	0.6 (N)	?
0084	N	Y	N	Y	N	0.6 (N)	11170.7
0173	Y	Y	Y	Y	Y	0.9 (Y)	?
0174	N	N	N	Y	N	0.4 (N)	?

*Developed nephrolithiasis after 16 weeks

Table 5: ACTG 395: Safety Summary – 24 Week Results

Patient Number	Nephrolithiasis	Hematuria or Occult Blood	Pyuria	Crystalluria	Proteinuria	Maximum Cr (Abnormal)	Peak on Day 14
O065	N	Y	N	N	Y	0.6 (N)	?
O423	N	Y	Y	Y	N	0.5 (N)	15456.1
O116	N	Y	Y	N	Y	0.6 (N)	18842
O354	N	Y	Y	Y	N	0.7 (N)	26178.9
O371	N	Y	Y	N	N	0.6 (N)	13501.1
O551	N	Y	Y	N	N	0.5 (N)	12453.6
O530	N	N	N	N	N	0.8 (N)	?
1 357	N	N	N	N	Y	0.8 (N)	12346.9
3 399	Y	Y	Y	N	N	0.8 (N)	1078
4 667	Y	Y	Y	N	N	0.5 (N)	1258.4
4 668	N	Y	Y	Y	Y	1.0 (N)	19929.6
O025	N	Y	N	Y	Y	0.6 (N)	8507.4
O049	Y	N	N	N	N	0.6 (N)	?
O084	N	Y	Y	Y	Y	0.8 (Y)	11170.7
O 173	Y	Y	Y	Y	Y	0.9 (Y)	?
O 174	N	N	N	Y	N	0.4 (N)	?

/s/

Mellisse Baylor
2/13/01 12:51:34 PM
MEDICAL OFFICER

Stanka Kukich
2/13/01 01:30:08 PM
MEDICAL OFFICER
Additionally, please refer to group leader's memorandum

Debra Birnkrant
3/9/01 12:51:40 PM
MEDICAL OFFICER

Christine Lincoln
3/15/01 03:22:46 PM
CSO

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-685 SE8-043

DRUG: Crixivan[®], Indinavir Sulfate

Submission Dates: 12/22/1999, 01/13/2000, 05/25/2000, 05/04/2000, 05/03/2000, 08/18/2000, 10/19/2000, 03/31/2001

Formulation: 100 mg Indinavir Capsules

Applicant: Merck and Co, Inc.

Reviewer: Robert O. Kumi, Ph.D.

EXECUTIVE SUMMARY

Indinavir sulfate (Crixivan) is a protease inhibitor approved for treatment of HIV, in combination with other antiretroviral agents, in adults at a dose of 800 mg every 8 hours. In this submission, the applicant requests approval of a pediatric indication for indinavir (IDV) in children 3 years of age and older who are able to swallow capsules. The proposed dosage of Crixivan in pediatric patients is 500 mg/m² every 8 hours. Three clinical studies were performed to assess the efficacy, safety and pharmacokinetics of IDV in pediatric patients. Information regarding a new 100 mg capsule was also presented. The 100 mg capsule was approved in April 2000 in a Chemistry Supplement.

Pharmacokinetics of IDV in pediatric patients following administration of 500 mg/m² IDV every eight hours were not comparable to those in adults following administration of 800 mg IDV every 8 hours and exposure-response information was absent. Pharmacokinetic information provided in this submission was considered insufficient to support approval of the pediatric regimen, because the information does not indicate that a safe and effective dose has been identified. The proposed pediatric regimen was efficacious in the pivotal clinical studies. However, the Medical Reviewer considered the small number of patients and the short duration of the trial inadequate to support approval of the pediatric indication. There are also some safety concerns, particularly related to renal adverse events. The Division of Antiviral Drug Products does not intend to approve the proposed pediatric indication. The label will be updated to report the findings from the pharmacokinetic, safety, and efficacy studies, but will indicate that a safe and effective dose for IDV in pediatric patients has not been established.

ISSUES

1. Are the pharmacokinetic exposure measures, AUC, C_{max}, and C_{min}, comparable in HIV-infected pediatric patients and adults? (Pages 3-4)
2. Has an exposure-response relationship been identified in adults or pediatric patients receiving indinavir, and does it allow for distinction among different exposure measures, particularly C_{min}? (Pages 5-7)
3. Are the exposures produced by administration of the intact capsule comparable enough to those of the opened capsule in applesauce slurry to allow for switching of the two formulations? (Page 8)
4. Are there any specific safety concerns associated with indinavir administration in pediatric patients? (Page 9)

Introduction

Studies 068 and 395 evaluated the pharmacokinetics (PK), efficacy, and safety of *de novo* triple combination therapy of IDV with stavudine (d4T) and lamivudine (3TC) in HIV-infected pediatric patients. The pediatric patients were naïve to protease inhibitors and to at least one of the two nucleoside reverse transcriptase inhibitors (d4T or 3TC) administered. Study 395 had a similar design to Study 068, with the exception of an additional PK study involving the use of IDV in an applesauce slurry. According to the applicant, Study 395 was initiated because of slow enrollment in Protocol 068. The Medical Reviewer (Melisse Baylor, M.D.) indicates that the patient populations are sufficiently similar (see Table I: Demographics, in individual Study Reports) to combine results from both studies. This clinical pharmacology and biopharmaceutics (CPB) report will review the pharmacokinetic results presented in this submission.

Relevant Submissions

- Summary of Merck's pediatric program in March 1999; IND 41,413 SN 820
- Clinical pharmacokinetics, clinical efficacy, and safety data to support use of CRIVAN in treatment of HIV-1 in pediatric patients are provided in NDA 20-685 SE8-043
- Revisions to product label to reflect new information in NDA 20-685 SE8-043

Studies Submitted and Reviewed

Pivotal Studies

- Protocol 068 Clinical Study Report (24-week data)- Pediatric Patients (n= 19 completed)
- ACTG 395 Clinical Study Report (16-week data)- Pediatric Patients (n= 12 completed)

Supportive Studies and Information

- Protocol 041 Dose-ranging study- Pediatric Patients
- Protocol 058 Crossover study of indinavir slurry- Adult Patients
- Protocol 021 Historical Data for Comparison- Adult Patients
- Protocol 069 Clinical Summary Report- Adult Patients (BID vs. TID indinavir regimen)
- CMC Section containing information on 100 mg capsule for pediatric patients

Selection of the Pediatric Dosing Regimen (Study 041)

The applicant selected the proposed pediatric regimen of 500 mg/m² every 8 hours on the basis of results from Study 041. Study 041 was a dose finding study conducted in pediatric patients aged 4-15 years. Doses of IDV were calculated using body surface area (BSA) approximate to adult doses of 400, 600, and 800 mg q 8hr, respectively. For this calculation, it was assumed that the average adult BSA was 1.73 m². The results of the calculations were rounded off to yield the tested pediatric doses: 250 mg/m² (e.g., 400 mg/1.73 m² = 231 mg/m²), 350 mg/m², and 500 mg/m² every 8 hours (q 8hr). According to the applicant, pediatric patients receiving 500 mg/m² IDV q 8hr had exposure measures (AUC and C_{max}) that were comparable to those produced in adult patients receiving 800 mg IDV q 8hr.

Age Distribution Studied and Effect of Age on Clearance

The average age of children participating in the pivotal clinical trials was 8 years old. Stratification of ages into two groups, 2-11 years and 12-18 years, demonstrated an apparent under-representation of children from the 12-18 year group. The age range in the two pivotal trials was 4 to 15.

No clear relationship between IDV apparent clearance (CL/F, using Dose/AUC as a surrogate for CL/F) and age was shown in the pediatric population. However, the CL/F of IDV in pediatric patients was clearly greater than in adult patients, as evidenced by the higher C_{max} and lower C_{min} in pediatric patients compared to adults. It is noteworthy that _____ report that a correlation appeared to occur between

weight-adjusted IDV CL/F and the age of children. Younger patients tended to have higher CL/Fs than older children.

SYNOPSIS

A. Comparability of Pediatric and Adult Pharmacokinetic Exposure (Use of Confidence Intervals)

The exposure of indinavir (IDV) in children receiving combination therapy including 500 mg/m² IDV q 8hr was not comparable to those in adults receiving 800 mg IDV q 8hr as monotherapy or as part of combination therapy. Assessment of comparability between these two populations was based on the examination of individual data, arithmetic and geometric means (90 % confidence intervals) for the exposure measures AUC, C_{max}, and C_{min}.

As shown in Table I, arithmetic mean trough concentrations in pediatric patients receiving 500 mg/m² q 8hr were approximately one half the value observed in adult patients receiving 800 mg q 8hrs. On the other hand, arithmetic mean AUCs and C_{max}s were comparable or slightly higher in pediatric patients than in adult patients. Adult AUC and C_{max} values were less variable than pediatric AUC and C_{max}.

Table I: Indinavir Exposure Measures from Adult Studies 021, 031 and 035 (Re NDA 20-685, CPB Review), and Pediatric Studies 395 and 068

Exposure Measure	Adult Studies 021, 031 and 035 (N = 36)	Pediatric Studies 068 and 395 (N = 32)
AUC _{0-8 hr} (nM·hr)	32,067 ± 11685	38,742 ± 24098
C _{max} (nM)	14,032 ± 3977	17,181 ± 9808
C _{8 hr} (nM)	252 ± 203	134 ± 91 [^]

[^] n = 28

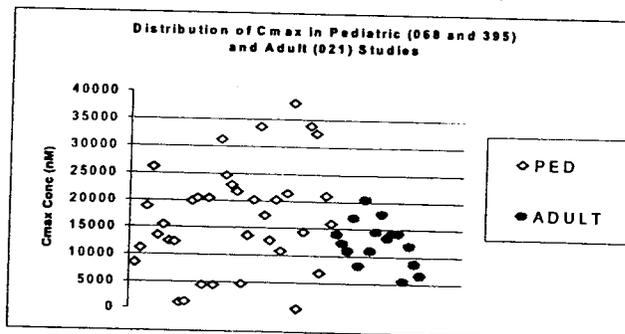
Geometric mean ratios (pediatric studies 068 and 395:adult study 021) for the exposure measures, and associated 90 % confidence intervals are presented in Table II.

Table II: Indinavir Exposure Measures (Geometric Mean Ratio, 90% CI)- Pediatric Patients (Studies 395 and 068)/Adult Patients (Study 021)

Exposure Measure	GMR (Pediatric:Adult)	90% Confidence Intervals
AUC _{0-8 hr} (nM·hr)	0.96	0.59 – 1.55
C _{max} (nM)	1.02	0.61 – 1.70
C _{8 hr} (nM)	0.59	0.40 – 0.87

The use of adult PK data from Study 021 for the pediatric-to-adult comparisons was acceptable because adult PK data were comparable across all adult studies. The geometric mean ratios for AUC and C_{max} were approximately 1, and C_{min} was significantly less than 1. Confidence intervals for C_{max} and AUC geometric mean ratios crossed the value of 1 and were wide, apparently due to pharmacokinetic variability (figure 1). The CI associated with C_{min} was narrower (less variable) and did not cross the value of 1, indicating that the geometric mean C_{min} in pediatrics was lower than that in adults. The applicant's interpretation of the confidence intervals differed from those of the Agency.

Figure 1: Distribution of C_{max} in Pediatric (Studies 068 and 395) and Adult Studies (Study 021)



Confidence Intervals

Supported by statistical principles (power, observed variability and sample size), the applicant indicated that a 90 % confidence interval range of 0.5 – 2.0, for the ratio of geometric means, would show general comparability between adults and pediatric patients. Prior to submission of this sNDA, the Agency informed the applicant that this comparability region is unacceptable, because it is not supported by exposure-response data.

How have confidence intervals been used historically to show comparability of exposure?

Generally, 90 % CI limits (0.8 – 1.25) of the geometric mean ratio (GMR) for exposure measures are used to establish bioequivalence (BE) between different products. This BE guideline may be extrapolated to the comparison of exposure measures obtained from other PK studies, such as drug-drug interaction, food effects and adult-to-pediatric comparisons. For an adult-to-pediatric exposure comparison, flexibility can be applied to the guideline, because it is often impractical or difficult to exactly match all exposure measures. However, in choosing a no-effect or no-difference CI range, the clinical significance (e.g. exposure-response relationship) of the confidence region must be taken into consideration. As previously noted, the applicant's rationale for selecting this relatively wide CI range of 0.5-2.0 appears to have a valid statistical basis. However, the clinical ramifications of such a wide range for IDV were not presented, and may not have been considered by the applicant. Generally, CIs are widened when

- variability exists due to extrinsic factors
- small patient numbers are present (CI calculation affected by number of patients)
- inherent PK variability of drug occurs due to metabolism or absorption.

Ultimately, sufficient supporting clinical evidence, such as an exposure-response relationship, should be available to justify the widening of the CI to claim “no effect”.

What evidence is available to support or refute the widening of confidence intervals for indinavir exposure measures to show comparability?

The applicant's proposed range is unacceptable for IDV because:

- **Lower bound** of 0.5 presents the potential for lack of efficacy and possibility of resistance emerging due to low IDV exposure.
- **Upper bound** of 2.0 presents the potential for increased incidence of adverse events (e.g., nephrolithiasis) which are associated with increased IDV exposure (high C_{max} and AUC)

The hypotheses concerning the lower and upper CI bounds are supported by observations in the literature concerning protease inhibitors, and dose escalation studies with IDV. Safety data from previous adult studies with IDV (Study 021 and the literature) do not support an increase in CI upper limit for IDV. In particular, increasing the upper bound with IDV is problematic because administration of IDV in adults at doses higher than the recommended dose (1000 mg vs. 800 mg q 8hr) produced an increase in the occurrence of nephrolithiasis. Changing the IDV dose from 800 mg to 1000 mg q 8hr resulted in the following Day 15 exposures:

- Arithmetic Mean C_{max} (nM): 800 mg q 8h \approx 13,000; 1,000 mg q 8h \approx 17,000
- Arithmetic Mean AUC (nM·hr): 800 mg q 8h \approx 31,000; 1,000 mg q 8h \approx 38,000

The proposed pediatric dose produces average exposures comparable to the 1000 mg q 8hr dose in adults; therefore, further increases in exposure, via widened CIs, may pose additional safety concerns.

What were the conclusions regarding IDV exposures, based on confidence intervals: Applicant vs. FDA

The applicant concluded that AUC and C_{max} were generally comparable in pediatric and adult patients receiving the proposed pediatric dose and the approved adult dose, respectively, because 90 % confidence CIs for the geometric mean ratios (GMR; pediatric: adult) were between 0.5 and 2.0. The FDA did not consider the AUC and C_{max} to be comparable in the two populations, because the evidence supporting the creation of an essentially new “therapeutic equivalence window” for IDV was insufficient. AUC and C_{max}

were more variable in the pediatric patients than in adult patients. Based on GMRs and 90 % CIs, both the applicant and the FDA agreed that C_{min} in the pediatric patients was lower than in adult patients.

