CLINICAL REVIEW

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Submission Number	034; 017
Submission Code	SE5
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Reviewer Name	Andreas Pikis, M.D.
Review Completion Date	October 4, 2005
Established Name	Ritonavir
Trade Name	NORVIR
Therapeutic Class	Antiretroviral; HIV protease inhibitor
Applicant	Abbott Laboratories
Priority Designation	P
Formulation	100 mg soft gelatin capsules 80 mg/mL oral solution
Dosing Regimen	Adults: 600 mg twice daily Pediatric patients: 350 to 400 mg/m^2 twice daily and not to exceed 600 mg twice daily
Indication	Treatment of HIV infection in combination with other antiretroviral drugs
Intended Population	Children > 1 month to 2 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The pharmacokinetic, safety, and activity data submitted in this supplemental NDA (sNDA), together with the previous demonstration of efficacy in adult patients, support the approval of ritonavir (RTV) for the treatment of HIV-1 infected pediatric patients > 1 month to 2 years of age. The submitted data complete the applicant's presentation of their pediatric development program for RTV. The Pediatric Exclusivity Board members agreed with the Division and concluded Abbott provided an adequate response to the Written Request. As a result, Pediatric Exclusivity was granted on June 15, 2005.

The applicant submitted data from two clinical trials conducted by the Pediatric AIDS Clinical Trial Group (PACTG) in response to the final amended Pediatric Written Request to provide information on the multiple-dose pharmacokinetic, safety, and activity of RTV in combination with other antiretroviral agents in HIV-1 infected children > 1 month to 2 years of age. The original Pediatric Written Request was issued on April 19, 1999 and was last amended on November 4, 2004. Study PACTG 345 is the pivotal study to support Pediatric Exclusivity and use of RTV in patients > 1 month to 2 years of age. Study PACTG 366 provided supportive pharmacokinetic and safety data.

Overall, the pharmacokinetic, safety, and activity data submitted in this sNDA allow for a reasonable recommendation for dosing RTV in pediatric patients > 1 month to 2 years of age. Pharmacokinetic results from study PACTG 345 showed that higher RTV exposures were not evident with 450 mg/m^2 BID dose compared to 350 mg/m^2 BID dose. Moreover, study PACTG 345 showed that RTV exposures after 350 or 450 mg/m^2 BID dosing in infants and children less than two years of age were similar to that previously observed in older children after 250 to 350 mg/m^2 BID dosing with the exception that steady–state trough concentrations were somewhat lower in children <2 years. The 250 and 350 mg/m^2 BID dosing in older children resulted in 58% and 33% higher $C_{trough,ss}$ values, respectively, compared to the $C_{trough,ss}$ values after 350 or 450 mg/m^2 BID dosing in the younger children (< 2 years). Based on these data, a dose regimen up to 350 to 400 mg/m^2 BID is recommended for children > 1 month to 2 years of age.

The antiviral activity and the overall adverse event profile of RTV in children appear similar to that observed in adults.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific Risk Management Activities were requested from the applicant.

1.2.2 Required Phase 4 Commitments

There were no recommendations for additional phase 4 studies or risk management steps based on the review of this supplement.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

RTV is a peptidomimentic inhibitor of both the HIV-1 and HIV-2 proteases. RTV selectively inhibits the virus-specific processing of viral Gag and Gag-POL polyproteins in HIV-1 infected cells, thus preventing the formation of mature infectious virions. The mechanism of action of RTV is similar to other protease inhibitors (PIs) used for the treatment of HIV-infection. Currently, the approved dose in adults is 600 mg twice daily in combination with other antiretroviral agents. The currently recommended dose in children > 2 years of age is as follows:

> 400 mg/m^2 twice daily by mouth and should not exceed 600 mg twice daily. RTV should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily. If patients do not tolerate 400 mg/m^2 twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered. When possible, dose should be administered using a calibrated dosing syringe.

As previously stated, this sNDA provides data to support dosing in pediatric patients > 1 month to 2 years of age.

