Clinical Review for NDA 20-778, SE5-022, NDA 20-779, SE5-042, NDA 21-503, SE5-001

BPCA Executive Summary

I. Recommendations

A. Recommendation on Approvability

This efficacy supplement to NDA 20-778 (and also NDAs 20-779 and 21-503) containing pharmacokinetic (PK), safety, and activity data regarding the use of nelfinavir mesylate (Viracept, NFV) in HIV-infected pediatric patients should be approved. NFV was previously granted approval for use as part of combination antiretroviral treatment in adults and in pediatric patients 2 years of age and older. The dose originally approved in pediatric patients was 20-30 mg/kg TID but there have been clinical concerns that this dose resulted in frequent virologic failure. The current supplement presented additional data confirming that doses of 25-35 mg/kg TID or 45-55 mg/kg BID provided NFV exposure associated with clinical evidence of activity over 48 weeks of dosing in patients 2 to 13 years of age. In this age group, HIV RNA levels decreased over time and CD4 cell counts increased in all groups receiving NFV in combination with other drugs. In the only randomized, placebo-controlled, pediatric study (Study 556), a significantly greater proportion of patients receiving NFV achieved virologic response over 48 weeks than those receiving placebo (21% vs. 3%). For patients less than 2 years of age, a reliably effective dose of NFV could not be determined due to marked variability in drug exposure and efficacy results poorer than those documented in older children.

The studied doses of NFV produced an acceptable tolerability and safety profile across the pediatric age range. While adverse events were common in the study populations, relatively few were considered drug-related (diarrhea being the exception), relatively few were severe in intensity or required discontinuation of study drug, and many were attributable to common childhood illnesses or conditions. As was seen in the adult treatment trials, the most common adverse event associated with NFV was diarrhea, reported in up to 39-47% of pediatric patients. Neutropenia/leukopenia was the most commonly observed significant laboratory abnormality, occurring as a Grade 3 or 4 abnormality in 14-16% in some of the submitted studies. Lesser degrees of neutropenia occurred in up to 70% of patients < 3 months of age who received NFV in the submitted studies. Laboratory abnormalities rarely led to discontinuation of NFV.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

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

The review team considered the variability in NFV exposure the greatest barrier to achieving efficacy in pediatric patients. Inadequate drug exposure may lead to failure of virologic suppression of HIV and emergence of resistance. The product label was revised to contain statements emphasizing this variablility in NFV exposure observed in the pediatric studies and the difficulties encountered maintaining adherence and adequate food intake in the pediatric population.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

NFV is an oral protease inhibitor approved in both tablet and powder formulations for the treatment of HIV infection in patients 2 years of age or older. This supplement presented additional clinical and PK data on the use of NFV as part of combination drug regimens for the treatment of HIV infection in pediatric patients. Five studies were submitted for review. These included: Study 524 (enrolling ages < 3 months to 13 years, N=65), Study 556 (ages 3 months to 12 years, N=141), PACTG 377 (ages 4 months to 17 years, N=181) with its PK substudy PACTG 725 (ages 3 to 11 years, N=12), PENTA-7 (age < 3 months, N=20), and PACTG 353 (neonates, N=31). These studies covered the pediatric age range from birth to 13 years of age using a variety of different NFV doses and schedules (for details of study design and dose schedules see Section VI, C, Detailed Review of Trials by Indication and Appendix B of the Clinical Review). Studies 524 and 556 were conducted by Agouron. PACTG 377/725 and PACTG 353 were conducted by the Pediatric AIDS Clinical Trials Group, Division of AIDS, NIH, and PENTA-7 was conducted by the Paediatric European Network for the Treatment of AIDS, all in collaboration with Agouron.

B. Efficacy

Collectively, the four pediatric treatment studies provide evidence of NFV's activity as part of a combination antiretroviral regimen for pediatric patients. All of the studies document that pediatric patients receiving NFV achieved significant mean decreases in HIV RNA levels over time and most also achieved increases in CD4 cell counts or percentages. These surrogate endpoints have been shown to predict improved clinical outcome in other antiretroviral drug studies. However, because of the differences in study design, doses and regimens studied, and age groups studied it was difficult to identify an effective dose in all age groups.