B. Exposure-response relationship(s) for HIV-infected patients receiving indinavir.

No significant exposure-response relationships were identified in the pediatric studies (068 and 395), and none have been identified in adult studies (021, 035, and 031). The current studies were not designed to determine what exposure measure(s) was associated with a pharmacodynamic response measure (efficacy or safety). The OCPB review for the original IDV NDA indicates that the applicant observed a general relationship between pharmacokinetic exposure measures and increased efficacy (using surrogate markers) when data were combined across several dose levels. However, the OCPB reviewer concluded that "formal PK/PD relationships can not be established with the data that were collected". The data presented did not indicate that a particular exposure measure is most important for efficacy. Some articles in the literature indicate that high AUC and C_{max} may be associated with increased incidence of nephrolithiasis. Efficacy was evaluated at only one dose in the pediatric studies, and no meaningful exposure-response relationships were found. It is noteworthy that AUC and C_{max} were highly correlated with each other, but were not correlated with C_{min} .

1. Potential significance of IDV C_{min} value and inhibitory concentration (IC)

For protease inhibitors, the literature suggests that C_{min} is critical in determining efficacy and resistance development. If the dosing regimen does not provide and maintain adequate drug levels in plasma, treatment with these agents is ineffective and the patient may develop resistance to treatment by the drug and possibly to other drugs in that class of compounds. The minimum plasma concentration required for IDV efficacy is not clear; however, in the original NDA, the applicant stresses the importance of using an optimal IDV dosage regimen to insure that the IDV concentrations are above 100 nM throughout the dosing interval. The designation of 100 nM as a critical value was apparently derived from *in vitro* studies, which indicated that the IC_{95} was between 25-100 nM. The IC_{95} value determination did not appear to take protein binding into account (IDV is approximately 60 % plasma protein bound). In a recent communication (August 2000) to the Agency, the applicant reported that the wild type HIV IC_{95} is 34 nM (68 nM accounting for serum protein binding). Arithmetic mean C_{min} in the adult clinical efficacy studies was approximately 250 nM, compared to 130 nM in the pediatric studies. If mean values are considered as representative of an individual's value, the IDV C_{min} produced by the proposed pediatric regimen and the recommended adult regimen are above the IC_{95} . However, adult clinical efficacy was not demonstrated in any clinical trials where arithmetic mean C_{min} was less than 200 nM. Since submission of the original NDA, the applicant has not provided additional data to support or refute the somewhat arbitrary cut off value.

What is the applicant's perspective on the significance of C_{min} with indinavir?

In the pediatric application, the applicant implies that attainment of low C_{min} (< 100 nM) is not an important determinant of efficacy, which is in direct contradiction to their previous assertions and that of the findings of other investigators. The applicant supports this assertion with the results from Studies 068 and 395 and a study conducted by Gatti *et al* in which the 500 mg/m² q 8hr dose was administered. In the Merck studies, IDV was efficacious over a 16-week treatment period, and in the Gatti study, efficacy was observed over a one year period, even with low trough values. The applicant indicates that these results suggest attainment of IDV concentrations at the high end of the concentration-response curve, therefore the applicant does not expect low IDV exposure (C_{min} < 100 nM) to contribute to suboptimal antiviral response. No additional exposure or concentration-response data were provided to support this claim. The Medical Reviewer notes that these studies were conducted in a relatively small number of patients and for a short duration, and are not considered indicative of long term efficacy.

What evidence is available in the literature about the relationship between C_{min} and indinavir efficacy?

As previously mentioned, none of the IDV efficacy studies in the literature have investigated and identified the critical C_{min} value for efficacy. However, certain C_{min} values are targeted by investigators, apparently based on personal preference or experience. None of the studies have provided strong evidence that low C_{min} leads to decreased efficacy. In a published pediatric study by Kline *et al.*, the IDV dose was changed from 500 mg/m² q 8hr to 500 mg/m² q 6hr, because most subjects receiving the 500 mg/m² q 8hr IDV dosage regimen had IDV trough levels that were below 160 nM (100 ng/mL). If 160 nM is the critical minimum trough level, the study by Kline *et al.* does not support the use of the applicant's proposed dose in pediatric patients. From a discussion with another investigator _____ teleconference, held in May 2000) involved in AIDS research, DAVDP was informed that the proposed IDV dosage regimen was inappropriate. _____ indicated that, based on their clinical experience, more frequent dosing (e.g. q 6hr rather than q 8hr) or use of alternative treatment regimens (e.g. low dose ritonavir as PK "enhancer") would be most suitable for IDV dosing in pediatric patients. In an article by Fletcher *et al.*, the authors indicate that the 500 mg/m² q 8hr IDV dose is not likely to show long term efficacy, because IDV levels would not be maintained above the putative critical C_{min} in the majority of patients. Fletcher *et al.* observed a statistically significant correlation between AUC and C_{min} and antiviral response in 9 patients.

What additional evidence is available to support the role of C_{min} in impacting efficacy?

The potential for lack of long-term efficacy produced by a regimen with low IDV C_{min} is indirectly supported by Merck Study 069, where the regimen with lower C_{min} (1200 mg BID) was inferior to that with the higher C_{min} (800 mg TID) after 24 weeks of treatment. In Study 069, the efficacy of combination therapy including IDV in HIV-infected adult patients was evaluated. A PK substudy was conducted on Day 28. It is noteworthy that confounding variables (e.g. role of coadministered drugs) may have existed in the efficacy assessment of Study 069. Additionally, drug levels were assayed by different laboratories, which had different lower limits of quantitation that impacted C_{min} determination. The 1200 mg IDV BID regimen produced IDV C_{min} values that were approximately 2-fold lower (100 nM) than C_{min} values produced by 800 mg IDV TID (200 nM). AUC and C_{max} in the BID regimen were greater than those in the TID regimen. The BID regimen had similar efficacy with the TID regimen from weeks 4 - 16, but was inferior to the TID regimen at week 24. Interestingly, the geometric mean C_{min} (95 nM) obtained following BID administration was comparable to that obtained in pediatric patients (115 nM and 108 for Protocols ACTG 395 and 068, respectively). The significance of the similar C_{min} values following the adult BID regimen and the pediatric 500 mg/m² q 8hr regimen is not known. No definite exposure-response (PK/PD) model correlating C_{min} to efficacy was established in this study, but the results suggest that maintenance of low C_{min} may have an impact on long term efficacy of IDV containing regimens.

What is the consensus amongst experts from the antiviral advisory committee on the role of C_{min} in determining efficacy of antiretrovirals?

At a recent antiviral advisory committee meeting (July 2000), the members of the committee indicated that for pediatric studies the C_{min} was a critical parameter to be "matched", if PK was to be used as the basis for establishing a pediatric regimen.

Role of C_{min} in Indinavir Exposure-Response Summarized

Although the C_{min} value necessary for IDV efficacy has not been established, the majority of investigators indicate that C_{min} is an important parameter, if not the most important parameter, in establishing efficacy of IDV and other protease inhibitors. Therefore the applicant's claim of C_{min} not being important in determining IDV efficacy is not considered acceptable by DAVDP, especially in the absence of a definitive exposure-response relationship that eliminates C_{min} as an efficacy determinant. Based on observations in the literature with other protease inhibitors, it is reasonable to assume that the maintenance of low C_{min} may have an impact on efficacy and potentially the development of resistance during combination therapy with IDV.

2. Distribution of C_{min} across Studies: Pediatric-to-adult Comparisons

Minimum concentrations in adult and pediatric populations were analyzed in detail, because it is considered an important exposure measure for efficacy. Mean IDV C_{min} s in HIV-infected adults and pediatric patients following administration of IDV are summarized in Tables III and IV, respectively.

Table III: Arithmetic and Geometric Mean Indinavir Minimum Concentrations in HIV-Infected Adults (Studies 021, 031, and 035)

	IDV Minimum Concentration at End of Dosing Interval* Following 800 mg IDV q 8hr		
Study #	021	031	035
N	16	11	9
Geo. Mean	206.5	181.9	198.3
Mean \pm SD	251.3 \pm 177.9	203.7 \pm 86.7	203.7 \pm 47.1

*Data from only quantifiable and credible (suspected outliers excluded) plasma samples included in table.

Table IV: Arithmetic and Geometric Mean Indinavir Minimum Concentrations in HIV-Infected Children (Studies 068 and 395)

	IDV Minimum Concentration at End of Dosing Interval* Following 500 mg/m ² IDV q 8hr	
Study #	068	395
N	20	8
Geometric Mean	109	115.4
Mean \pm SD	133.6 \pm 96.0	136.0 \pm 83.0

* Data from only quantifiable and credible (suspected outliers excluded) plasma samples included in table.

From Tables III and IV, it is clear that the average C_{min} in the studied pediatric patients is lower than that in the adult patients. The distribution of individual data for a given C_{min} threshold varied between the adult and pediatric population, as shown in Table V. If one considers the 100 nM trough value to be the critical parameter in determining efficacy, only 50 % of the pediatric patients achieved this level; whereas, more than 80 % of adults achieved this threshold. Using the 150 nM critical trough cited in the literature, approximately 40 % of pediatrics will attain this level and approximately 70 % of the adults will attain this level. These findings suggest that long term efficacy in pediatric and adult populations are not likely to be comparable, if both populations have similar exposure-response relationships and efficacy is dependent on attainment and maintenance of a critical IDV C_{min} (100–150 nM). It is noteworthy that the mean value was generally not reflective of the distribution of C_{min} . Less than 50 % of the patients had $C_{min} \geq$ average arithmetic C_{min} ; therefore, analysis based on average arithmetic C_{min} may give misleading conclusions.

Table V : Percentage of Subjects with IDV C_{min} above a Given Threshold

STUDY#	Percentage (%) of Subjects IDV Plasma Concentrations at End of Dosing Interval > Cutoff			Cmin (nM)
	100 nM	150nM	200 nM	Mean^ (SD)
Pediatrics TID				
068 (n=20)	50.0	35.0	20.0	134 (96)
395 (n=9*)	55.6	44.4	33.3	136 (83)
Mean	52.8	39.7	26.7	135
Adults TID				
021 (n=16)	93.8	62.5	62.5	251 (178)
031 (n=11*)	81.8	72.7	63.6	204 (87)
035 (n=9)	100	77.8	66.7	204 (47)
Mean	91.9	71.0	64.3	220

*One patient in group had value more than 3x greater than next highest value, suspected to be "outlier" (may not be representative of group) but included in the percentage analysis

^ Mean (SD) – arithmetic mean calculated excluding suspected outlier

C. Suitability of indinavir slurry in applesauce as a substitute for indinavir capsules

The IDV slurry was developed to provide an option for pediatric patients that could not swallow intact IDV capsules. Safety and efficacy data are not available using the IDV slurry. The IDV slurry, which is made by sprinkling the contents of an IDV capsule into two tablespoons of applesauce, should not be used as a substitute for intact capsules. This is because the C_{max} s produced by the slurry are significantly greater than those produced by the intact capsule and do not satisfy the BE criteria. This increase in IDV exposure poses safety concerns as increased IDV exposure is associated with increased incidence of IDV treatment related adverse events. In the absence of long-term clinical evidence to indicate otherwise, the IDV slurry should not be used in lieu of IDV capsules.

Studies 058 (adult healthy volunteers) and 395 (pediatric patients) were conducted to support inclusion of the IDV slurry dosing instructions in the label. Several IDV formulations (See Study 041 Report) for pediatric use were developed; however, according to the applicant, only the IDV slurry formulation had appropriate pharmacokinetic properties. It is noted that an independent investigator, _____, reported that an IDV suspension in _____ had adequate pharmacokinetic properties (Re: Teleconference in May 2000 held between DAVDP and _____ claimed that the IDV _____ was BE to the intact capsule. The applicant is currently pursuing development of pediatric syrup-based formulation. The Chemistry Reviewer indicates in his review that the stability of IDV sulfate in applesauce was assessed, and IDV sulfate was stable in applesauce for up to 4 hours. Relevant pharmacokinetic data for study 395 are summarized in Table VI.

Table VI : Geometric Mean, Geometric Mean Ratio and 90% CI for Indinavir Exposure Measures (Study 395 with Indinavir Slurry)

Exposure Measure	GMR* (IDV Slurry:IDV Intact Capsules)	
	Point Estimate	90% CI
AUC _{0-8 hr} (nM hr)	1.28 (n=10)	0.91 - 1.82
C_{max} (nM)	1.60 (n=10)	1.07 - 2.39
$C_{8 hr}$ (nM)	1.27 (n=8)	0.63 - 1.34 [^]

*Applesauce (Day 16)/Capsules in Fasted State (Day 15)

[^] Confidence interval calculated from n=9, which includes C_{min} value from suspected outlier

It is likely that the presence of the slurry increases the absorption of IDV rather than modifies the IDV clearance. GMRs (slurry:intact) and associated confidence intervals for AUC and C_{max} indicate that the study failed to demonstrate BE between the slurry and intact capsule. It should be noted that the slurry is being considered as an alternative form of IDV administration in pediatric patients, therefore, it must satisfy the BE criteria, or appropriate exposure-response data should be available. In summary, the IDV slurry should not be used as a substitute for intact IDV capsules, because of the potential to increase IDV exposure, which may increase the incidence of IDV treatment-related adverse events.

PK data from Study 058 are summarized in Table VII. As in study 395, slurry administration is not BE to intact capsule administration.

Table VII: Pharmacokinetic Exposure Measures (Geometric Mean Ratio) for Indinavir Slurry in Applesauce Versus Capsules (N=12)

Exposure Measure	GMR (Applesauce/ Intact Capsule)	
	Point Estimate	Confidence Interval
AUC _{0-24 hr} (nM h)	1.11	0.75 - 1.65
C_{max} (nM)	1.11	0.70 - 1.75
$C_{8 hr}$ (nM)	0.87	0.59 - 1.29

D Potential Safety concerns associated with indinavir administration in pediatric patients

According to the Medical Reviewer, Melisse Baylor, MD, the adverse event profile in children receiving 500 mg/m² IDV q 8hr is similar to that of adults receiving 800 mg q 8hr. However, Dr. Baylor indicated that the incidence of adverse events in the pediatric patients was greater than in adults, especially renal adverse events (including nephrolithiasis). The applicant reports that these renal adverse events were reversible and no permanent renal dysfunction was observed.