2.2 Currently Available Treatment for Indications

At present, 23 antiretroviral drugs are approved in the United States for the treatment of HIV infection in adult patients. Pediatric dosing recommendations are presented in the product labels of 12 of these drugs and pediatric dosing is not recommended in another two product labels because of dose constraints (the two fixed-dose combination products, Combivir and Trizivir). HIV PIs prevent cleavage of protein precursors essential for viral replication. The use of PIs, in combination with other antiretroviral drugs, has led to significant improvement and prolonged survival in HIV-infected patients. However, the development of resistance to these agents continues and the need for new drugs with improved resistance profiles remains critical. Accurate dosing across all pediatric age groups remains an important issue in limiting the

emergence of resistance and the impact of adverse events which are not uncommon with these drugs. The initial pediatric dosing recommendation for RTV (1997) was for children older than two years of age. The current submission attempts to provide dosing recommendations for children between 1 month and 2 years of age.

2.3 Other Relevant Background Information

RTV was the first protease inhibitor for which clinical benefit was demonstrated based on the reduction of death and CDC Class C AIDS defining events. RTV was approved on March 1, 1996, for the treatment of HIV infection in adults in combination with other antiretroviral medications. In April 1997, RTV was approved by FDA for use in children older than 2 years of age. In fact, RTV was the first PI approved by FDA for children. However, due to poor tolerability, RTV is infrequently used today for its antiviral effect in combination treatment regimens. RTV is mainly used in lower doses to extend the half-life of other medications, particularly other protease inhibitors. The initial Pediatric Written Request was issued at a time when only few antiretroviral agents with formulations appropriate for pediatric administration were available. Although, RTV at the recommended doses is not widely used in clinical practice, dosing information in children > 1 month to 2 years of age may be important for those who are unable to receive other protease inhibitor based antiretroviral agents.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

No new chemistry and manufacturing data or animal pharmacology and toxicology data were submitted with this sNDA. Please refer to section 5.5 for a summary of the pharmacokinetic data. Please also refer to Dr. Derek Zhang's review for a detail review of the pharmacokinetic data.

4 SUMMARY OF CLINICAL FINDINGS

4.1 Brief Overview of Clinical Program

Trade Name: Norvir (ritonavir)
Class: Protease Inhibitor
Formulation: Oral Solution
Dosage: Children > 1 month: 350 to 400 mg/m^2 twice daily by mouth and should not exceed 600 mg twice daily.

Trials: Two studies, PACTG 345 (pivotal) and PACTG 366 (supportive) were submitted.

PACTG 345 is a phase I/II, dose-finding, open-label study designed to assess the safety, tolerance, pharmacokinetics, and activity of RTV (350 mg/m^2 and 450 mg/m^2 twice daily) alone and in combination with lamivudine (4 mg/kg q 12h) and zidovudine (160 mg/m^2 q 8h) in HIV-1 infected infants and children.

PACTG 366 is a phase I/II, open-label, management algorithm for highly antiretroviral experienced HIV-infected children and adolescents between six months and 21 years of age with rapidly progressive or advanced HIV disease for whom current antiretroviral therapy was failing. Patients received RTV 350 mg/m^2 twice daily.

Number of patients enrolled in these trials:

Fifty HIV-1 infected children were enrolled in PACTG 345 and received at least one dose of RTV. In PACTG 366, 164 children six months to 21 years of age received antiretroviral regimen containing RTV (350 mg/m^2 BID). Fourteen of the 164 children were less than two years of age.

Indications studied: Treatment of HIV infection

4.2 Data Quality and Integrity

As previously stated, studies PACTG 345 (pivotal) and PACTG 366 (supportive) were submitted in support of this sNDA. At the request of the Division, the Division of Scientific Investigations (DSI) audited the clinical data from one site participating in PACTG 345. Specifically, Dr. Anne Gershon's site at the Department of Pediatrics, Columbia University, College of Physicians & Surgeons, New York, NY and the Internal Review Board (IRB) of the same institution were inspected. The selection of Columbia University for inspection was based on previous accusations in the 'lay' media stating researchers at this Institute enrolled foster children in HIV trials often without providing children with independent advocates to protect their rights and interests. In addition, DSI audited the analytical portion of study PACTG 366. The analytical portion of PACTG 345 study was not audited. DSI inspected the analytical site of PACTG 345 study (b) (4) on numerous occasions for other bioequivalence studies and believes their analytical capabilities are adequate.