Only one of the studies, Study 556, provided efficacy results from a randomized, blinded study that allowed analysis of the contribution of NFV to the success or failure of a multi-drug regimen. This study compared NFV (TID) + ZDV + ddI to placebo + ZDV + ddI in patients with minimal prior treatment over a 48 week study period. In this study, the NFV-containing regimen clearly performed better than the placebo regimen with a greater proportion of patients achieving and maintaining HIV RNA < 400 copies/mL (21% compared to 3%, p=0.0002) and the NFV patients achieving a longer median time to loss of virologic response (122 days compared to 0, p=0.0026). PACTG 377, evaluated 4 different 3- and 4-drug combinations of antiretroviral agents in a randomized, open-label study design and the substudy PACTG 725 allowed comparison of similar BID and TID NFV regimens. None of the regimens provide a direct comparison of TID NFV to another PI or NNRTI, however, the NFV-containing arms of the study achieved undetectable HIV RNA levels in 30% to 52% of patients. In the small substudy PACTG 725 evaluating the BID NFV regimen, 55% of patients achieved HIV RNA < 400 copies/mL at 48 weeks.

While the benefit of NFV was demonstrated with these studies, the magnitude of the virologic response rate at 48 weeks in pediatric patients was generally less than expected, particularly that observed in Study 556. Efficacy in treatment-naïve adults receiving NFV in a 3-drug regimen has been demonstrated to be about 60% after 48 weeks. Response rates for patients less than 2 years of age appeared to be significantly worse than those in patients 2 years of age and older in Study 556 and reached only 37% in infants < 3 months in PENTA-7, the study administering the highest doses of NFV. Consequently, associations between the doses studied and a reasonable level of effectiveness could not be concluded for all age groups. Although the applicant proposed dose recommendations for pediatric patients from birth to 13 years of age, the review team could not select reliably effective doses for use in patients less than 2 years of age.

The review team identified several factors that may explain the low response rates observed in the pediatric trials submitted. Some of the studies (Study 556, PENTA-7) failed to achieve the adult target NFV exposure. Study 556 produced PK data that were the most variable of any of the studies submitted. This variability in the PK in this population may have accounted for the low proportion of patients who achieved durable virologic response in this study and it limited the interpretability of the PK data. Also, patients enrolled in some pediatric studies had median HIV RNA levels at baseline (5.0 to 5.5 log) that were higher than those generally seen in adult studies. Finally, these studies were designed and initiated between 1997-99 at a time when treatment-experienced pediatric patients did not always receive an optimized, resistance-minimizing background regimen of antiretroviral drugs in addition to the study drug.

C. Safety

The safety database for assessment of NFV in patients across the pediatric age range from birth to 13 years of age was adequate. A total of 302 patients received NFV in the 4 pediatric treatment trials (Studies 524, 556, PACTG 377/725, and PENTA-7) for up to 96 weeks. The primary safety review was conducted over 48 weeks of study drug dosing in these studies. Another 31 HIV-exposed neonates were evaluated for safety after 3rd trimester prenatal exposure and 6 weeks of infant dosing. Across the pediatric studies, the safety profile of NFV was generally similar to that previously described in adults and in the small number of children presented in the original NDA. Although minor differences were noted in individual studies, no major differences in the safety profile for NFV could be identified in different pediatric age groups. Serious adverse events were rarely considered related to NFV and no deaths were attributed to the drug.

As in adults, the most commonly reported side effect was diarrhea. Because of differences in study reporting it was difficult to determine the frequency of diarrhea attributable to NFV. In Study 556 in which it was combined with ddI, another drug known to be associated with diarrhea, 39% to 43% of patients in the NFV and placebo arms, respectively, reported some degree of diarrhea. Moderate to severe diarrhea was reported in 6-11% of patients enrolled in Studies 524 and 556 and "gastrointestinal events" of moderate to severe intensity were reported in 18-27% of the patients receiving a NFV-containing regimen in PACTG 377/725. In studies of NFV in adults, higher rates of diarrhea have been correlated with higher drug exposures. Because of the marked variability of drug exposure found in the pediatric studies, no exposure-response relationship for diarrhea could be identified in children.