RECOMMENDATIONS

- 1) Clinical efficacy studies in pediatric patients were required for the proposed indinavir pediatric dosage regimen, because the pharmacokinetic evidence provided in NDA 20-685 SE8-043 does not support the proposed dosing regimen.
- 2) The pharmacokinetic evidence presented in NDA 20-685 SE8-043 does not support the administration of the indinavir slurry formulation as a substitute for the capsule administration.
- 3) Results from the pharmacokinetics studies should be incorporated into the indinavir label. Wording in the label should indicate potential concerns with the evaluated dosing regimen.

COMMENTS

The applicant is encouraged to consider alternative dosage schemes in order to achieve comparable exposures in pediatric and adult patients. In developing these schemes, particular attention should be paid to achieving comparable trough levels over the dosing interval in both populations, as recommended by the antiviral advisory committee. Potential avenues to be explored are increasing the dosing frequency, combining low dose ritonavir with indinavir, or changing the drug input rate using alternative formulations.

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VII. Findings from other Disciplines

A. Medical Reviewer: Efficacy Evaluations

The applicant summarized efficacy evaluations from studies 395 and 068 in which pediatric patients received 500 mg/m² IDV q 8hr as follows:

- Combination therapy with IDV, d4T, and 3TC results in substantial decreases from baseline in plasma viral RNA at Week 16.
- Combination therapy with IDV, d4T, and 3TC results in increases from baseline in CD4 cell counts and percent CD4 cell counts at Week 16.
- Combination therapy with IDV, d4T, and 3TC results in increases from baseline in body weight at Week 16.

The Medical Reviewer agrees with the applicant's conclusions, but indicates that the number (n = 31) of patients was insufficient to be extrapolated to the pediatric population. Hence, conclusions regarding the efficacy should be made cautiously. The caution is warranted because results from this population may not be representative of the overall pediatric population. Furthermore, the studies reported were following only 16-weeks treatment and the efficacy results may not be indicative of long term efficacy.

B. Chemistry Reviewer: Formulation Evaluation

The applicant introduced a new 100 mg capsule for pediatric use. According to the Chemistry Reviewer, the capsule fill used for the 100 mg capsule is the same as that for the approved dosage forms. In addition, specifications (including dissolution), test methods and container/closure system are practically the same as in the original NDA (200 and 400 mg capsules). The Chemistry Reviewer concludes that the Supplement is recommended for approval. Additionally, the applicant indicated that the 100 mg capsules will not be marketed until the related efficacy supplement (043) has been approved.

Table VIII: Composition of 100 mg Indinavir Capsules for Pediatric Use

Ingredient	Quantity (mg)
Indinavir sulfate as ethanol solvate	_____
Anhydrous lactose, NF	_____
Magnesium Stearate	_____
Total Fill Weight	_____

The 100 mg capsule formulation was approved in April 2000, prior to completion of this review.

VIII. Bioanalytical Assay Methods

A validated HPLC assay for the quantitation of IDV from plasma samples was used by the applicant and was acceptable. Plasma samples from the pivotal efficacy studies, 068 and 395, were analyzed in the same laboratory with the same limit of quantitation; however, samples in other studies were analyzed in different laboratories that tended to have different limits of quantitation. No cross validation reports were submitted to allow for reliable cross-study comparisons between the pivotal studies and other supporting studies.

IX. Comments Regarding Pharmacokinetic (PK) Analyses

IDV concentrations were converted to a molar basis using a molecular weight of 613.81 prior to PK analysis. AUC was calculated by a modified trapezoidal rule using piecewise cubic polynomials.

Pediatric to Adult Comparisons

Geometric mean ratios for IDV exposure measures (AUC, C_{max}, and C_{8hr}), and their corresponding 90 % confidence intervals were determined to compare exposure in HIV-infected children to adults. The IDV exposure measures were determined on Days 15 (Studies 068 and 395) and 16 (Study 395) in children

and on Day 15 in adults (Study 021). In the submission, the applicant chose to compare PK data from the pediatric studies to adult Study 021 PK data only, although other relevant adult data were available. For this review, comparisons with Study 021 alone were considered acceptable, because data across adult studies at the same dose appeared to be comparable (see comment below).

Comment

PK data from adult studies 031 and 035 were available at the time this submission was filed; however, the applicant chose to compare only Study 021 data to pediatric data. The reason for the exclusion of other adult data was not stated. The exclusion may be due to the fact that Studies 031 and 035 were drug interaction studies, and PK assessments were made on Day 8 rather than on Day 15 (Study 021 and the pediatric studies). Furthermore, the current Crixivan label has data from only Study 021.*

*** Relevant Adult Studies**

Study 031: Multiple Dose Drug Interaction between IDV and d4T in HIV-infected patients PK on Day 8

Study 035: Efficacy and drug interactions between IDV and 3TC and ZDV in HIV-infected patients PK in subset on Day 8

As previously discussed, the applicant indicated that a 90 % confidence interval range of 0.5 – 2.0 would be considered a region showing general comparability, but this region was neither acceptable nor used in this review.

List of References

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APPENDIX: Individual Study Reports

The two pivotal efficacy studies, 068 and 395, included a pharmacokinetic substudy (Days 15/16). Due to the similarity in study design, and the fact that the pharmacokinetics and efficacy findings for the studies were combined, common aspects of the studies will be presented.

PHARMACOKINETIC QUESTIONS:

Studies 068 and 395

- 1) Are the pharmacokinetics and pharmacodynamics of indinavir (IDV) in children receiving combination therapy including 500 mg/m² IDV q 8hr comparable to those in adults receiving combination therapy including 800 mg IDV q 8hr?
- 2) Are indinavir exposures achieved following administration of opened IDV sulfate capsules, as a slurry in applesauce, comparable to exposures achieved following administration of intact IDV capsules in the fasted state?

Table I: Study Information

	Study Number	
	068	395
Investigators and Sites	6 Investigators/United States	10 Investigators/United States
Clinical Dates	01/98 – 03/99 corresponding to acute portion of study (extension in progress).	05/98 – 03/99 corresponding to acute portion of study (extension in progress).
Analytical Dates	September 2, 1998 and May 10, 1999	September 11, 1998 and May 10, 1999
Analytical Site		

Doses administered in both studies were as follows:

- **indinavir sulfate:** 500 mg/m², p.o. q 8hr,
- **stavudine:** dose-adjusted for weight, p.o. q12h
- **lamivudine:** dose-adjusted for weight and age, p.o. q12h.

Table II: Dosage Forms Administered in Pediatric Studies

	Formulations (Batch Numbers) used in Pediatric Studies	
	Study 395	Study 068
indinavir sulfate capsules	100 mg (0639DFC015B001) 200 mg (0639DFC032C008)	100 mg (0639DFC015B001) 200 mg (0639DFC032C006)
lamivudine tablet	150 mg (7ZP1254, 8ZP1522, 9ZP0027)	150 mg (7ZP0336)
lamivudine liquid	10 mg/mL (0779, 5933, 5733)	10 mg/mL (8963)
stavudine capsules	20 mg (MCH42), 30 mg (MLH43, MNM68), 40 mg (MMH85)	20 mg (MCH31), 30 mg (MCH28), 40 mg (MDH57)
stavudine powder	1 mg/mL (MFH13, MDN28, MHN39, MJN40, MBS52)	1 mg/mL (MAH05)

Blood Sample Collection

Blood samples were collected at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0 and 8.0 hours after drug administration to determine IDV plasma concentrations.

Bioanalytical Methodology

Plasma concentrations of IDV were determined using a validated HPLC chromatographic method with UV detection. Assay performance was acceptable for the method as shown in Table III.

Table III: Assay Performance for Indinavir HPLC Samples in Pediatric Studies 395 and 068

Assay Parameter	Study Protocol Characteristics		Comment
	Protocol 068 [^]	Protocol 395	
Linearity Range			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Sensitivity (LLOQ*)			Satisfactory
Specificity			Satisfactory

LLOQ* lower limit of quantitation

[^] It was noted that two samples had chromatographic interference and were excluded from the analysis. The exclusion of these samples is acceptable.

Review of Study 068

Study Design

An open-label, multicenter study design was employed. Patients were treated with triple combination therapy consisting of IDV plus stavudine and lamivudine for 24 weeks. Pharmacokinetic assessments were made on Day 15.

Demographics of Patients in the Pharmacokinetic Analysis

Demographic characteristics of the 23 patients who had data available for the pharmacokinetic analysis are summarized in Table I.

Table I : Patient Demographics in the Pharmacokinetic Analysis

Demographic Characteristics	IDV/D4T/3TC	
	(N=23)	
	n	%
Gender		
Male	8	34.8
Female	15	65.2
Race		
Caucasian	7	30.4
Black	16	69.6
Age (years)		
4 to 11	20	87
12 to 15	3	13
Mean	7.78	
SD	2.97	
Median	8	
Range	4 to 15	

No clear relationships between pharmacokinetics and any of the demographic characteristics were identified.

Baseline HIV Disease Characteristics

The baseline HIV disease characteristics of patients participating in the clinical efficacy trial are presented in Table II.

Table II: Baseline HIV Disease Characteristics for Study 068

Parameter	Value
Mean CD4 Count (cells/mm ³)	594
Percentage (%) CD4	25.5
Geometric Mean Viral RNA (log copies/mL)	4.002
Mean Viral RNA (Amplicor)	10,048

It was noted that the disease state of children in this study appeared to be slightly more advanced than in Study 395. However, a comparative PK analyses of the effects of disease state on IDV PK was not undertaken.

RESULTS AND DISCUSSION:

A) Indinavir pharmacokinetics in Children:

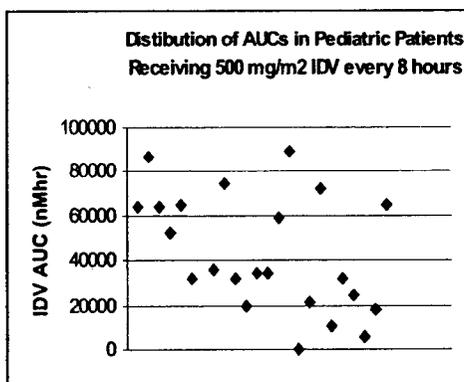
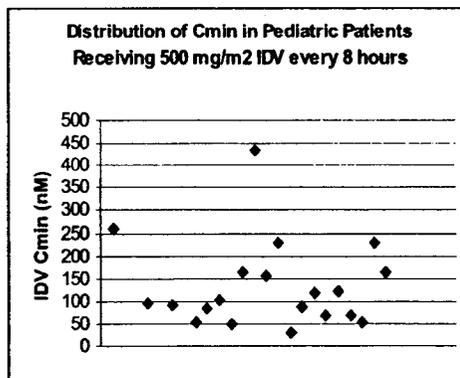
Arithmetic means for IDV AUC_{0-8 hr}, C_{max}, and C_{8 hr} are summarized in Table III. Individual C_{min}s and AUCs are depicted in Figures 1a and 1b.

Table III: Indinavir (IDV) Pharmacokinetic Parameters (Arithmetic Mean ± SD) in Study 068

Treatment: IDV/d4T/3TC		
Pediatric Patients treated with 500 mg/m ² IDV Dose- Capsules in Fasted State (Day 15)		
Pharmacokinetic Parameter	Arithmetic Mean ± SD	N
AUC _{0-8 hr} (nM hr)	43230 ± 25988	23
C _{max} (nM)	19279 ± 10215	23
C _{8 hr} (nM)	134 ± 96	20
T _{max} (hr)	1.0 ± 0.7	23

IDV pharmacokinetics were highly variable (CV > 50 %), which is consistent with other studies in pediatric patients (Studies 395, 041, literature) and in adults (Studies 021, 031, 035, literature). The variability is attributed to metabolism of IDV by the CYP3A4 metabolic pathway but may also be due to variable absorption or P-glycoprotein.

Figure 1 a: AUC Distribution

Figure 1 b: C_{min} Distribution

* x-axis does not have definitive units (plotted for individual subjects)

Three patients had increased IDV concentrations near the end of the dosing interval; therefore, these data were not included in the analysis of the C_{8hr} data. This exclusion is acceptable, based on the assumption that the unexpectedly high concentrations were due to incorrect dosing or blood sampling schedules in

these individuals. The most likely explanation for these findings is that the patients received a subsequent dose of IDV prior to the end of sampling.

B) Pharmacokinetics of Indinavir: Children vs. Adults

Geometric mean pharmacokinetic parameters for IDV in HIV-infected children and adults are summarized in Table IV.

Table IV : Day 15 Indinavir Pharmacokinetics (Geometric Mean and 90 % Confidence Interval) in Fasted, HIV-Infected Children (Study 068) and Adults (Study 021)

	Geometric Mean (90% Confidence Interval)		
	IDV Administered as Sulfate Capsules while fasted		
	AUC _{0-8 hr} (nM hr)	C _{max} (nM)	C _{min} (nM)
Protocol 068 (Pediatric)	30,500	13,922	109
90 % CI	21,776 - 42,720	9,785 - 19,808	85 - 139
N	23	23	20
Protocol 021 (Adult)	28,719	11,948	208
90 % CI	19,013 - 43,379	7,760 - 18,397	158 - 275
n	16	16	16

The geometric mean ratios (GMR, pediatrics:adults) and resulting 90 % confidence intervals were constructed to compare IDV exposure parameters between children (Protocol 068) and adults (Protocol 021). These data are presented in Table V.

Comment:

Use of Study 021 was deemed acceptable for the purposes of this review (See Pharmacokinetic Analysis-Pediatric: Adult Comparisons on Page 8).

Table V: Relative Indinavir Pharmacokinetic Measures (Geometric Mean Ratio, 90% CI)- Pediatric (PD) Patients in Study 068/Adult (AD) Patients in Study 021

Pharmacokinetic Measure	GMR (PD/AD)	90% CI
AUC _{0-8 hr} (nM hr)	1.06	0.63 - 1.78
C _{max} (nM)	1.17	0.68 - 2.00
C _{8 hr} (nM)	0.52	0.37 - 0.75

The combination to monotherapy comparison is acceptable, since d4T and 3TC are not expected to have a drug-drug interaction with IDV. Evidence supporting this lack of effect of d4T and 3TC on IDV PK is provided in pediatric Study 041 and in the literature.

Comparability of Exposure Measures- Geometric Means and Confidence Intervals

Children receiving IDV 500 mg/m² q 8hr in combination with d4T and 3TC had geometric mean AUC values that were comparable to historical values in adults receiving IDV 800 mg q 8hr as monotherapy. The geometric mean C_{max} values were also comparable in adult and pediatric patients. This comparability is reflected in the geometric mean ratio (GMR) point estimates for AUC and C_{max} that were ≅ 1.0. On the other hand, the geometric mean C_{8 hr} value in children (109 nM) was approximately one-half the value observed in adults (208 nM).