Findings from PACTG 366 analytical inspection:

In PACTG 366, pharmacokinetic data were obtained in 31 patients, 9 of whom were ≤ 2 years of age. The RTV pharmacokinetic data from these 9 children between 6 months and 2 years of age were submitted in part to fulfill the requirements as outlined in the Pediatric Written Request. The analytical portion of study 366 was conducted at the Pediatric ACTG Pharmacology Laboratory, the Department of Pediatrics, University of California at San Diego. Several major deficiencies were identified during the inspection of this site. Given these deficiencies, the data were not included for pharmacokinetic analysis (for more details see the report by Nilufer Tampal, Ph.D., from the Division of Scientific Investigations, CDER, FDA)

Findings from PACTG 345 Clinical and IRB Inspections:

Clinical inspection: The clinical inspection of the Department of Pediatrics at the Columbia University, College of Physicians & Surgeons did not identify any major deficiencies that would compromise the integrity of the study. Based on the DSI report the deficiencies noted were related to incorrect dose adjustments for lamivudine based on weight changes during the trial. These deficiencies do not compromise the RTV pharmacokinetic or safety data.

IRB inspection: The IRB inspection closed without issuance of a Form FDA 483. However, final determination by the DSI has not been made because the inspection report has not been received from the field investigator.

Conclusions/recommendations based on DSI findings :

Given the DSI IRB inspection report is not final, we also reviewed the data from PACTG 345 and 366 taking into consideration the worst case scenario, that is eliminating the pharmacokinetic data from PACTG 366 and the pharmacokinetic and safety data from the four subjects enrolled in PACTG 345 by Dr. Gershon. Of note, the pharmacokinetic data from PACTG 366 were supportive. Pediatric Exclusivity determination and dosing recommendations could be based on the pharmacokinetic and safety data from PACTG 345 alone. Specifically, Study PACTG 345 enrolled 50 HIV-infected pediatric subjects between one month and two years of age and pharmacokinetic results are available for 41 of the 50 patients:

1 month to < 3 months: 20 subjects (pharmacokinetic data available from 18 subjects)
3 months to < 6 months: 15 subjects (pharmacokinetic data available from 10 subjects)
6 months to < 2 years: 15 subjects (pharmacokinetic data available from 13 subjects)

Table. Data from the four infants enrolled at Columbia University Medical Center in study PACTG 345.

Patient I.D.	Age group	Pharmacokinetic data available
410424	3 months to < 6 months	Yes
410425	3 months to < 6 months	No
410436	1 month to < 3 months	Yes
411027	3 months to < 6 months	Yes

If the pharmacokinetic and safety data from the four children enrolled at Dr. Gershon's site were excluded the following data are available for review:

1 month to < 3 months: 19 (pharmacokinetic data available from 17 subjects)
3 months to < 6 months: 12 (pharmacokinetic data available from 8 subjects)
6 months to < 2 years: 15 (pharmacokinetic data available from 13 subjects)

Although no specific numbers are cited in the original Written Request, it is noteworthy that the number of patients with complete pharmacokinetic data from PACTG 345 after elimination of data from the four children enrolled at Columbia University Medical Center exceeds the minimal number of patients needed for pharmacokinetic evaluation cited in the current Written Request template:

6 weeks to < 6 months: 6
6 months to < 2years: 6

Overall, these findings clearly indicate that exclusion of the pharmacokinetic data from PACTG 366 study or exclusion of the pharmacokinetic data from the four patients enrolled in PACTG 345 at Dr. Greshon's site does not have any impact on the pediatric exclusivity determination, dosing recommendations or approvability of this sNDA.

4.3 Compliance with Good Clinical Practices

All study protocols were written to conform to accepted ethical standards and were reviewed and approved by Institutional Review Boards overseeing each investigative site prior to enrollment of patients.

