CLINICAL REVIEW FOR NDA 20-659, SE5-034 AND NDA 20-945, SE5-017

1. BPCA 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.

1.3 Summary of Clinical Findings

1.3.1 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

1.3.2 Efficacy

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.

1.3.3 Safety

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/m2), 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.

1.3.4 Dosing Regimen and Administration

The applicant proposed RTV dose of 350 to 400 mg/m^2 twice daily for children > 1 month to 2 years of age. After a thorough review, the review team agreed that the submitted data in this sNDA are adequate to support the proposed dose.

The pharmacokinetic profile of RTV has been well characterized in adults. The adult approved dose has been correlated with clinical efficacy in large treatment trials. The goal of the pediatric pharmacokinetic studies is to achieve the same RTV exposure that was associated with efficacy in adults. Analyses of the pharmacokinetic data obtained in 41 of 50 pediatric patients enrolled in PACTG 345 study supported the proposed dose. Briefly, the pharmacokinetic analyses showed that in children > 1 month to 2 year of ages higher 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 adults dosed with 400 mg BID. However, the area under the ritonavir plasma concentration-time curve and trough concentrations were somewhat lower than that obtained in adults receiving 600 mg BID.

1.3.5 Drug-Drug Interactions

No new drug-drug interaction data are included in this sNDA.

1.3.6 Special Populations

This submission completes the applicant’s presentation of their pediatric development program for RTV. Based on the submitted studies, the applicant was granted Pediatric Exclusivity on June 15, 2005.

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