The 90% confidence interval (CI) for the GMR for all exposure measures were close to or just outside the comparability boundaries proposed by the applicant. However, the DAVDP does not consider these boundaries to be therapeutically equivalent (see Synopsis). CIs for the AUC and C_{max} GMR were between 0.5 and 2.0; whereas, CI for C_{8 hr} was outside this range. The CI for C_{8hr} did not cross one, indicating that

C_{8hr} levels in this study were lower than those observed in adult patients. These low minimum plasma concentrations may lead to decreased antiviral efficacy possibly leading to the development of resistance. It is noteworthy that no studies have identified critical trough values for efficacy or resistance development associated with IDV therapy.

Prior to the submission of the NDA, the applicant was informed that the range of 0.5 –2.0 was not considered suitable to show comparability of exposure measures for review and approval purposes. Reasons for the unacceptability of the applicants comparability region were discussed previously (See synopsis). Consequently, although the geometric mean ratio for AUC and C_{max} indicate similarity in pediatric and adult average exposure, the wide CIs indicate that interindividual exposures are highly variable. The high variability may require therapeutic drug monitoring for effective and safe dosing in pediatrics. Furthermore, the C_{min} for the two populations was clearly different. Due to the lack of PK comparability between adult and pediatric subjects, particularly with C_{min} , the proposed dosing regimen can not be approved on the basis of PK data. Approval will require other forms of evidence, such as exposure-response data or clinical efficacy studies.

Conclusion

Exposure measures for pediatric patients receiving 500 mg/m² q 8hr are not comparable to those in adults receiving 800 mg, q 8hr.

Review of Protocol 395

Protocol 395 Study Design

An open-label, multicenter study design was employed. Male and female pediatric patients were treated with triple combination therapy consisting of IDV, stavudine and lamivudine, for 48 weeks. Efficacy data presented are for 16 weeks of treatment. Sixteen patients entered the study, but only 12 patients completed the study (16 weeks).

Demographics of Patients in Study 395

Demographics of patients, who took part in the pharmacokinetic analysis, are summarized in Table I. Eleven patients participated in the IDV pharmacokinetic analysis of fasted dosing on Day 15, and 10 patients participated in the Day 16 PK analysis with applesauce (AN 0116, who was a 6-year-old Caucasian male, did not participate).

Table I: Patient Demographics in the Pharmacokinetic Analysis

	Number of Subjects (%) Undergoing IDV/D4T/3TC Treatment
Gender	
Male	6 (54.5)
Female	5 (45.5)
Race	
White	1 (9.1)
Black	7 (63.6)
Hispanic	3 (27.3)
Age (Years)	
6 to 11	10 (90.9)
12 to 13	1 (9.1)
Mean	8.5
SD	2.2
Median	8.0
Range	6 to 13

No clear relationships between pharmacokinetics and any of the demographic characteristics were identified.

Baseline HIV Disease Characteristics

The baseline HIV disease characteristics of patients participating in the efficacy trial are presented in Table II

Table II: Baseline HIV Disease Characteristics in Study 395

Parameter	Value
Mean CD4 Count (cells/mm ³)	678.1
Mean Percentage (%) CD4	30.1
Mean Viral RNA (log copies/mL)	3.89
Mean Viral RNA (Amplicor)	7820.3

I. RESULTS AND DISCUSSION

A) Indinavir pharmacokinetics in Children:

Arithmetic means for IDV AUC_{0-8 hr}, C_{max}, and C_{8 hr} are summarized in Table III. Individual C_{min}s and AUCs are depicted in Figures 1a and 1b.

Table III : Pharmacokinetic Measures (Arithmetic Means ± SD) for Indinavir (Study 395)

Treatment: IDV/D4T/3TC		
Pediatric Patients treated with 500 mg/m ² IDV Dose- Capsules in Fasted State (Day 15)		
Pharmacokinetic Measure	Arithmetic Mean ± SD	# of Subjects
AUC _{0-8 hr} (nM hr)	29,356 ± 16,951	11
C _{max} (nM)	12,793 ± 7,523	11
C _{8 hr} (nM)	136 ± 83	8
T _{max} (hr)	1.0 ± 0.5	11

* Calculated arithmetic mean excludes the value of one suspected outlier, which had value (2002.7 nM) that was > 9-fold higher than next (243.6 nM) highest C_{8 hr}. Inclusion of the suspected outlier gives C_{8 hr} arithmetic mean ± SD = 343 ± 627 nM

IDV PK were highly variable (CV > 50 %), which is consistent with previous study results. The variability is attributed to metabolism of IDV by the CYP3A4 metabolic pathway. Exposure measures obtained in this study were comparable to those in Study 395 and those reported in the literature at a comparable pediatric dose.

Figure 1a: Distribution of AUC

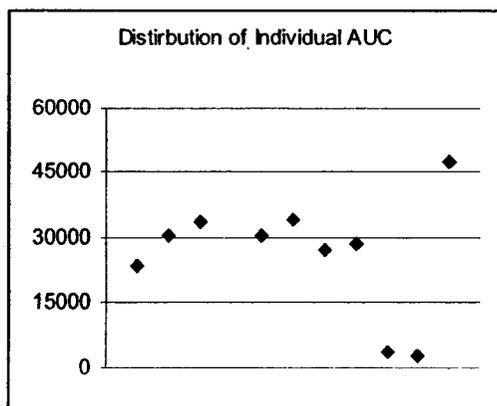
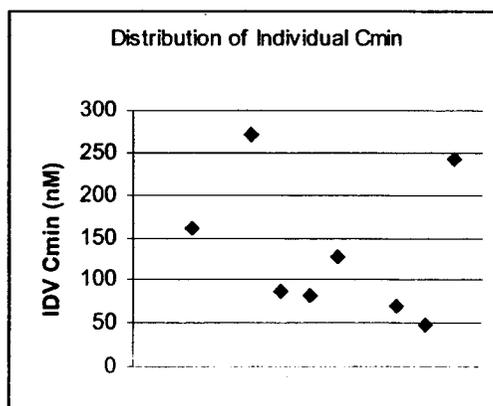


Figure 1 b: Distribution of C_{min}



* x-axis does not have defined units (plotted for individual subjects)

As noted in Table III, one minimum plasma concentration was suspected to be an outlier, but no statistical analysis was conducted to confirm this suspicion. A possible explanation for the unexpected high concentration is that the sample was not taken at the correct time. Removal of this single data point greatly impacts the mean and standard deviation; furthermore, removal of this subject's data renders the C_{min} results more consistent with data from other studies. Consequently, some of the subsequent C_{min} analyses in this review were conducted without including data from this suspected outlier. The applicant noted that two additional patients had increased IDV concentrations at the end of the dosing interval; therefore data from these patients were excluded from all PK analyses and are not included in Table III. Exclusion of these data is acceptable.

B. Pharmacokinetics of Indinavir: Children vs. Adults

Geometric mean pharmacokinetic parameters for IDV in HIV-infected children and adults are summarized in Table IV.

Table IV: Indinavir Pharmacokinetics in Fasted, HIV-Infected Children and Adults- 500 mg/m² IDV q 8hr in Children and 800 mg q 8hr in Adults as Sulfate Capsules while Fasted

	Geometric Mean (90% Confidence Interval)		
	Indinavir Administered as Sulfate Capsules While Fasted		
	AUC _(0-8 hr) (nMhr)	C _{max} (nM)	C _{8 hr} (nM)
Protocol: ACTG395	Children: with D4T and 3TC and IDV (n = 11*)		
	21,927	9,215	115
90 % CI	15,035 - 31,977	6,209 - 13,675	96 - 262
Protocol: 021	Adults: monotherapy (n = 16)		
	28,719	11,948	208
90 % CI	21,188 - 38,927	8,691 - 16,425	145 - 298

For C_{8 hr}, n = 8; mean calculated excluding suspected outlier

The geometric mean ratios (GMR, pediatrics:adults) and resulting 90 % confidence intervals (CI) were constructed to compare IDV exposure parameters between children (Protocol 395) and adults (Protocol 021). These data are presented in Table V.

Comment

Use of Study 021 data only was deemed acceptable for the purposes of this review (See Pharmacokinetic Analysis- Pediatric:Adult Comparisons on Page 8).

Table V: Relative Indinavir Exposure Measures (Geometric Mean Ratio, 90% CI)- Pediatric Patients (Study 395)/Adult Patients (Study 021)

Pharmacokinetic Measure	GMR (PD:AD)	90% CI
AUC _{0-8 hr} (nMhr)	0.76	0.48 - 1.22
C _{max} (nM)	0.77	0.47 - 1.26
C _{8 hr} (nM)	0.76	0.42 - 1.37

The monotherapy to combination therapy comparison is acceptable, because d4T and 3TC are not expected to have a drug interaction with IDV. Evidence supporting this lack of effect of d4T and 3TC on IDV PK is provided in pediatric Study 041 and in the literature.

Comparability of Exposure Measures- Geometric Means and Confidence Intervals

Average exposure measures for children administered IDV 500 mg/m² in combination with d4T and 3TC were lower than average exposure measures in adults given IDV 800 mg q 8hr as monotherapy. The lack of comparability between the regimens is reflected in the point estimates that were ≈ 0.76 . The

clinical relevance of this magnitude of reduction in exposure measures for the pediatric population was not established in this study and is not known.

The 90% confidence interval (CI) for the GMR for all exposure measures were close to or just outside the comparability boundaries proposed by the applicant. However, the DAVDP does not consider these boundaries to be therapeutically equivalent (see Synopsis). Confidence intervals for all exposure measures fell below the applicant's lower bound of 0.5, but were within the upper bound. The lower mean AUC and C_{max} observed may suggest a reduction in the incidence of adverse events resulting from high IDV exposure. The role of AUC or C_{max} on IDV efficacy is not known. The low minimum plasma concentrations observed may lead to decreased antiviral efficacy, possibly leading to the development of resistance. It is noteworthy that no studies have identified critical trough values for efficacy or resistance development associated with IDV therapy.

Conclusions

Average indinavir exposure measures for pediatric patients receiving 500 mg/m² q 8hr are not comparable to average exposure measures in adults receiving 800 mg q 8hr.

C. Pharmacokinetics of Intact Indinavir Capsule (IDVINT) vs. Indinavir Slurry (IDVSLY) In HIV-infected Children

Table III shows IDV pharmacokinetic values as geometric means with 90% confidence intervals following administration of IDV, as an intact capsule, and as a slurry in applesauce.

Table III: Pharmacokinetic Measures (Geometric Means) for Indinavir

Treatment IDV/D4T/3TC		
Geometric Mean (number of subjects)		90% CI
Capsules in Fasted State on Day 15		
AUC _{0-8 hr} (nM·hr)	21,927 (n = 11)	12,747.5 - 37,716.0
C_{max} (nM)	9,215 (n = 11)	5,141.6 - 16,514.1
$C_{8 hr}$ (nM)	115* (n = 8)	79.6 - 315.7
With Applesauce (Day 16)		
AUC _{0-8 hr} (nM·hr)	26,980 (10)	19,794 - 36,775
C_{max} (nM)	13,711 (10)	10,130 - 18,557
$C_{8 hr}$ (nM)	146 (9)	86 - 248

* Calculated geometric mean excludes the value of one suspected outlier, which had value (2002.7 nM) that was > 9-fold higher than next (243.6 nM) highest $C_{8 hr}$. Inclusion of the suspected outlier gives $C_{8 hr}$ geometric mean 159 nM.

As previously noted, IDV PK were highly variable (CV > 50 %) for all exposure measures following administration of the intact capsule. The PK variability appeared to be slightly lower following slurry administration than following administration of the intact capsule. The IDV geometric mean AUC, C_{max} , and C_{min} following administration of the slurry (IDV capsule contents sprinkled in two tablespoons of applesauce) were higher than those produced following administration of the intact capsule to fasted individuals. It is likely that the presence of the slurry increases the absorption of IDV rather than modifies the IDV clearance.

Geometric mean ratios and associated 90 % CIs for IDV (IDV slurry: intact IDV capsules) are summarized in Table IV.

Table IV : Relative Exposure Measures (Geometric Mean Ratio, 90% CI) for Indinavir

Pharmacokinetic Measure	GMR* (IDVSLY:IDVINT)	
	Point Estimate	90% CI
AUC _{0-8 hr} (nM·hr)	1.28 (10)	0.91 - 1.82
C _{max} (nM)	1.60 (10)	1.07 - 2.39
C _{8 hr} (nM)	0.92 (9)	0.63 - 1.34

* Applesauce (Day 16)/Capsules in Fasted State (Day 15)

The GMRs (slurry:intact) and associated confidence intervals for AUC and C_{max} indicate that the slurry is not bioequivalent to the intact capsule, because the CIs for exposure measures do not satisfy the BE criteria. However, the applicant claims that IDV exposure is comparable by both modes of administration, based on their *a priori* definition of general comparability (CI: 0.5 –2.0). This wide CI for assessing comparability is not acceptable from the OCPB perspective (See Pharmacokinetics Analysis: Discussion on Confidence Interval Selection); because, the proposed CI greatly exceeds the upper and lower bounds of the recommended BE limits by more than 60 % and the change in CI are not supported by clinical evidence. Ratios of individual AUCs and C_{max}s ranged from ~~0.63 to 2.39~~ respectively. The IDV slurry should not be used as a substitute for intact IDV capsules, because of the potential to increase IDV exposure, which may increase the incidence of IDV treatment-related adverse events.

Comment on Study Design and Conclusions

It is noteworthy that the PK study design employed to assess the BE between IDV administered in a slurry and intact IDV to fasted individuals was not ideal. The shortcomings of the design included:

- *Lack of Randomization of dosing schedule. All subjects received both treatments in the same sequence, rather than in the two possible orders (slurry followed by intact capsule or intact capsule followed by slurry)*
- *Absence of a washout period- however, this procedure is not clinically acceptable in the HIV patient population because of resistance concerns*

Due to these limitations in the study design, potential carry-over (not likely due to short half-life), period or sequence effects, could not be assessed. This study appeared to be exploratory in nature and had an inadequate number of subjects (n=11) to allow definitive statistical or pharmacokinetic interpretation or labeling claims to be made. Consequently, results and conclusions from the BA/BE analysis should be interpreted cautiously. With these caveats in place, the study results indicate that administration of the IDV slurry produces higher IDV AUC and C_{max} but slightly lower C_{min} than administration of IDV capsules to fasted individuals.

Conclusions

- The IDV slurry in applesauce is not bioequivalent to the intact capsule.