4.4 Financial Disclosures

The two studies submitted in this sNDA were evaluated for financial conflict of interest among investigators. The PACTG sent multiple communications to all investigators affiliated with studies PACTG 345 and PACTG 366 and asked them to complete and return the financial disclosure form. Despite multiple requests four of the 18 investigators affiliated with PACTG 345 and 18 of the 49 investigators affiliated with PACTG 366 did not return the financial disclosure form. Each of the four investigators affiliated with PACTG 345 who did not return the financial disclosure form enrolled 1 to 3 patients and their participation does not appear to bias the clinical study results.

Dr. Chadwick, the Protocol Vice Chair for PACTG 345 who was also directly involved in the treatment of patients at Children's Memorial Hospital, Chicago, IL, disclosed that she holds more than $25,000 financial interest in Abbott Laboratories because her husband is employed by Abbott Laboratories. Dr Chadwick's site enrolled 3 subjects and is not expected to bias the clinical study outcome.

5 REVIEW OF CLINICAL STUDY RESULTS

5.1 Review Methods

The applicant submitted data from two clinical trials conducted by the Pediatric AIDS Clinical Trial Group (PACTG) in response to the final amended Pediatric Written Request. Study

PACTG 345 is the main study submitted to support the Pediatric Exclusivity claim and dosing recommendations in children > 1 month to two years of age. Additional data supporting the clinical use of RTV were submitted from study PACTG 366. This review focused on the pharmacokinetic, activity, and safety data from pediatric patients > 1 month to two years of age enrolled in PACTG 345. Summaries of the analyses are presented in the sections below. Review of PACTG 366 study focused on safety and efficacy data in children < 2 years of age. The safety and efficacy results were consistent with those observed in PACTG 345 and from other RTV studies and therefore are not presented in detail in this review. Of note, only 14 patients less than two years of age were enrolled in PACTG 366. The safety data in children greater than two years of age are consistent with the current package insert. No new or unexpected safety findings were identified and therefore are not discussed in this review in detail.

5.2 Study Design

Study PACTG 345:

This is a phase I/II, dose-finding, open-label study designed to assess the safety, tolerance, pharmacokinetics, and activity of RTV alone and in combination with lamivudine (4 mg/kg q 12h) and zidovudine (160 mg/m^2 q 8h) in HIV-1 infected infants and children. The study includes 2 cohorts. In cohort I patients received 350 mg/m^2 BID RTV. The choice of the 350 mg/m^2 dose was based on anticipated RTV exposures similar to the 600 mg dose BID adult dose and preliminary data from older children in the National Cancer Institute study. Based on the pharmacokinetic data from patients in cohort I, the RTV dose in cohort II was increased to 450 mg/m^2 BID. Patients were stratified by age in each dose cohort as follows:

Group I: > 6 months to 2 years, documented HIV-infected infants. On Day 0, a single dose of RTV was administered and pharmacokinetic parameters were assessed. RTV q 12h monotherapy then began 12 hours after the single dose. On Day 7, 3TC and ZDV were added.

Group II: 3 months to 6 months, documented HIV-infected. Dosing was the same as Group I.

Group IIIA: 4 weeks to ≤ 10 weeks. On Day 0, a single dose of RTV was administered and pharmacokinetic parameters were assessed. RTV, 3TC, and ZDV combination therapy was then started once RTV PK results were available (Day 7-10) and if the infant was either HIV-infected or was presumed HIV-infected.

Group IIIB: 1 month to < 3 months, HIV-infected or presumed HIV-infected. This group was created to replace infants enrolled in Group IIIA who were not HIV-infected or presumed to have HIV-1 infection. On Day 0, these infants started on RTV, 3TC, and ZDV combination treatment.

All patients were to receive treatment for 104 weeks. If a patient's viral load was < 400

copies/mL at the end of 104-week study period, the patient was eligible to extend treatment for additional 104 weeks.

Patients were followed for safety and efficacy every four weeks to Week 104, every 12 weeks from Week 104 to Week 200, and then at Week 208.

