

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-814s005/22-292

OFFICE DIRECTOR MEMO

Deputy Office Director Memo

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

NDA #s: NDA 21-814 Aptivus® (tipranavir) 250 mg capsules
NDA 21-822 Aptivus® (tipranavir) 100mg/mL oral solution

Drug: tipranavir

Trade Name: Aptivus®

Indication: APTIVUS® (tipranavir), co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors

Date of submission: December 22, 2004

PDUFA goal date: June 22, 2005

Recommended Regulatory Action:

- NDA 21-814 Aptivus® (tipranavir) 250 mg capsules
Approval under 21 CFR 314.510 Subpart H, accelerated approval for NDA 21-814
- NDA 21-822 Aptivus® (tipranavir) 100mg/mL oral solution
Approvable for NDA 21-822

The pre-clinical and clinical reviewers have reviewed the issues in their disciplines in detail with regards to the safety and efficacy of Aptivus® (tipranavir). For a detailed review of the individual disciplines the reader is referred to these individual reviews. The reader is also referred to Dr. Johann-Liang's Medical Team Leader Memos and Dr. Birnkrant's Division Director's Memo. This review will focus on selected findings and issues from the application.

The Chemistry for Aptivus® (tipranavir) capsules and oral solution is discussed in Dr. Lo's review and she has recommended approval for NDAs 21-814 (capsule) and 21-822 (oral solution) with regards to Chemistry. Pre-approval inspections of the manufacturing and testing facilities were found to be acceptable

The Pharmacology/Toxicology studies for tipranavir are reviewed in detail in Dr. Anita Bigger's review. The target organs in repeat dose studies were primarily the liver and gastrointestinal tract (with GI effects of emesis, soft stool, diarrhea, or excessive salivation). Liver-related findings in animal studies included histopathologic changes consistent with tipranavir's induction of microsomal enzymes, increases in liver analytes (alkaline phosphatase, AST, and ALT), and histopathologic effects on the biliary system that were more commonly noted in tipranavir-treated dogs. Liver-related findings in mice included AST and ALT elevations at high doses that was correlated with hepatocellular necrosis.

Tipranavir demonstrated inhibition in a HERG assay, but did not demonstrate an effect on action potential in guinea pig papillary muscle at concentrations up to 10 µM. In beagle dogs at doses up to 160 mg/kg, tipranavir did not demonstrate effects on the QT interval. Tipranavir is labeled as Pregnancy Category C. Carcinogenicity studies are currently ongoing.

The Clinical Pharmacology of tipranavir is described in Dr. Derek Zhang's Review. Tipranavir 500 mg administered in combination with ritonavir 200 mg twice daily is a net inhibitor of CYP3A. *In vitro* studies indicate that CYP3A is the predominant cytochrome isoform involved in the metabolism of tipranavir. Tipranavir is also a P-gp substrate. Tipranavir co-administered with ritonavir should be taken with food; the bioavailability of tipranavir is increased in the setting of a high fat meal. Tipranavir is highly protein bound in human plasma (>99.9%).

The Aptivus (tipranavir) product label provides a listing of drug interactions for tipranavir co-administered with ritonavir (TPV/r). TPV/r should not be co-administered with the following drugs: the antiarrhythmics, amiodarone, bepridil, flecainide, propafenone, or quinidine; rifampin; the ergot derivatives dihydroergotamine, ergonovine, ergotamine, or methylergonovine; cisapride; St. John's wort; the HMG CoA reductase inhibitors lovastatin or simvastatin; pimozone; or the sedative hypnotics midazolam or triazolam. The label also provides a listing of other drugs with which there are established or potential drug interactions with TPV/r. Additional drug interaction studies are planned, many of which are postmarketing commitments.

The dose for the phase 3 studies was selected largely based upon data from study 1182.52 which examined doses of TPV/r of 500/100 mg; 500/200 mg; and 750/200 mg. The selection of the 500/200 mg dose for the phase 3 studies was based upon virologic response and tolerability of 500/200 mg dose.

Exposure-response data from the clinical studies were analyzed. The data demonstrated that response was related to the Inhibitory Quotient (IQ) defined as the C_{min}/IC_{50} , corrected for protein binding. As noted in the Aptivus label "Among the 206 patients receiving APTIVUS/ritonavir without enfuvirtide, the response rate was 23% in those with an IQ value < 75 and 55% in those with an IQ value ≥ 75. Among the 95 patients receiving APTIVUS/ritonavir with enfuvirtide, the response rates in patients with an IQ value < 75 versus those with an IQ value ≥ 75 were 43% and 84%, respectively.

These IQ groups are derived from a select population and are not meant to represent clinical breakpoints.” Also noted was an exposure-response relationship with grade 3/4 ALT elevations. Boehringer Ingelheim will continue to work with the agency to develop a protocol for a pilot study to investigate therapeutic drug monitoring in HIV-infected patients receiving TPV/r.

Tipranavir solution 100mg/mL was not found to be bioequivalent to tipranavir capsules. The solution was found to be approximately 30% more bioavailable than the capsule when administered under fasted conditions. This may relate to the differences in the excipients for the two formulations and possibly their effects on CYP3A and P-gp. In addition, because of the effects on enzymes/transporters, the relative bioavailability should be evaluated at steady state.

The microbiology of tipranavir is described in Dr. Lisa Naeger’s microbiologist’s review for NDAs 21-814/21-822. Tipranavir is an HIV protease inhibitor. Ninety percent (94/105) of HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, and ritonavir had a ≤ 3 -fold decrease in tipranavir susceptibility. Mutations in the HIV-1 protease associated with reduced susceptibility to tipranavir were characterized by genotypic evaluation of resistant isolates and additional *in vitro* studies utilizing site-directed mutagenesis.