Review of Protocol No. 058

Investigator and Study Site: _____

Clinical Study Dates: November 12, 1996 to November 26, 1996 (Phase I)

Title: An Open-Label, 3-Period, Crossover Study to Compare the Tolerability and Pharmacokinetics of Single 800-mg Doses of Indinavir Sulfate Capsule Administered Fasted Versus With Applesauce Versus After a Heavy Meal (Protocol #058)

PHARMACOKINETIC QUESTIONS:

- Are the indinavir exposures obtained following administration of opened indinavir sulfate capsules in an applesauce slurry comparable to those following administration of intact indinavir sulfate capsules?
- Does a food effect occur when an indinavir sulfate capsule is administered 5 minutes after a high fat meal?
- If a food effect occurs, does the food effect require an alteration in indinavir dosage?

Study Design: An open-label, 3-period, crossover study design was employed. Twelve healthy adult volunteers received IDV treatment. All subjects completed the study. Subjects received Treatments A, B and C, in randomized order as summarized in Table I. Six treatment sequences were used. The washout between treatment groups was at least 6 days.

Table I: IDV Treatment Schemes

Treatment Regimen	Entered	Completed
ABC	2	2
BCA	2	2
CAB	2	2
ACB	2	2
BAC	2	2
CBA	2	2

A = Indinavir sulfate capsules, 800 mg given in the fasted state.

B = Single doses of indinavir given as a slurry of indinavir sulfate (from opened capsules) in 2 teaspoons of applesauce.

C = Indinavir sulfate capsules, 800 mg administered 5 minutes following a bacon and eggs breakfast.

Demographic Characteristics of Subjects:

- Gender 6 females, 6 males
- Age Mean (Range) 29.55 (19-43) years
- Weight Mean (Range) 68.5 (50.9 – 90.0) kg

Blood Sampling

Blood samples were drawn immediately predose, 15 and 30 minutes postdose, and 1, 2, 3, 4, 6, 8, 10, 12, 14 and 24 hours postdose.

Taste Analysis

Fifteen minutes after IDV administration, the taste of IDV sulfate was evaluated by means of a questionnaire. Data regarding the taste of IDV were reviewed by tabulating the number of responses for each score for each treatment. Taste was compared amongst the following groups: IDV sulfate administered as a slurry in applesauce versus IDV sulfate capsules after a bacon and eggs breakfast versus IDV sulfate capsules administered in the fasted state.

Pharmacokinetics Analysis

The pharmacokinetic parameters analyzed for IDV were $AUC_{(0-24 \text{ hr})}$, C_{max} , C_{8hr} , and T_{max} . Geometric means were calculated and log-transformed values of $AUC_{(0-24 \text{ hr})}$, C_{max} , and C_{8hr} were compared between treatments by ANOVA appropriate for a 3-period crossover design. Ninety percent confidence intervals (CI) were calculated for the geometric mean ratio. According to the applicant, the absence of a substantial treatment difference was concluded if the 90% CI for the ratio of the geometric means of $AUC_{(0-24 \text{ hr})}$ was included in the interval 0.5 to 2.0.

Dosage Formulations

- Indinavir sulfate, 400 mg capsule WP-C478, 0639 DFC007E002;
- Indinavir sulfate, 400 mg capsule WP-C479 0639 DFC007E002;
- Gerber Stage 2 Applesauce WP-C478A 431V.

Bioanalytical and Pharmacokinetic Methods

Plasma concentrations of IDV were determined using HPLC chromatographic with UV detection by using a molecular weight of 613.81 prior to PK analysis. The assay limit of quantitation (LOQ) was _____ IDV concentrations were converted to a molar basis. Inspection of representative chromatograms indicated that the assay was selective for IDV. The assay was linear over the concentration range _____ The assay was accurate _____ difference between nominal concentrations and observed concentrations) and precise _____

I. RESULTS AND DISCUSSION

A. Pharmacokinetics

1. Comparison of Indinavir as a Slurry of Indinavir Sulfate in Applesauce Versus (IDVSLY) Intact Indinavir Sulfate Capsules Administered in the Fasted State (IDVINT)

Arithmetic mean PK parameters obtained following administration of IDV sulfate as a slurry in applesauce, and IDV sulfate as a capsule in the fasted state are summarized in Table II.

Table II: Pharmacokinetic Measures (Arithmetic Means) for Indinavir Slurry in Applesauce and Indinavir Capsules (N=12)

Pharmacokinetic Measure	Single Dose Administration of 800 mg IDV Formulations	
	IDV Slurry in Applesauce	IDV Capsules Fasted
AUC _{0-24 hr} (nM hr)	32137.3 ± 12038.6	28172.1 ± 9268.1
C _{max} (nM)	14717.0 ± 5403.6	13273.7 ± 5116.2
C _{8 hr} (nM)	149.7 ± 65.1	171.4 ± 91.6
T _{max} (hr)	0.6 ± 0.2	1.2 ± 0.5

Plasma concentration-time data were highly variable (CV 30-150 %). The rate and extent of IDV absorption following slurry administration appeared to be greater than that following administration of the intact capsule, as evidenced by the shorter T_{max} and higher AUC and C_{max}. The clinical significance of this apparent increased rate of absorption is unknown.

Geometric mean ratios (GMRs; Slurry: Intact Capsule) and confidence intervals for IDV AUC, C_{8hr}, and C_{max} are summarized in Table III.

Table III: Geometric Mean Ratios and associated 90 % Confidence Intervals for Indinavir Slurry in Applesauce Versus Capsules (N=12)

Pharmacokinetic Measure	Geometric Mean Ratio (Slurry/ Intact)	
	Point Estimate	Confidence Interval
AUC _{0-24 hr} (nM h)	1.11	0.75 - 1.65
C _{max} (nM)	1.11	0.70 - 1.75
C _{8 hr} (nM)	0.87	0.59 - 1.29

GMRs for AUC_(0-24 hr) and C_{max} indicated that the IDV slurry formulation produced 11 % higher AUC and C_{max} than the intact capsule in the fasted state. Conversely, the GMR for IDV C_{8 hr} indicated that the C_{min} produced by slurry administration was lower than the C_{min} following administration of the intact capsule. Administration of IDV slurry may influence efficacy, because the minimum concentration (after a single

dose) is decreased by 13 % compared to when IDV capsules are given in the fasted state. The 90 % confidence interval values fall within the applicant's proposed confidence interval limits of 0.5 to 2.0, but are outside the limits (0.80 -1.25) that satisfy the BE criteria. Therefore the IDV slurry is not BE to intact IDV capsules. From the applicant's perspective, the differences observed in IDV pharmacokinetics following administration of IDVSLY or IDVINT are unlikely to be clinically significant. However, no additional data, such as an exposure-response relationship, were presented to support this claim. The applicant suggests that the differences in exposure between the two modes of administration may be due to IDV sulfate powder partially dissolving in the slurry. No data were presented to support this hypothesis. In summary, the PK data presented do not support the claim that IDV PK following administration of IDV slurry are similar to IDV PK after administration of intact IDV capsules to fasted individuals.

Conclusions

IDV exposure following IDV slurry administration is not equivalent to IDV exposure following capsule administration in the fasted state; therefore, these two modes of administration are not interchangeable.

2. Comparison of Indinavir Sulfate Capsules Administered Following a Standard Bacon and Eggs Breakfast Versus Indinavir Sulfate Capsules Administered in the Fasted State

The PK measures obtained in fasted individuals and those following administration of a high fat meal (fed state) are summarized in Table IV.

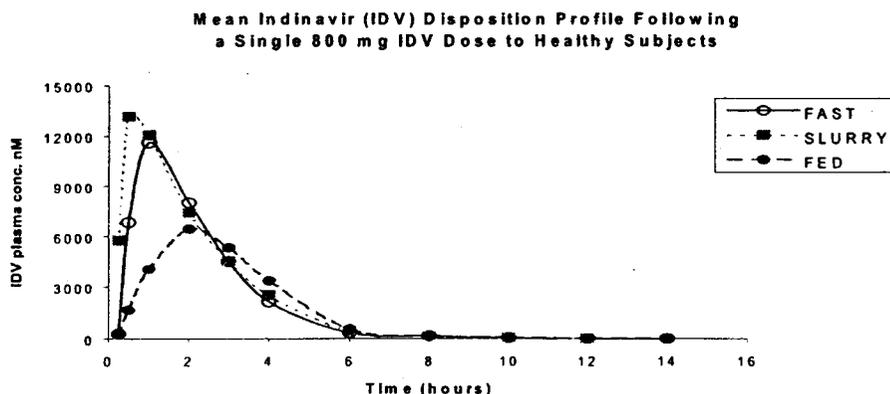
Table IV: Arithmetic Mean* Pharmacokinetic Measures for IDV in fasted and fed states

Pharmacokinetic Measure	Single 800 mg IDV Doses	
	After Bacon and Eggs Breakfast	Indinavir Capsules Fasted
AUC _{0-24 hr} (nM hr)	21952.2 ± 8714.3	28172.1 ± 9268.1
C _{max} (nM)	7613.1 ± 3436.8	13273.7 ± 5116.2
C _{8 hr} (nM)	167.7 ± 99.4	171.4 ± 91.6
T _{max} (hr)	2.0 ± 0.9	1.2 ± 0.5

*According to the applicant, plasma concentrations for one subject were very low following administration of indinavir sulfate capsules after a bacon and eggs breakfast; however this subject's values were included in the analysis since re-examination of these values revealed no error.

The average AUC and C_{max} were significantly lower in the fed state compared to the fasted state, suggesting that a food effect occurred. C_{max} and AUC were approximately two-fold higher and 1.3-fold higher, respectively in the fasted state than in the fed state. On the other hand, average C_{8 hr} appeared comparable in both states. Based on T_{max}, absorption was prolonged by almost 100 % in the fed state, compared to the fasted state.

Figure 1: Indinavir Plasma Concentration-Time Profile (800 mg IDV Fasted, Slurry, Fed)



The geometric mean ratios (Fed: Fasted), and 90% CI for AUC_{0-24 hr}, C_{max}, and C_{8 hr} for IDV capsules given after a standard bacon and eggs breakfast (IDVFED) and administered in the fasted state (IDVFST) are summarized in Table V.

Table V: Geometric Means (Fed/Fasted) and 90 % CI for IDV (n = 12)

Pharmacokinetic Measure	GMR (Bacon and Eggs/Fasted)	
	Point Estimate	90% CI
AUC _(0-24 hr) (nM hr)	0.69	0.47 - 1.02
C _{max} (nM)	0.51	0.32 - 0.80
C _{8 hr} (nM)	0.85	0.57 - 1.26

*Plasma concentrations for one subject were very low following administration of indinavir sulfate capsules following a bacon and eggs breakfast; however this subject's values were included in the analysis since reexamination of these values revealed no error.

GMR ratio point estimates for C_{max} and AUC were less than 0.70, indicating that there is a pronounced food effect with IDV. Because both the rate and extent of absorption are significantly reduced in the presence of a heavy meal, IDV should not be administered with a heavy meal. The C_{8 hr} value was lower in the fed state than in the fasted state, which may have an impact on efficacy if development of resistance is associated with attainment of suboptimal plasma levels.

Food effect studies with lower IDV doses (200- and 400-mg) have been conducted. The food effect with the 800 mg IDV dose is less pronounced than with the lower doses. This decreased food effect may be consistent with the observed nonlinear pharmacokinetics of IDV (more than dose proportional increases in exposure with increasing dose). In some previous studies, light meals (fewer calories and lower fat content) were given with 800 mg single doses. In those studies, the plasma pharmacokinetics following administration of IDV capsules with the light meal were comparable to those when capsules were administered in the fasted state. Hence, results from the IDV food effect studies suggest that the type of meal (light vs. heavy) is important when evaluating food effect with IDV.

Conclusion

Indinavir AUC and C_{max} are significantly decreased in the presence of a high fat meal.

Recommendation

IDV should not be administered with, shortly before, or shortly after a heavy meal.

B. Taste of Indinavir Sulfate Capsules Administered as a Slurry in Applesauce Versus After a Bacon and Eggs Breakfast Versus Administered in the Fasted State

Table VI shows the results of the taste evaluation study.

Table VI: Taste Evaluation for Indinavir Sulfate

	Slurry (Applesauce)	Bacon and Eggs	Fasted
Evaluation			
No taste	1	12	10
Better than average taste for medication	0	0	2
Average taste for medication	0	0	0
Worse than average taste for medication	2	0	0
Awful taste for medication	3	0	0
Worst taste for any medication ever taken	6	0	0

The majority of subjects ($\approx 92\%$) rated the IDV applesauce slurry as worse than average for a medication, awful taste, or the worst taste for any medication ever taken. Conversely, all subjects rated IDV sulfate capsules after a bacon and eggs breakfast or administered in the fasted state as no taste or

better than average for a medication. These findings suggest that the use of applesauce to form an IDV slurry may be problematic in the targeted pediatric population. Some pediatricians administer medicines to children, who cannot swallow capsules or pills, in a semi-solid food, such as applesauce after the drug has been mixed in the food. However, results from this pilot study in adults indicate that the taste of the slurry is not acceptable. It is noteworthy that the palatability of IDV sulfate in applesauce has not been evaluated in children, although the pharmacokinetics of the slurry were evaluated in pediatric patients (Study 068).

Conclusion

Most subjects found that indinavir sulfate mixed in applesauce had a disagreeable taste, whereas, indinavir administered in the fed or fasted state had acceptable taste.

C. Safety Evaluations and Conclusion

All treatment regimens were generally well tolerated in this study. No serious or severe clinical adverse experiences occurred in the study. No clinically significant deviations were found in elevation of clinical safety tests such as physical examination, vital signs, and ECG.

Conclusion

Single 800-mg doses of indinavir sulfate administered as a slurry in applesauce, as capsules following a bacon and eggs breakfast, or as capsules fasted are generally well tolerated.

Review of Protocol No. 041

Principal Investigators/Study Site: Phillip Pizzo M.D. (041-00 to 041-05) followed by Brigitta Mueller, M.D., (Protocol 041-06) NIH, Bethesda, MD. / Pediatric Branch, NCI, at entry, Day 14, Weeks 12/13, and 16. Interim visits at NCI or Children's Hospitals in St. Petersburg, or Gainesville, FL.

Clinical Study Dates: 18-Jul-1995 to 02-Dec-1996

Analytical Sites Merck Research Laboratories (Woolf and Eisenhandler laboratories), West Point, PA and by _____

Title: A Phase I/II Study of the Protease Inhibitor Indinavir (MK-0639) in Children With HIV Infection (Protocol #041)

Primary Objectives (summarized)

- To determine the safety and tolerance of the protease inhibitor IDV in HIV-infected children who have not received prior antiretroviral therapy as well as in children who have become refractory to prior therapy or who have experienced toxicity to prior therapy.
- To define the toxicities of IDV
- To determine the pharmacokinetic profile of IDV after a single oral dose, after monotherapy, and after combination therapy
- To assess the preliminary antiviral and clinical effects of IDV and combination therapy (IDV, ZDV and 3TC) in children

Secondary:

- To determine the pharmacokinetics of IDV with ZDV and 3TC.
- To determine whether viral resistance to IDV is present at the time of entry, or develops during treatment, and to correlate the emergence of resistance with clinical, virologic, and immunological parameters
- To determine the viral and CD4 kinetics before and after initiation of antiretroviral therapy.