A total of 50 HIV-infected children between 1 month (4 weeks) and 2 years of age were enrolled in this study; seventeen patients were enrolled in Cohort I (350 mg/m^2 BID) and the remaining 33 in Cohort II (450 mg/m^2 BID). The age distribution of the enrolled patients was as follows:

1 month to < 3 months: 20 (pharmacokinetic data available from 18 patients)
3 months to < 6 months: 15 (pharmacokinetic data available from 10 patients)
6 months to < 2 years: 15 (pharmacokinetic data available from13 patients)

Pharmacokinetic data are available for 41 of the 50 enrolled patients.

Disposition and baseline characteristics of patients:

In cohort I, 59% were male and 65% were black, non-Hispanic patients. In cohort II, 33% were male and 70% were black, non-Hispanic patients. The median CD4 cell count was 2399 cells/μL in cohort I compared to 1579 cells/μL in cohort II. The median baseline HIV RNA was similar between cohort I and II and was 5.3 $\log_{10}$ copies/mL.

In cohort I, 10 of the 17 patients (59%) prematurely discontinued study treatment: 6 (35%) after reaching a virologic endpoint, 3 (18%) due to intolerability, and 1 (6%) due to growth retardation.

In cohort II, 22 of the 33 patients (67%) prematurely discontinued study treatment: 14 (42%) after reaching a virologic endpoint, 3 (9%) due to intolerability, 2 (6%) due to treatment toxicity, 2 (6%) due to parent/guardian request, and 1 (3%) due to a study team decision related to difficulties in obtaining the blood samples.

Overall, 26/50 (52%) patients remained on study beyond 52 weeks and 21 (42%) remained on study for at least 104 weeks. The majority of patients (20/32; 63%) prematurely discontinued study treatment because they met the protocol specified virologic endpoint (HIV RNA > 400 copies/mL at or after Week 16 confirmed on repeat testing)

Study PACTG 366

This is a phase I/II, open-label, management algorithm for highly antiretroviral experienced HIV-infected children and adolescents between 6 months and 21 years of age with rapidly progressive or advanced HIV disease for whom current antiretroviral therapy was failing. Of the 201 enrolled patients, 164 received antiretroviral regimens containing RTV (350 mg/m^2 BID). The age distribution of the 164 enrolled patients who received antiretroviral regimen containing RTV was the following:

< 2 years: 14
2 to 6 years: 70
7 to 12 years: 55
≥ 13 to 21 years: 25

The majority of patients in this study were black, non Hispanic (64%) or Hispanic (26%).

5.3 Efficacy Results

In Study PACTG 345 no statistically significant differences were noted between Cohorts I and II during the first 104 weeks of follow-up with respect to HIV-1 RNA levels, CD4 cell count or CD4 percentage. Of note, no child met the protocol specified criteria for virologic failure prior to Week 16. The major virologic failure criterion in this study was HIV RNA > 400 copies/mL at or after Week 16. At Week 48, 8/17 (47%) of patients from Cohort I and 22/33 (67%) of patients from Cohort II had confirmed HIV-1 RNA levels > 400 copies/mL or treatment discontinuation. At Week 104, the patients from Cohorts I and II who had HIV-1 RNA levels > 400 copies/mL or treatment discontinuation were 9/17 (53%) and 23/33 (70%), respectively.

Analyses of CD4 cell count and CD4 percentage were restricted to measurements obtained while the patient was on study treatment and, after Week 16, prior to confirmed HIV-1 RNA levels > 400 copies/mL. In a non-randomized comparison of Cohorts I and II, no significant differences were noted in the median change in CD4 percentage from baseline to Week 48 or from baseline to Week 104.

It is important to keep in mind this is a small non-randomized study, and potential differences in demographic and baseline characteristics and changes in patient management may have confounded the comparisons between the two cohorts. In addition, the study was not designed to show efficacy (as assessed by HIV-RNA and CD4) differences between RTV dosing regimens, but to provide pharmacokinetic, safety, and activity data in children in order to determine an appropriate dosing regimen. One should also keep in mind that from a regulatory perspective, a pediatric dosing regimen may be approved if it is supported by efficacy in well-controlled studies in adults and by data identifying a dose that achieves a similar pharmacokinetic profile. Nevertheless, RTV has demonstrated activity in this population.