Neutropenia/leukopenia occurred more frequently in the pediatric studies than was observed in the adult clinical trials. Study 556 was the only study not reporting Grade 3 or 4 neutropenia in patients receiving NFV. Neutropenia was defined and reported differently across the studies, with some reporting "neutropenia" as an AE while in others it was included in the laboratory data analysis. In PACTG 353 and PENTA-7, some degree of neutropenia was reported in 40-70% of infants enrolled using very conservative cut-off values for all grades of neutropenia in infants < 3 months of age. Neutropenia was also reported in studies enrolling older children, with Grade 3 or 4 abnormalities reported in 14-16% of patients in Studies 524 and PACTG 377. Again, no exposure-response relationship could be identified for neutropenia.

Because all studies administered NFV as part of combination antiretroviral therapy, it was difficult to determine the exact contribution of NFV to any clinical or laboratory toxicity. Many of the approved antiretroviral drugs have overlapping toxicity profiles so it is possible that drugs such as ddI may have

contributed to diarrhea in some studies or that ZDV may have contributed to neutropenia in some.

D. Dosing

The applicant proposed NFV dose recommendations of 25-35 mg/kg TID or 50-60 mg/kg BID for patients from 2 to 13 years of age and dose recommendations of 40-50 mg/kg TID or 60-75 mg/kg BID for patients < 2 years of age. Additionally, a dose of 40 mg/kg BID was proposed for neonates. The review team agreed with the applicant's proposed dose of 25-35 mg/kg TID for children 2 years of age or older but recommended a lower dose of 45-55 mg/kg BID in this age group. We also agreed that dose recommendations in pediatric patients applied to both the oral powder and 250 mg tablet formulations. As noted above, the review team could not confirm reliably effective dose recommendations for children < 2 years.

The PK profile of NFV has been characterized in adults receiving both TID and BID dosing schedules. The adult approved doses have been correlated with clinical efficacy in large treatment trials. The goal of the pediatric PK studies was to achieve the same NFV exposure, as measured by AUC_{24}, that was associated with efficacy in adults (AUC_{24} of 44 to 53 mg∗h/L for TID and BID regimens, respectively). The most important PK characteristic of NFV is the remarkable variability of exposure. This variability appears to be greater in children than in adults. Variability in drug exposure appears to be due to the marked drug-food effect observed with NFV. The effect of food on NFV exposure varies depending on meal content with higher calorie/higher fat meals increasing exposure more than low calorie/low fat meals. Consequently, it is recommended that all doses of NFV be taken with a meal.

In patients 2 to 13 years of age, the weight of clinical and PK evidence from 3 treatment studies (Studies 524, 556 and PACTG 377) supported the proposed dose of 25-35 mg/kg TID, a slight change from the originally approved dose in this age group. In PACTG 725 evaluating the BID regimen of NFV, the mean NFV exposure exceeded the target adult exposure although there was still significant variability. However, the dose studied was reasonably well-tolerated and proved to be effective in this small group. It was not considered appropirate to recommend a dose higher than the studied dose and we recommended making the study dose the upper limit of a dose range to allow for some flexibility. Studies in patients < 2 years of age either failed to achieve both the target NFV exposure and adequate response rates (PENTA-7) or achieved the target exposure in a very narrow age group (PACTG 353). These studies included very young patient populations in whom the requirement for taking NFV with a meal may be the most difficult to accomplish and the drug-food effect may have a significant impact.

E. Special Populations

This submission completes the applicant's presentation of their pediatric development program for NFV. Agouron/Pfizer was granted pediatric exclusivity in September, 2003, as a result of submitting these studies. Because the numbers of patients in individual studies or treatment arms were relatively small, a subgroup analysis of treatment differences between sexes or among racial/ethnic backgrounds could not be performed. A full evaluation of the pediatric development program for NFV including detailed descriptions of the pediatric clinical studies is contained in this review.

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