Introduction

This study review summarizes the contents of Study Report 041, which was submitted as a supportive study to sNDA 20-685 SE8-043: Indinavir for treatment of HIV-1 infection in pediatric patients. In Protocol 041, the applicant tested various IDV doses and formulations in an attempt to select a pediatric IDV formulation and arrive at a suitable pediatric dose. Pharmacokinetic (PK) and efficacy data from these dose finding studies are presented comprehensively by the applicant. Preliminary results from Study 041 were presented to the Agency previously and briefly reviewed by DPE III. The applicant concluded that none of the liquid formulations tested were adequate for pediatric use, due to "inadequate pharmacokinetics" (bioinequivalence relative to marketed IDV capsule formulations). Subsequently, the applicant selected the 500 mg/m² q8 hr dose for pediatric use, and the dose would be evaluated using only the sulfate capsule formulation. The Agency agreed with the applicant's conclusion, however, the Agency had some reservations on the safety and PK characteristics of IDV produced by the selected dosage.

The review focuses on results from studies with the sulfate capsule formulation with brief mention of the liquid formulations. The appendix to this study contains pharmacokinetic data from administration of the various liquid formulations.

Study Design

An open-label study design with a time-lagged, dose-escalation scheme was used to evaluate the safety and tolerability of IDV monotherapy in HIV-infected male or female children. Six protocol amendments were made during the course of the study. A list of the amendments and reasons for these amendments are summarized in the appendix to Study 041. In brief, the amendments were made to allow testing of various formulations in an attempt to obtain suitable IDV bioavailability. Children were entered into 2 age blocks (<12 years and ≥ 12 years), and the dose levels in each age group were sequentially increased, independent of the other block. The dose of IDV was calculated by body surface area (BSA) to be approximately equivalent to adult doses of 400, 600, and 800 mg q 8hr, respectively. For this calculation, it was assumed that the adult average BSA was 1.73 m². Various IDV treatments were tested and are listed below:

- _____ fasted
- _____
- _____ fasted
- _____ fasted
- _____ fasted
- _____
- _____
- _____

Table I: Number of Patients Treated at Each Dose Level with Various IDV Formulations

IDV Dose (mg/m ²)	250	350	250	350	500
Formulation	Suspension	Suspension	Capsules	Capsules	Capsules
# of Patients (N)	8	13	8	11	14

Subjects

Asymptomatic HIV-infected male or female children from 6 months to 18 years of age participated in the study. Demographic characteristics of these subjects are presented in Table II.

Table II: Demographic Characteristics of Pediatric Patients in Study 041

Patient Characteristics by Treatment Group number (%)						
IDV Dose (mg/m ²) And Formulation	250 SUS	350 SUS	250 CAP	350 CAP	500 CAP	Total
<i>Number</i>	(N=8)	(N=13)	(N=8)	(N=11)	(N=14)	(N=54)
Gender						
Male	2 (25)	11 (85)	6 (75)	8 (73)	9 (64)	36 (67)
Female	6 (75)	2 (15)	2 (25)	3 (27)	5 (36)	18 (33)
Race						
White	6 (75)	7 (54)	6 (75)	7 (64)	8 (57)	34 (63)
Black	2 (25)	5 (38)	2 (25)	3 (27)	4 (29)	16 (30)
Hispanic	0 (0)	1 (8)	0 (0)	0 (0)	1 (7)	2 (4)
Middle east	0 (0)	0 (0)	0 (0)	1 (9)	0 (0)	1 (2)
Biracial	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (2)
Age (Years)						
3 to 11	5 (63)	7 (54)	5 (63)	7 (64)	8 (57)	32 (59)
12 to 18	3 (38)	6 (46)	3 (38)	4 (36)	6 (43)	22 (41)
Mean (SD)	10.0 (3.6)	8.8 (4.5)	10.4 (4.6)	10.7 (4.3)	9.8 (4.4)	9.9 (4.2)

It is noteworthy that some patients received more than one IDV treatment. In addition, subjects were on IDV capsules (median and mean ~ 110 days) for a longer period than on the IDV suspensions (median and mean ~ 83 days) because patients were switched from the poorly bioavailable suspension to the capsules per a Protocol Amendment (see Study 041 Appendix).

Dosage Forms and Batch Numbers

- IDV 200-mg/mL oral suspension 06390SU001A004, 06390SU001A005, 06390SU001A006
- IDV 100-mg capsules 0639DFC002B015, 0639DFC002B016
- IDV 200-mg capsules 0639DFC015C008, 0639DFC015C023, 0639DFC015C022, 0639DFC015C024
- IDV powder for reconstitution 06390S0001A002 _____ oral solution D06390S0002A003
- IDV 200-mg/mL _____ 06390SU004A001

Bioanalytical Methods and Assay Performance

Plasma concentrations of IDV were determined using HPLC chromatography with UV detection. Samples were assayed in three different laboratories. The assay limits of quantitation (LOQ) were:

- **Wolff** _____
- **Eisenhandler** _____
- _____

Inter-day precision varied from _____, whereas mean accuracy varied from _____ % for the standard curve samples. With QC samples, the inter-day precision was : _____ and _____, whereas, the accuracy was _____ or the high, middle and low samples, respectively. The assay was linear over the region _____. Sample chromatograms were acceptable, indicating that the assay was specific for IDV.

Pharmacokinetic Methods and Analysis

Pharmacokinetic evaluations were performed on the following occasions:

- Week 1: Days 1 and 2
- Day 14
- Week 16 and possibly on
- For some subjects, 2 additional treatment Days occurred during Weeks 1 to 16

IDV concentrations were converted to a molar basis using a molecular weight of 613.81 prior to PK analysis. The PK measures, $AUC_{(0-8\text{ hr})}$, C_{\max} , $C_{8\text{ hr}}$, T_{\max} were estimated from plasma concentration time data. AUC was calculated by a modified trapezoidal rule using piecewise cubic polynomials. In the AUC calculation, concentrations below LOQ were given a value of zero to be consistent with previous studies. For $C_{8\text{ hr}}$, concentrations below LOQ were given a value of one-half LOQ to allow log transformation of $C_{8\text{ hr}}$ data (see Comment below). Treatment comparisons were made without regard to the study day, based on the assumption that accumulation upon multiple dosing was negligible. Geometric means and corresponding 90% confidence intervals were computed for $AUC_{0-8\text{ hr}}$, C_{\max} , $C_{8\text{ hr}}$. In addition to geometric means, arithmetic means and standard deviations were calculated for $AUC_{0-8\text{ hr}}$, C_{\max} , $C_{8\text{ hr}}$, and T_{\max} .

Comment

The procedures (AUC: concentrations below LOQ given a value of zero and $C_{8\text{ hr}}$: concentrations below LOQ given a value of one-half LOQ) employed for AUC and $C_{8\text{ hr}}$ calculations introduce errors that can not be quantified. Consequently, interpretation of data using these assumptions should be made cautiously. It is noted that all doses with the exception of the 500 mg/m² capsule dose used this approximation.

RESULTS AND DISCUSSION

Pharmacokinetics

Pharmacokinetics measures for IDV following administration of IDV liquid formulations and capsules are summarized in Table IV

Table IV: Pharmacokinetic Parameters (Arithmetic Means \pm SD) for IDV Monotherapy—Fasted State

	250 SUS (N=5)	350 SUS (N=6)	250 CAP (N=9)	350 CAP (N=13)	500 CAP (N=14)
Pharmacokinetic Measure					
$AUC_{(0-8\text{ hr})}$ (nM hr)	6463 \pm 6931	7869 \pm 11,426	8608 \pm 3641	17,053 \pm 6837	30,536 \pm 13,169
C_{\max} (nM)	5381 \pm 5864	5702 \pm 6142	6321 \pm 3186	10,451 \pm 4729	15,832 \pm 5899
$C_{8\text{ hr}}$ (nM)	24.2 [†] \pm 8.3	33.1 [†] \pm 31.0	32.3 [†] \pm 15.8	57.4 [†] \pm 48.1	192.5 \pm 275.9
T_{\max} (hr)	0.6 \pm 0.2	0.8 \pm 0.3	1.1 \pm 0.5	1.0 \pm 0.4	1.1 \pm 0.6

[†] Values below the assay limit of reliable quantification assay () were set equal to half of the threshold of reliable quantification ()

Data from several patients were either unavailable or compromised for a variety of reasons. The reasons for exclusions and absence of data from the PK analyses will not be addressed in this review. PK data were highly variable as observed in other pediatric studies (Studies 068 and 395). Greater than proportional increases in exposure measures were observed with increasing dose, which is line with IDV's reported nonlinearity due to saturable metabolism. It is noted that several C_{\min} determinations for the 250 and 350 mg/m² IDV q 8hr doses were below the lower limit of quantitation (LLQ) and these C_{\min} were estimated as 1/2 LLQ. This approach was described in the protocol, but may not be reflective of the true

C_{min} value. An alternative and possibly more accurate approach would be to extrapolate a minimum concentration (at 8 hours) from the terminal portion of the plasma concentration time curve. Consequently, reported C_{min} data for the suspensions and capsules at these two lower doses should be interpreted with caution. Generally, PK exposure measures produced by administration of the IDV suspension or capsule at the 250 mg/m² q8 hr or 350 mg/m² q8 hr IDV:

- had C_{min} for both dose levels below 100 nM
- were not comparable to targeted adult exposure values

The sponsor indicates that the 500 mg/m² liquid suspension was not tested because of the poor bioavailability observed at the lower dose levels.

Dose Selection: Comparison of exposure measures obtained in Children and Adults Following Administration of Intact Capsules

The applicant compared the PK of IDV in children receiving the proposed pediatric regimen (Protocol 041) to adults (Study 021) receiving the recommended adult dosage. This comparison was deemed acceptable for purposes of this review. Geometric means and geometric mean ratios with their associated 90 % confidence intervals are presented in Table V.

Table V: Indinavir Pharmacokinetics in HIV-Infected Children Receiving Indinavir 500 mg/m² q 8hr and Adults Receiving Indinavir 800 mg q 8hr as Sulfate Capsules While Fasted

PK Parameter	Geometric Means (90% CI)		GMR (90% CI)
	Protocol 021 (Adult) IDV 800 mg q 8hr (N=16)	Protocol 041 (Pediatric) IDV 500 mg/m ² q 8hr N=14)	
AUC _{0-8 hr} (nM hr)	28,719	27,965	0.97
90 % CI	23,932 - 34,463	22,967 - 34,051	0.75 - 1.26
C_{max} (nM)	11,948	14,823	1.24
90 % CI	10,171 - 14,036	12,457 - 17,640	0.99 - 1.56
C_{8hr} (nM)	208	100	0.48
90 % CI	142 - 305	66 - 151	0.28 - 0.83

Based on geometric means and 90% confidence intervals, AUCs for adults and pediatric patients appeared comparable. Geometric mean C_{max} was greater in pediatric patients than in adults. Conversely, the geometric mean C_{min} in adult patients was almost 2-fold higher than in pediatric patients. IDV C_{max} values have been previously correlated to the incidence of nephrolithiasis. Therefore, results from the cross-study comparison suggest that the incidence of nephrolithiasis in pediatric patients may be greater than that in adults receiving IDV doses that produce comparable AUC. A comparison of adult-to-pediatric C_{min} indicates that the efficacy of IDV at the selected pediatric dose may be decreased relative to adults, if the two populations have similar exposure-response relationships that are dependent on C_{min} . Potentially this decreased efficacy may lead to the development of resistance, if resistance development is associated with obtaining low plasma concentrations. The relationship, if any, between C_{min} and clinical efficacy was not identified. Exposure-response relationships were not established for any of the IDV exposure measures in this study. The finding of lower C_{min} and higher C_{max} with the 500 mg/m² q8 hr dose in pediatrics compared to the recommended adult dose, suggests that a critical assessment of the risk: benefit ratio should be made prior to approving the proposed pediatric dose.

II. Efficacy Evaluations as Summarized by the Applicant

The following section summarizes the efficacy finding from the applicant's perspective.

- The IDV 500-mg/m² capsules group was associated with the largest median decrease in plasma viral RNA over the 16 weeks of therapy.

- The profile of plasma viral RNA changes from baseline over the 16-week study period for this group was similar to that seen in the IDV 800 mg q 8hr monotherapy arm of Protocol 039
- A return towards baseline after an initial decrease in plasma viral RNA was observed and may be of concern with respect to the emergence of resistant viral populations during IDV monotherapy treatment.
- Monotherapy with IDV results in an elevation of CD4 cell counts and percent CD4 cell counts, compared to baseline, in all treatment groups.

The Medical Reviewer agrees with the applicant's assessment.

III. Conclusions and Discussion

A. Dosage Formulations

None of the IDV liquid dosage formulations tested produced comparable bioavailability to the currently marketed indinavir dry-filled capsule formulation. Hence, none of these liquid formulations are suitable as an indinavir pediatric formulation.

B. Dose Selection Rationale

According to the applicant, the 500 mg/m² IDV q 8hr was the most efficacious of the doses studied in this dose ranging study. The Medical Reviewer agrees with the applicant's assertion, but disagrees on 500 mg IDV/m² q 8hr being the optimal pediatric dose. The applicant identified a pediatric dose of 500 mg IDV/m² q 8hr using the intact capsule, but the PK data presented does not support this dose.

Generally, a suitable pediatric regimen is obtained by identifying the pediatric dosing regimen that achieves exposure similar to the adult dosing regimen that is effective in the adult patient population. By following this approach, one makes the following two assumptions:

- attainment of similar exposure will result in similar efficacy in the two different patient populations
- the disease process in the two populations is comparable.

The selected pediatric dose matched adult AUC produced by the approved adult regimen (800 mg q 8hr), but did not match the C_{max} and C_{min}. For protease inhibitors, such as IDV, the matching of C_{min} is considered critical (see Synopsis). Because there is a lack of comparability between adult and pediatric exposure measures, especially C_{min}, the presented PK data are not sufficient to support approval of the selected pediatric dose. Consequently, clinical efficacy studies in pediatric patients will be required for approval of the pediatric indication and regimen. It is noted that the applicant originally concluded that the 350 mg/m² dose was preferable to the 500 mg/m² dose because the 500 mg/m² dose resulted in unacceptable renal adverse events. However, the applicant decided to pursue the 500 mg/m² dose after reanalysis of the safety data.