5.4 Safety Results

Overall, the toxicity profile of RTV seen during the clinical trial PACTG 345 appears similar to that observed in adults. No statistically significant differences were noted between Cohorts I and II with respect to the proportion of patients experiencing toxicities related to or possibly related to study treatment during the 104 weeks of follow-up [41% (7/17) vs. 27% (9/33)]. The most frequently reported Grade 2-4 adverse events and clinical laboratory abnormalities considered related/possibly related to study treatment were vomiting (12%; 6/50) and neutropenia (10%;

5/50). Potentially life-threatening, Grade 4 toxicities were experienced by 5 patients in Cohort II (RTV 450 mg/m^2), while no patient in Cohort I experienced Grade 4 toxicity. These events were elevated ALT and AST levels (in the same child), anemia, abnormal glucose level, neutropenia and thrombocytopenia. Three of these Grade 4 events (affecting 2 children) were considered possibly related to study treatment and the other three Grade 4 events were considered not treatment related.

Grade 3-4 laboratory abnormalities were experienced by 24% (4/17) of patients in Cohort I and by 45% (15/33) of patients in Cohort II. The following Grade 3-4 laboratory abnormalities occurred in at least 2 patients: elevated amylase (12%; 6/50), neutropenia (8%; 4/50), sodium serum altered (8%; 4/50), and anemia (4%; 2/50).

Because RTV was a part of combination antiretroviral therapy, it is difficult to determine the exact contribution of RTV to any clinical or laboratory toxicities. It noteworthy, that many of the approved antiretroviral drugs have overlapping toxicities. Therefore, it is possible that drugs such as zidovudine may have contributed to neutropenia or anemia in some patients.

5.5 Pharmacokinetic Results

Pharmacokinetic data were obtained in 41 of the 50 patients enrolled in PACTG 345 study:

1 month to < 3 months: 18 (Cohort I: 6; Cohort II: 12)
3 months to < 6 months: 10 (Cohort I: 2; Cohort II: 8)
6 months to < 2 years: 13 (Cohort I: 6; Cohort II: 7)

A full complement of pharmacokinetic measurements was drawn on Day 1 and at Week 4 in Cohort I and after one and four weeks in Cohort II. Analyses of these measurements showed that in children > 1 month to 2 years of age higher RTV exposures were not evident with 450 mg/m^2 BID dose compared to 350 mg/m^2 BID dose. Study PACTG 345 also showed that RTV exposures after 350 or 450 mg/m^2 BID dosing were similar to that previously observed in older children after 250 to 350 mg/m^2 BID dosing with the exception that steady–state trough concentrations were somewhat lower in children < 2 years. The 250 and 350 mg/m^2 BID dosing in older children resulted in 58% and 33% higher $C_{trough,ss}$ values, respectively, compared to the $C_{trough,ss}$ values observed after 350 or 450 mg/m^2 BID dosing in children less than two years of age. Based on these data, and despite the high degree of variability in RTV exposure observed in younger children, a dose regimen up to 350 to 400 mg/m^2 BID is recommended for children > 1 month of age.

As previously stated, given the DSI IRB report is not final, we also reviewed the pharmacokinetic data without including the data from the four patients enrolled in PACTG 345 at the site of Columbia University Medical Center. The analyses showed that exclusion of these data has no impact on the overall conclusions of this review. For more details please see the review by Derek Zhang, the Clinical Pharmacology and Biopharmaceutics reviewer.

6 OVERALL ASSESSMENT

6.1 Conclusions

There is a need for pediatric use information for many of the recently approved antiretroviral drugs. Children have less treatment options than adults due to lack of pediatric formulations and information to guide clinicians in dosing HIV-infected children.

This supplement includes pharmacokinetic, safety, and activity data from children > 1 month to two years who had received two dose levels of RTV. After a thorough review, the review team agrees that the submitted data in this supplement are adequate to approve dose recommendations for the use of RTV in children > 1 month to 2 years of age. The recommended dose of RTV in children > 1 month is 350 to 400 mg/m^2 twice daily and will be included in the product label.