The detailed results of the clinical trials are discussed in Dr. Andrea James’ Medical Officer’s review and Dr. Bhore and Dr. Zhou Statistical reviews and Dr. Johann-Liang’s Medical Team Leader memo. For a detailed review of the findings, the reader is referred to their reviews.

For the indication of combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors, the applicant provided data from two phase 3 studies in highly treatment experienced patients. The studies evaluated tipranavir 500 mg co-administered with ritonavir 200 mg twice daily in highly treatment experienced patients. On average patients had received treatment with 4 protease inhibitors prior to enrollment. The studies included an escape clause at Week 8 that provided a means for patients with virologic failure at Week 8 to be classified as failures and receive tipranavir in a rollover study. The primary endpoint was confirmed ≥ 1 log reduction in viral load from baseline at 24 weeks. In both studies the tipranavir treatment arm of the study was superior to the comparator arm which included a ritonavir boosted protease inhibitor. The observed outcomes by treatment arm through week 24 for the primary endpoint of virologic response was 40% for the TPV/r arm and 18% for the comparator arm. The secondary endpoints corroborated the findings for the primary endpoint.

The results of the studies support the efficacy of tipranavir for the treatment of HIV-1 adults patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

The clinical safety data for tipranavir is derived from approximately 3200 subjects who received at least one dose of tipranavir. Approximately 1400 patients received doses of tipranavir 500 mg with ritonavir 200 mg with 761 patients receiving this regimen for a duration of at least 24 weeks.

Review of patients with changes in liver-associated enzymes in phase 2 studies shows that the incidence of grade 3/4 ALT elevations were related to tipranavir exposure. In the phase 3 trials 6% (45/732) of patients on the tipranavir arm experienced grade 3 or 4 elevations in ALT/AST compared to 2% (18/723) of patients in the comparator arm. The risk for elevations in transaminases was greater in patients with underlying chronic hepatitis B or C. The Aptivus label provides a boxed warning about clinical hepatitis and hepatic decompensation including some fatalities and the increased risk in patients who are co-infected with hepatitis B or C. Monitoring of liver function tests should be performed prior to initiating therapy and during therapy with TPV/r.

Rashes of mild to moderated severity have been observed in patients receiving ritonavir. In phase 2 and 3 trials rash was reported in 14% of female patients and 8 to 10 % of males. In a drug interaction study of ethinyl estradiol 33% (17/51) of female patients experienced rash. The product label describes the rash adverse events from the clinical program.

Elevations in plasma triglycerides and cholesterol occurred in patients receiving TPV/r. Grade 3 or 4 treatment emergent laboratory abnormalities in cholesterol or triglycerides were reported more frequently in patients receiving TPV/r than comparator in the phase 3 studies. Monitoring of triglycerides and cholesterol should be performed prior to and during therapy with TPV/r.

The drug-drug interactions profile of tipranavir co-administered with ritonavir is detailed in the product label. TPV/r is metabolized predominantly by CYP3A and is a net CYP3A inhibitor and hence there are interactions with a number of other therapeutic agents. Additional drug interactions studies will be conducted as phase 4 studies.

The effect of tipranavir on cardiac repolarization was evaluated in vitro and in vivo. Tipranavir had an effect on the hERG-associated potassium channel. No effect was noted on action potential in the guinea pig papillary muscle in vitro. In a dog study no effect was noted on electrocardiograms. From analysis of ECGs performed in 5 phase 1 studies no findings regarding cardiac repolarization safety issues were noted. The company has agreed to a conduct a formal QT study as a postmarketing commitment.

The tipranavir application was discussed before the Antiviral Drug Products Advisory Committee on May 19, 2005. With regards to the question as to whether safety and efficacy had been demonstrated the votes were 11 Yes and 3 No that safety and efficacy had been demonstrated. The committee discussions also included discussion of hepatic adverse effects, rash, drug interactions, longer term data and a discussion of therapeutic drug monitoring.

Aptivus (tipranavir) 500 mg co-administered with ritonavir 200 mg twice daily provides a therapeutic option for patients with limited or no therapeutic options for HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. In this patient population where there are limited treatment options, the risk benefit for tipranavir co-administered with ritonavir as part of a regimen for treatment of HIV-1 infection is satisfactory. The product label provides a description of the safety profile of tipranavir.

The applicant has agreed to perform a number of studies as phase 4 commitments including studies to further characterize drug interactions, perform a formal QT study, and perform a pilot study that investigates therapeutic drug monitoring. As part of the accelerated approval of Aptivus the applicant will provide 48-week data to confirm the findings from the 24-week data from the phase 3 trials.

Summary Recommendations

- NDA 21-814 Aptivus® (tipranavir) 250 mg capsules
Approval under 21 CFR 314.510 Subpart H, accelerated approval for NDA 21-814
- NDA 21-822 Aptivus® (tipranavir) 100mg/mL oral solution
Approvable for NDA 21-822
To address the deficiencies in NDA 21-822 the applicant should
 - (1) Provide steady-state relative bioavailability or bioequivalence data for the oral solution compared to the capsules.
 - (2) In the absence of acceptable bioequivalence or relative bioavailability data for tipranavir oral solution compared to the capsules, the applicant should provide adequate exposure data in the relevant patient population that demonstrate that the selected dose of the oral solution achieves tipranavir concentrations similar to those achieved following administration of tipranavir capsules at a dose of 500 mg with 200 mg ritonavir twice daily in adult patients. If the applicant chooses to provide exposure data from pediatric patients, data on the safety and activity of Aptivus (tipranavir) overall in HIV-infected pediatric patients should also be provided. Additional data from study 1182.14 may possibly provide such data on the safety and activity of tipranavir overall in the pediatric population.

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/s/

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MEDICAL OFFICER