Study 041 Appendix

Table I: Protocol Amendments

Amendment Date	Change	Reason
10-Aug-1995	Dose level was increased to 350 mg/m ² q 8hr for the first 12 weeks	Bioavailability of IDV for the first 8 patients was lower than expected.
13-Sep-1995	On Day 15, a subset of patients received IDV in the morning with: _____	BA of IDV suspension markedly lower than the BA of IDV capsules: _____ medium expected to increase IDV BA
2-Oct-1995	Capsules at the IDV 250-mg/m ² q 8hr dose level were administered to patients who could swallow capsules. study duration expanded to 16 weeks	
20-Nov-1995	Additional children enrolled in the IDV 250-mg/m ² group. IDV administered as a _____ PK on Days 1 and 2 of Week 1.	extremely variable bioavailability of IDV suspension, not only between patients, but also within the same patient
04-Mar-1996	Various liquid formulations tested _____ _____ given. Single-dose PK on Days 1 and 2.	_____ not a good alternative because of poor taste and large volume required. Alternative liquid formulations may be more viable.
10-May-1996	Pharmacokinetic analyses were performed comparing IDV 500-mg/m ² _____ on Days 1 and 14 to IDV 500-mg/m ² capsule on Day 2.	_____ appeared to have better BA than the standard suspension

Table II: AUC_(0-8hr) Summary Statistics for IDV

Dose/Formulation	N	GM (nMhr)	90% CI	GMR	90% CI
IDV 250 mg/m ² _____	4	3991.6	606.6 - 26,264.1	_____	_____
IDV 250 mg/m ² _____	4	1084.6	397.3 - 2960.7	0.27	0.05 - 1.55
IDV 350 mg/m ² _____	5	2243.6	789.0 - 6380.5	_____	_____
IDV 350 mg/m ² with _____	5	6689.6	2845.7 - 15,726.2	2.98	0.89 - 10.03

Table III: C_{max} Summary Statistics for IDV

Dose/Formulation	N	GM (nM)	90% CI	GMR	90% CI
IDV 250 mg/m ² _____	4	3508.8	582.1 - 21150.7	_____	_____
IDV 250 mg/m ² with _____	4	606.1	261.0 - 1407.6	0.17	0.04 - 0.84
IDV 350 mg/m ² _____	5	3767.6	1526.8 - 9296.8	_____	_____
IDV 350 mg/m ² with _____	5	2130.5	637.6 - 7118.2	1.77	0.44 - 7.07

Table IV: C_{8hr} Summary Statistics for IDV

Dose/Formulation	N	GM (nM)	90% CI	GMR	90% CI
IDV 250 mg/r	4	24.0	16.4 - 35.1		
IDV 250 mg/m ² with	4	21.2	19.3 - 23.4	0.89	0.67 - 1.18
IDV 350 mg/m	5	25.9	19.0 - 35.3		
IDV 350 mg/m ² with		20.4	20.4 - 20.4	1.27	0.93 - 1.73

Table V: Summary Statistics for AUC(0-8 hr) (nM·hr) for IDV

IDV Dose	N	IDV		IDV Sulfate		GMR	90% CI
		Geo. Mean	90% CI	Geo. Mean	90% CI		
250 mg/m ²	2	3698.6	40.4 - 338,343.2	5991.3	2044.7 - 17,555.7	0.62	0.20 - 19.27
350 mg/m ²	9	4171.1	1308.8 - 13,293.2	16,077.7	10,932.6 - 23,644.2	0.26	0.07 - 0.95
500 mg/m ²	11	7392.3	3394.9 - 16,096.6	27,628.3	21,046.3 - 36,268.8	0.27	0.12 - 0.59

Table VI: Summary Statistics for C_{max} (nM) for IDV

IDV Dose	N	IDV		IDV Sulfate		GMR	90% CI
		Geo. Mean	90% CI	Geo. Mean	90% CI		
250 mg/m ²	2	3098.2	11.9 - 808,856.2	4334.1	3374.5 - 55,667	0.72	0.00 - 145.30
350 mg/m ²	9	3456.0	1265.0 - 9442.1	9811.5	7268.3 - 13,244.4	0.35	0.11 - 1.14
500 mg/m ²	11	4430.3	1895.8 - 10,353.3	14,012.5	11,331.4 - 17,327.8	0.31	0.15 - 0.68

Table VII: Summary Statistics for C_{8hr} (nM) for IDV

IDV Dose	N	IDV		IDV Sulfate		Geo. Mean	90% CI
		Geo. Mean	90% CI	Geo. Mean	90% CI		
250 mg/m ²	2	†	†	†	†	†	†
350 mg/m ²	9	28.5	18.9 - 43.0	37.8	2.20 - 65.0	0.75	0.40 - 1.42
500 mg/m ²	11	35.5	25.8 - 48.7	110.0	56.3 - 215.2	0.32	0.19 - 0.55

† All values less than assay threshold of quantification for both formulations.

Table VIII: Pharmacokinetic Parameters (Geometric Means; N = 4) for IDV at 250 mg/m²

	IDV		IDV Sulfate		GMR	90% CI
	Geo M	90% CI	Geo. M	90% CI		
AUC _(0-8hr) (nM·hr)	9138.0	4450.7 - 18,761.9	10,387.3	6539.3 - 16,499.7	0.88	0.37 - 2.11
C _{max} (nM)	4753.2	2649.4 - 8527.4	7196.9	3821.2 - 13,555.0	0.66	0.35 - 1.24
C _{8hr} (nM)	34.7	16.8 - 71.5	29.3	17.9 - 48.3	1.18	0.52 - 2.69

**This is a representation of an electronic record that was signed electronically and
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/s/

Robert Kumi
6/27/01 06:04:26 PM
BIOPHARMACEUTICS

Kellie Reynolds
7/10/01 10:11:30 AM
BIOPHARMACEUTICS

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-685/S-043
APPLICANT: Merck Research Laboratories
NAME OF DRUG: Crixivan[®] (indinavir)
INDICATION: Treatment of HIV Infection in
Children
TYPE OF REVIEW: Clinical
DOCUMENTS REVIEWED:
MEDICAL INPUT: Melisse Baylor, M.D. (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-685

Trial Designs: The efficacy of indinavir 500 mg/m² every eight hours in pediatric patients was supported by the results of two open-label, single arm, 24-week studies. Merck 068 enrolled 25 HIV-infected children and 20 completed 24 weeks of treatment. ACTG 395 enrolled 16 children with 12 completing 24 weeks of indinavir. The children were aged 4 to 15 years and were all protease inhibitor naive. In both trials, indinavir was used in combination with stavudine and lamivudine.

Results: The primary efficacy endpoint for both studies was the proportion of children with plasma HIV RNA levels less than 400 copies/ml at 16 weeks. In Merck 068 14/25 = 56% had undetectable plasma HIV RNA levels at 16 weeks of treatment. In ACTG 395 9/16 = 56% had undetectable plasma HIV RNA at 16

weeks of treatment.

Only 31 of the 41 children enrolled in the two studies continued past 25 weeks. The applicant has provided the FDA with HIV RNA data extending beyond the original 24 weeks of treatment. In this data, 14/19 children still had undetectable levels at one year in trial 068. With 95% confidence, the probability of being undetectable at one year was between 53% and 93%. In trial 395, 9/12 children still had undetectable levels at six months. With 95% confidence, the probability of being undetectable at six months was between 50% and 100%. These confidence intervals reflect only the probabilistic uncertainty in the estimates. Uncertainty due to open-label assessment, non-measurement of subjects lost to follow-up, differences between the cohorts recruited to the two studies or between those cohorts and the target pediatric population are not reflected in these confidence limits. Nonetheless, the confidence are quite wide.

Conclusion: Because both studies were open-label trials without comparator arms, it is impossible to determine from the data in the trials whether the observed rates are better than would be observed with only stavudine and lamivudine. Any determination of clinical efficacy requires the data from these trials be compared to known rates of undetectable in children treated with only stavudine and lamivudine. Even if such rates were available, the comparison would be fraught with all of the perils common to the use of unmatched, historical controls.

These trials were not designed to test clinical efficacy and they do not permit conclusions of clinical efficacy.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:

Archival NDA #20-685

HFD-530

HFD-530/Dr. Jolson

HFD-530/Dr. Birnkrant

HFD-530/Ms. Lincoln

HFD-530/Dr. Kukich

HFD-530/Dr. Baylor

HFD-725/Dr. Hammerstrom

HFD-725/Dr. Soon

HFD-725/Dr. Huque

HFD-725/Ms. Robinette

March 31, 2000



Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, Maryland 20850

NDA 20-685/S-043: CRIXIVAN™ (Indinavir Sulfate)

SAFETY UPDATE REPORT

Reference is made to the supplemental New Drug Application (sNDA) cited above for CRIXIVAN™ (indinavir sulfate) submitted as an electronic archive on December 22, 1999 in support of the use of CRIXIVAN™ in the treatment of HIV-1 infection in pediatric patients. Reference is also made to a May 7, 1999 submission to IND 41,413: CRIXIVAN™ (indinavir sulfate), Serial Number 837 in which MRL (Merck Research Laboratories, a division of Merck & Co., Inc.) committed to submit the 24-week CSR for ACTG 395 entitled "*A Multicenter, Open-Labelled, 48-Week Study to Investigate the Safety, Pharmacokinetics, and Efficacy of Indinavir in Combination with Stavudine and Lamivudine in Pediatric Patients with HIV-1 Infection (weeks 0 through 24)*" as an amendment to the December 22, 1999 supplemental application cited above within 3 months of submission of the supplement.

With this submission, MRL is providing a Safety Update Report (SUR) to sNDA 20-685/S-043. This SUR provides updated safety information through January 10, 2000 for indinavir sulfate in patients aged 3-18 years. The supplemental application cited above included information from 3 pediatric clinical trials with indinavir (Protocols 068, ACTG 395, and 041) to assess the pharmacokinetics, efficacy and safety of indinavir for the treatment of HIV infection in children (3-11 years of age) and adolescents (12-18 years of age). Included in supplemental application S-043 was a 16-week Clinical Study Report (CSR) for ACTG 395. This SUR includes additional safety data available for Protocols 041 and 068 since the time of the individual study cutoff dates for the supplemental application cited above through the SUR cutoff data of January 10, 2000 and also includes cumulative nephrolithiasis information from Protocols 068, ACTG 395, and 041. Additionally, a 24-week CSR for ACTG 395 is included in this submission as a reference [P395X1] to the SUR per our May 7, 1999 commitment cited above. This CSR provides additional safety and efficacy information through 24 weeks of indinavir exposure in this study. A more detailed summary of the safety information included in this submission can be found in the Executive Summary of the SUR.

Central Document Room

NDA 20-685/S-043: CRXIVAN™ (Indinavir Sulfate)

Page 2

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This Safety Update Report is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the Safety Update Report. All documents requiring signatures for certification are included as paper for archival purposes. All information in this submission is in an electronic format as indicated in the Table of Contents. Review copies of the Safety Update Report Summary and the 24-week CSR for ACTG 395 are provided in hardcopy.

All of the information is contained on one CD and has an approximate size of 100MB. We have taken precautions to insure that any software on the CD is free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Viral Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Christine Kelly, Regulatory Project Manager, Division of Anti-Viral Drug Products. MRL will follow-up with Ms. Kelly to ensure that the appropriate reviewers have been given access to this electronic submission.

We consider the filing of this information to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,



Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs

Attachment: CD

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Federal Express #1

Desk Copy: Ms. Christine Kelly, Regulatory Project Manager (cover letter)
HFD-530, Room S405

Federal Express #2

HFD-550/Kelly

NDA 20-685/S-043

AUG 10 2000

Merck Research Laboratories
Attention: Michelle Kloss, Ph.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

Please refer to your December 23, 1999 Supplemental New Drug Application submitted under section 505 (b) of the Federal Food, Drug and Cosmetic Act for Crixivan (indinavir sulfate) 200mg and 400mg capsules. This supplement provides for the treatment of HIV-1 infection in pediatric patients. We are currently in the process of completing our review of your application.

The supplement contains the results from two pediatric trials, Merck 068 and ACTG 395, which are intended to support the claim of safety and efficacy of Crixivan in the treatment of HIV-1 infection in children. The results of Merck 041, a dose finding study, are provided as further support of safety. In addition, the results of Merck 058, a small pharmacokinetic study of indinavir used as a slurry, were included to support use of a slurry preparation in children.

You base your claim that Crixivan is safe and efficacious in the treatment of HIV-1 in children on the comparability of indinavir 500 mg/m² three times daily with the adult dose of 800 mg three times daily. However, certain pharmacokinetic parameters noted in Merck 068 and ACTG 395 were outside of the confidence intervals needed for comparability with the adult dose. Therefore, the dose proposed for use in children is not comparable to the adult dose of 800 mg three times daily.

As soon as possible, please submit any additional information or analyses you may have that are relevant to support your claim.

Should you have any questions or comments, please contact Ms. Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

HSI

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

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

45 DAY FILING MEETING MINUTES

NDA: 20-685/SE1-043

DATE: 9 February 2000

DRUG: Crixivan (indinavir sulfate) 200mg, 333 mg and 400mg capsules.

SPONSOR: Merck Research Laboratories

PARTICIPANTS: Heidi Jolson, M.D., M.P.H., Division Director
Debbie Birnkrant, M.D., Deputy Division Director
Walla Dempsey, Ph.D., Associate Division Director
Stanka Kukich, M.D., Medical Team Leader
Melisse Baylor M.D., Medical Reviewer
Girish Aras, Ph.D., Statistical Team Leader
Kellie Reynolds, Pharm.D., Biopharmaceutical Team Leader
Robert Kumi, Ph.D., Biopharmaceutical Reviewer
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Lalji Mishra Ph.D., Microbiology Reviewer
Steve Miller, Ph.D., Chemistry Team Leader
George Lunn, Ph.D., Chemistry Reviewer
Christine Kelly, RN, MS, MBA, Project Manager

BACKGROUND: Merck Research Laboratories submitted this supplemental application on December 23, 1999. It has a filing date of February 21, 2000 and a user fee date of October 23, 2000. This meeting was held to determine if the application is fileable. This supplement provides for clinical pharmacokinetics, clinical efficacy and safety data in support of the use of Crixivan in the treatment of HIV-1 infection in pediatric patients and proposes revisions to various sections of the product label to reflect this new information. With this submission, MRL plans to fulfill their Phase 4 commitment of establishing a dose, safety and tolerability in pediatric patients.

CHEMISTRY: This supplement is fileable.

It was decided that the supplement would be split into two supplements. A second chemistry supplement for change in formulation will be added to account for the 100-mg capsule. The level of impurities in the capsule formulation will be addressed with this submission.