With respect to safety considerations, there were no unexpected adverse events. The overall adverse event profile of RTV in children appears similar to that observed in adults.

6.2 Labeling Review

CLINICAL PHARMACOLOGY

This section was modified to include pharmacokinetic data in children 1 month to 2 years of age. The new Clinical Pharmacology section for Pediatric Patients reads as follows:

Pediatric Patients
Steady-state pharmacokinetics were evaluated in 37 HIV infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m^2 twice-daily to 400 mg/m^2 twice daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses 350 and 450 mg/m^2 twice daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m^2) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m^2 twice daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m^2 twice daily compared to the 350 mg/m^2 twice daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice daily. The area under the ritonavir plasma concentration-time curve and trough concentrations obtained after administration with 350 or 450 mg/m^2 twice daily were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice daily.

PRECAUTIONS

The following information was added under the section of Pediatric Use subsection:

Pediatric Use

In HIV-infected patients age > 1 month to 21 years, the antiviral activity and adverse event profile seen during clinical trials and through postmarketing experience were similar to that for adult patients.

ADVERSE REACTIONS

The following information was added under the section of Pediatric Use subsection. Of note, the treatment-emergent adverse events and laboratory abnormalities shown in the label reflect the summary of the adverse events and laboratory abnormalities observed in pediatric studies M95-310, PACTG 366, and PACTG 345.

Pediatrics

Treatment-Emergent Adverse Events

NORVIR has been studied in 265 pediatric patients > 1 month to 21 years of age. The adverse event profile observed during pediatric clinical trials was similar to that for adult patients.

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in ≥ 2% of pediatric patients enrolled in NORVIR clinical trials.

Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in ≥ 3% of pediatric patients who received treatment with NORVIR either alone or in combination with reverse transcriptase inhibitors: neutropenia (9%), hyperamylasemia (7%), thrombocytopenia (5%), anemia (4%), and elevated AST (3%).

DOSAGE AND ADMINISTRATION

The section of Pediatric Patients has been modified to include dosing recommendations for children > 1 month to 2 years of age. The new Dosage and Administration section for Pediatric Patients is:

Pediatric Patients
Ritonavir should be used in combination with other antiretroviral agents (see General Dosing Guidelines). The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m^2 twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily. If patients do not tolerate 400 mg/m^2 twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative

therapy should be considered. When possible, dose should be administered using a calibrated dosing syringe.

Pediatric Dosage Guidelines[1]

Body Surface Area* (m^2)	Twice Daily Dose 250 mg/m^2	Twice Daily Dose 300 mg/m^2	Twice Daily Dose 350 mg/m^2	Twice Daily Dose 400 mg/m^2
0.20	0.6 mL (50 mg)	0.75 mL (60 mg)	0.9 mL (70 mg)	1.0 mL (80 mg)
0.25	0.8 mL (62.5 mg)	0.9 mL (75 mg)	1.1 mL (87.5 mg)	1.25 mL (100 mg)
0.50	1.6 mL (125 mg)	1.9 mL (150 mg)	2.2 mL (175 mg)	2.5 mL (200 mg)
0.75	2.3 mL (187.5 mg)	2.8 mL (225 mg)	3.3 mL (262.5 mg)	3.75 mL (300 mg)
1.00	3.1 mL (250 mg)	3.75 mL (300 mg)	4.4 mL (350 mg)	5 mL (400 mg)
1.25	3.9 mL (312.5 mg)	4.7 mL (375 mg)	5.5 mL (437.5 mg)	6.25 mL (500 mg)
1.50	4.7 mL (375 mg)	5.6 mL (450 mg)	6.6 mL (525 mg)	7.5 mL (600 mg)

* Body surface area can be calculated with the following equation:

$$BSA\ (m^2) = \sqrt{\frac{Ht\ (Cm) \times Wt\ (kg)}{3600}}$$

Andreas Pikis, M.D.
Medical reviewer

Concurrences:
HFD-530/ActTL/Kstruble
HFD-530/DepDir/JMurray

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