PHARMACOLOGY/TOXICOLOGY: The supplement is fileable.

The pharmacologist was unable to attend the meeting, but she did not have any issues or concerns.

MICROBIOLOGY: The supplement is fileable.

The microbiologist wants to make labeling changes to bring this applicant's label in line with the other protease inhibitors' labels.

STATISTICS: The supplement is fileable.

BIOPHARMACEUTICS: The supplement is fileable.

1. The sponsor will be asked to provide dissolution data for the 100-mg capsule.
2. The reviewer will be reviewing studies ACTG 395, and Merck 041, Merck 068, and Merck 058.
3. It is possible that the dose selected by the sponsor (500 mg/meter squared) may be unsupported by the studies submitted.
4. The use of the capsule contents as a slurry with applesauce will also be examined with this submission.

CLINICAL: The supplement is fileable.

The sponsor will be asked to provide additional drug exposure data, line listings, and data for individual subjects in all pediatric studies, for data past 16 weeks in ACTG 395, and for individual patient data for the pediatric study performed by Kline et. al.

DISCUSSION:

It was determined that this supplement will have a standard review, with a 10-month review clock.

CONCURRENCE:

HFD-530/BP/Kumi/2-11-00
HFD-530/Micro/Connors/4-10-00
HFD-530/MO/Baylor/2-11-00
HFD-530/MO TL/Kukich/
HFD-530/Chem/Lunn/ 2-11-00

cc:

NDA 20-685
Division File
HFD-530/TL /Kukich
HFD-530/MO/Baylor
HFD-530/Chem/ Lunn
HFD-530/Pharm/Yuen
HFD-530/Micro/Connors
HFD-530/Biopharm/Kumi
HFD-530/Stat/Hammerstrom
HFD-530/CSO/Kelly

45 Day Filing Meeting

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: October 23, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530
Melisse Baylor, M.D., Medical Reviewer, HFD-530

NDA: 20-685

Subject: Labeling changes regarding the Pediatric Supplement (NDA 20-685, SE1-043).

The following labeling changes are being conveyed on behalf of Dr. Baylor.

CLINICAL PHARMACOLOGY, *Drugs That Should Not Be Coadministered With CRIXIVAN*, please add "See **WARNINGS**" to the end of the paragraph:

Administration of indinavir (800 mg every 8 hours) with rifampin (600 mg once daily) for one week resulted in an $89\% \pm 9\%$ decrease in indinavir AUC.

In a published study, eight HIV-negative volunteers received indinavir 800 mg every eight hours for four doses prior to and at the end of a 14-day course of St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg three times daily. Indinavir plasma pharmacokinetics were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC_{0-8h} of indinavir was decreased $57\% \pm 19\%$ and the C_{8h} of indinavir was decreased $81\% \pm 16\%$ compared to when indinavir was taken alone. All subjects demonstrated a decrease in AUC 0-8h (range 36 to 79%) and a decrease in C_{8h} (range 49 to 99%). (See **WARNINGS**)

WARNINGS, *Nephrolithiasis/Urolithiasis*, please add "9.3%" to the following sentence:

Nephrolithiasis/urolithiasis has occurred with CRIXIVAN therapy. The frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (9.3%).

PRECAUTIONS, Pediatric Use, please delete the sentence with the strikethrough below and add the sentence following it:

Pediatric Use

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m² every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adults receiving the recommended dose (see **CLINICAL PHARMACOLOGY, Pediatric**).

Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see **WARNINGS, Nephrolithiasis/Urolithiasis**). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Christine Lincoln, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products



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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 18, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 10/18/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530
Kellie Reynolds, Pharm. D., Pharmacokinetic Team Leader, HFD-530 KSR 10/18/2000
Robert Kumi, Ph.D., Pharmacokinetic Reviewer, HFD-530 RCL 10/18/2000

NDA: 20-685

Subject: Labeling changes regarding the Pediatric Supplement (NDA 20-685, SE1-043).

The following labeling changes are being conveyed on behalf of Dr. Baylor and Dr. Kumi.

CLINICAL PHARMACOLOGY, *Pediatric:*

In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m² every 8 hours, produced AUC_{0-8hr} of 38,742 ± 24,098 nM•hour (n=34), C_{max} of 17,181 ± 9809 nM (n=34), and trough concentrations of 134 ± 91 nM (n=28). The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50 % of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

PRECAUTIONS, *Pediatric Use:*

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m² every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles

previously observed in adults receiving the recommended dose (see **CLINICAL PHARMACOLOGY, Pediatric**). In the 32 children who were followed through 24 weeks of treatment, rates of viral RNA suppression were similar to rates observed in adult trials; however a substantially higher rate of nephrolithiasis was observed when compared to adult historical data (see **WARNINGS, Nephrolithiasis/Urolithiasis**). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

We would like to bring to your attention another change to the Crixivan label that we are proposing at this time. Under **DOSAGE AND ADMINISTRATION** section, we would like to propose to delete the second sentence in the first paragraph because it is no longer accurate. The sentence to be deleted is as follows:

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Christine Lincoln, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 13, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 *SK 10/13/00*
Melisse Baylor, M.D., Medical Reviewer, HFD-530

NDA: 20-685

Subject: Labeling changes regarding the Pediatric Supplement (NDA 20-685, SE1-043).

The following labeling changes are being conveyed on behalf of Dr. Baylor.

16 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Christine Lincoln, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

Record of Teleconference

NDA: 20-685

Date: October 3, 2000

Drug: Crixivan (Indinavir sulfate)

Sponsor: Merck Pharmaceuticals

BETWEEN: Representatives of Merck

Michelle Kloss, Ph.D., Regulatory Affairs
Randi Leavitt, M.D., Ph.D., Director Clinical Research
Josh Chen, Ph.D., Statistics
Anita Cunningham, Labeling
Bonnie Goldmann, Ph.D., Regulatory Affairs
Leigh Anne Maione, Regulatory Affairs
Elizabeth Migoya, Ph.D., Clinical Pharmacology
Linda Hawe, Clinical Research
Greg Winchell, Ph.D., Drug Metabolism
Michael Nessly, Statistics

AND: Representatives of DAVDP

Heidi Jolson, M.D., M.P.H., Division Director
Stanka Kukich, M.D., Team Leader
Melisse Baylor, M.D., Medical Reviewer
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer
Christine Lincoln, RN, MS, MBA, Project Manager

SUBJECT: Pediatric Supplement SE1-043

Background: This telecon was requested by the sponsor to discuss the Agency's telephone facsimile sent to the sponsor on August 30, 2000. The facsimile contained labeling changes regarding the pediatric supplement (N20-685, SE1-043).

Discussion:

1. The sponsor requested that FDA explain their perspective on the pediatric supplement and the labeling changes that were recommended by the Division. FDA stated the information provided in the supplement on C_{\min} revealed that the indinavir 500 mg/m² every 8 hours was not comparable to the adult dose. Therefore, the safety and efficacy results of clinical trials in adults cannot be extrapolated to children and the pediatric data presented in the supplement has to support pediatric dosing on its own merit. The pediatric efficacy studies included in

the supplement, Merck 008 and ACTG 395, had small numbers of patients (only 31 subjects completed 24 weeks of indinavir), were open label, and had no comparator arm. In addition, numerous adverse events were reported in children raising questions about the safety of this dose of indinavir. Dr. Jolson stated that the clinical studies included in this supplement did not identify a safe and efficacious dose of indinavir and were inadequate to support pediatric labeling changes.

2. FDA stated that they recognize that the data showed a durable viral load response to 60 weeks. However, this was based on the studies of a small number of patients without a comparator arm, and was insufficient to support inclusion of efficacy data in the package circular.
3. FDA voiced their concern about the low indinavir trough values noted in HIV-infected children, which were 50% lower than historical adult controls. Dr. Jolson stated that during a recent Advisory Committee, experts in the field stated that the most important pharmacokinetic parameter for protease inhibitor dosing is the C_{min} . Although studies are still needed to confirm this position, the trough is still considered as the most critical pharmacokinetic parameter for efficacy. Because of this, more dose exploration should be done and this dose should not be included in the package circular.
4. The FDA also expressed concern about the safety profile of indinavir in children. Although the types of adverse events noted in children were similar to those seen in adults, the incidence of adverse events, particularly nephrolithiasis, were much higher in children. Dr. Kukich also recommended updating the package circular to reflect the increased incidence of nephrolithiasis in adults that has been reported in recent scientific publications.
5. The sponsor stated their concern that the Division's labeling recommendations did not reflect a balanced view of the pediatric clinical studies of indinavir. The sponsor stated that some efficacy data should also be presented in order to fairly represent the results of these studies. Dr. Jolson stated that the sponsor could submit proposed wording about pediatric efficacy and that the Division would review it.

Action:

1. The sponsor will submit a label with proposed wording to the Agency by the beginning of next week.
2. The Agency plans to take an action on this supplement by October 20, 2000.

Concurrence:

HFD-530/MO TL/Kukich 10-11-00

HFD-530/MO/Baylor 10-3-00

cc:

NDA 20-685

Division File 20-685

HFD-530/TL/Kukich

HFD-530/MO/Baylor

HFD-530/CSO/Lincoln

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 15, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530
Melisse Baylor, M.D., Medical Reviewer, HFD-530 *SK 9/15/00 MSB 9/15/00*

NDA: 20-685

Subject: Clinical comments regarding the Pediatric Supplement (NDA 20-685, SE1-043).

The following comments are being conveyed on behalf of Dr. Melisse Baylor and additional comments may follow.

As we review NDA 20-685, S-043, we would appreciate additional information in order to facilitate our review.

1. In the datasets included in the Safety Update Report submitted March 31, 2000, procedures were listed but the indications or results for these procedures were not included. Please provide the indications for and the results of the patient procedures that are included in the attached datasets (please see the following two pages).
2. Please provide a list of the study subjects with undetectable plasma HIV RNA levels (<400 copies/ml) at 24 weeks in both Merck 068 and ACTG 395. Please list each study subject by patient number for each study.

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LSI

Christine Lincoln, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 30, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 8/30/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 MSB 8/30/00

NDA: 20-685

Subject: Labeling changes regarding the Pediatric Supplement (NDA 20-685, SE1-043).

The following labeling changes are being conveyed on behalf of Dr. Baylor. The new information included under the **Clinical Pharmacology: Pediatric** section is still under discussion in the Division. Additional comments may follow.

22 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

151

Christine Lincoln, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 18, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Kelly, RN, MS, MBA, Regulatory Health Project Manager *LSI*

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-
Melisse Baylor, M.D., Medical Reviewer, HFD-530 *LSI*

NDA: 20-685

Subject: Clinical comments regarding pediatric supplement (sNDA 20-685, SE1-043).

Please refer to your supplemental New Drug Application for the use of Crixivan in the treatment of HIV infection in children.

1. Please provide further information on subjects who discontinued Merck study 041 for "other" reasons. There was one such patient in the combination phase and four patients in the study extension after 48 weeks. Please also provide the case report forms for these subjects.
2. Please provide the case report forms for the eight patients who withdrew from Merck study 041 during the combination and extension phases.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

LSI
Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 20, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Kelly, RN, MS, MBA, Regulatory Health Project Manager

Through: Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-531
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer, HFD-531
151 6/20/00

NDA: 20-685

Subject: Clinical Pharmacology Comments regarding Pediatric Supplement (sNDA 20-685, SE1-043).

As we continue to review data from Merck 069 and 058, we would appreciate the following information to facilitate our review:

Please provide bioanalytical assay validation reports for Study Protocols 069 and 058.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

6/20/00

Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 19, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Christine Kelly, RN, MS, MBA, Regulatory Health Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530
Melisse Baylor, M.D., Medical Reviewer, HFD-530

NDA: 20-685

Subject: Clinical Comments regarding Pediatric Supplement (sNDA 20-685, SE1-043).

As we continue to review data from Merck 069, we would appreciate the following information to facilitate our review:

Please provide viral RNA load data from baseline to study discontinuation for individual patients participating in Merck 069. Please provide this data as SAS transport files.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 22, 2000

To: Michele Kloss

Address: Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Fax-610-397-2516

From: Sean J. Belouin, R.Ph., Regulatory Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530
Melisse Baylor, M.D., Medical Reviewer, HFD-530

NDA: 20-685

Subject: Clinical Comments regarding Pediatric Supplement (sNDA 20-685, SE1-043).

The following are requests for additional information in order to facilitate our review of the pediatric efficacy supplement for indinavir (sNDA 20-685, SE1-043).

1. We appreciate your response of March 10, 2000 to our last request for information; in your response the drug exposure data for the pediatric studies of indinavir were supplied as pdf files. Please provide the drug exposure data for each study subject enrolled in Merck 068, ACTG 395, and Merck 041 as SAS transport files.
2. In the pediatric efficacy supplement, 24 week safety and efficacy data were provided for patients enrolled in Merck 068, and 16 week data were supplied for patients in ACTG 395. Please provide any safety and efficacy data currently available from ongoing follow-up of patients enrolled in these two pediatric trials and indicate when you plan to submit future follow-up information from these studies.
3. Because data from Merck 021 are proposed as a comparator group in the pediatric efficacy supplement, please provide the individual patient data including efficacy, safety, and pharmacokinetics from Merck 021 as SAS transport files.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please *feel free to contact me if you have any questions regarding the contents of this transmission.*

Sean J. Belouin, R.Ph.
Regulatory Health Project Manager
Division of Antiviral Drug Products

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 11, 2000

To: Michele Kloss, Ph.D.

Address: Merck Research Laboratories
P.O. Box 4 Sumneytown Pike, BLA-20
West Point, PA 19486-0004
Fax- 610-397-2516

From: Christine Kelly, RN, MS, MBA, Project Manager, HFD-530

Through: Stanka Kukich, M.D., Medical Team Leader
Melisse Baylor, M.D., Medical Reviewer

NDA: 20-685

Subject: Pediatric Supplement SE1-043 dated 12/22/99

The following are requests for information to facilitate the review of your Supplemental New Drug Application (sNDA) for the use of Crixivan for the treatment of HIV-1 infection in pediatric patients. As we continue our review, additional comments may follow.

1. Please provide additional drug exposure data for each study subject enrolled in Merck 068, ACTG 395, and in all phases of Merck 041. Please supply each subject's dose in mg/m² with start and stop dates for dosage changes and provide dates for any time in which indinavir was held.
2. Please provide data for individual study subjects as line listings for subjects enrolled in Merck 069. Please include efficacy, adverse event, and pharmacokinetic results and provide this data in an electronic format.
3. If it is available, please provide data for individual study subjects (efficacy, safety, and pharmacokinetic results) from Mark Kline's study of indinavir in pediatric subjects, which was published in *The Journal of Pediatrics* in 1998.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products