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RESEARCH**

APPLICATION NUMBER:
21-822

OTHER REVIEW(S)

TEAM LEADER MEMORANDUM

DATE: June 22, 2005

TO: Division Files for NDA 21-814 and NDA 21-822

FROM: Rosemary Johann-Liang, M.D.
Medical Officer Team Leader.
Division of Antiviral Drug Products
HFD-530

DRUG: APTIVUS (tipranavir), 250 mg capsules
APTIVUS (tipranavir), 100 mg/mL oral solution

PROPOSED INDICATION: APTIVUS, co-administered with low-dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are protease inhibitor treatment-experienced.

GRANTED INDICATION: APTIVUS, co-administered with low-dose 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.

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc

The New Drug Application (NDA) 21-814 for APTIVUS (tipranavir, a non-peptidic protease inhibitor) 250 mg capsules, is being recommended for regulatory approval under accelerated approval regulations: 21 CFR 314.510 Subpart H. This decision is based upon the surrogate endpoint analyses of plasma HIV RNA levels in controlled studies up to 24 weeks duration. In the current NDA, the applicant has provided evidence of APTIVUS' initial antiviral effect when co-administered with low-dose ritonavir and used in combination with other antiretroviral drugs for the treatment of HIV-1 infected, three-antiretroviral class-experienced patients with ongoing measurable viremia and with limited therapeutic options. I concur with the clinical review prepared by Dr. Andrea James (primary medical reviewer) with assistance from Dr. Melissa Baylor (on Phase 1, pediatric and naïve studies) and from Dr. Neville Gibbs (on Phase 2 studies). As stated in Dr. James' review, the applicant has demonstrated that APTIVUS co-administered with low-dose ritonavir, at the proposed doses for marketing (500 mg APTIVUS/200 mg ritonavir), has a benefit (antiviral effect over multiple protease-inhibitor resistant virus) which at this time of accelerated approval outweighs the safety concerns (particularly hepatotoxicity, drug-drug interactions, lipid abnormalities, and rash) in the HIV-1 population studied in their Phase 3 randomized trials (1182.12 and 1182.48, i.e. heavily pretreated with limited therapeutic options). Thus, this drug is being approved under the Subpart H regulations with the indication being restricted to the clinically advanced, highly treatment experienced and multiple protease inhibitor

resistant HIV-1 infected population with limited treatment options and ongoing measurable viremia. This restricted indication was recommended by the FDA Antiviral Advisory Committee which convened on this drug product (May 19, 2005). In this desperate population, novel and effective antiretroviral drug therapies are especially needed to suppress HIV-1 replication and thus arrest progression of/to AIDS.

The New Drug Application (NDA) 21-822 for APTIVUS (tipranavir) 100 mg/mL oral solution is not being recommended for regulatory approval at this time. I concur with Dr. Derek Zhang (Clinical Pharmacology Reviewer), Dr. Kelly Reynolds (Clinical Pharmacology Team Leader) and Dr. Melissa Baylor (Medical Reviewer), that neither the relative bioavailability study 1182.45, nor the Phase I/IIa study in pediatric patients (1182.14), provides adequate data to support approval of the NDA 21-822 (Please see Dr. Baylor's NDA Review).

Tipranavir oral solution is about 30% more bioavailable than tipranavir capsules when the dosage forms are administered with ritonavir under fasted conditions; thus, the solution and capsules are not bioequivalent. The relative bioavailability study design (single dose) does not provide definitive results. Due to the complex enzyme/transporter interactions during absorption, it is difficult to predict relative bioavailability of these two dosage forms at steady-state from single-dose data. The Applicant submitted preliminary results from 1182.14, an on-going pediatric study, for FDA's review. Antiviral activity data for the first four weeks were submitted for the first 37 subjects. Safety data for the first 12 study weeks were submitted for 74 subjects. The report does not include adequate exposure data, safety data or efficacy data to recommend a dose of the tipranavir solution for pediatric patients.

The Applicant will need to provide steady-state relative bioavailability or bioequivalence data for the oral solution compared to the capsules. In the absence of acceptable bioequivalence or relative bioavailability data for tipranavir oral solution compared to the capsules, the Applicant will need to 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 500 mg tipranavir capsules with 200 mg ritonavir twice daily in adult patients.

For the remainder of this document, my discussion will be focused on NDA 21-814 (tipranavir capsules) only. I will briefly highlight salient items which emerged during the review of the data from the tipranavir NDA and also take this opportunity to emphasize the valuable lessons learned regarding drug study design and conduct in a heavily pretreated HIV-1 infected population.

Background

The 24 week virologic data from the two pivotal on-going open-label controlled trials (1182.12 and 1182.48) forms the basis of this accelerated approval. This new molecular entity NDA for tipranavir was submitted originally in October of 2004. Due to a number of difficult issues with the reviewability of the Applicant's raw datasets by the FDA, the applicant chose to withdraw their New Drug Application (NDA) in December of 2004. The Applicant resubmitted this NDA on December 22, 2004 after resolving a number of the dataset issues. Data reviewed by the FDA from the December submission covered the tipranavir/ritonavir (TPV/r) development program up to June 11, 2004 (the data cutoff date for 24 week submission). This NDA was granted a priority (6 month) review period. A consultation to the FDA's Antiviral Advisory Committee also occurred during the 5th month of review.

In addition to the two Phase 3 trials, the NDA submission contained information from two roll-over (from Phase 3) open label safety studies (1182.17 and 1182.58), five Phase 2 trials (1182.2, 1182.4, 1182.6, 1182.51 and 1182.52), twenty-eight Phase 1 trials in HIV-negative healthy individuals, one limited pediatric safety and efficacy data (1182.14), and preliminary serious safety data on newly enrolling Phase 3 trial (1182.33) in antiretroviral treatment-naïve population. A safety update to the NDA was submitted by the Applicant on February 22, 2005. This additional submission provided safety data in the TPV/r development program through September 30, 2004.

Mechanism of action

Tipranavir (TPV) is a non-peptidic HIV-1 protease inhibitor (PI) that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

EFFICACY

Design and Baseline Characteristics

Of the 20 approved antiretroviral package inserts with CLINICAL STUDIES sections (last query to the Physician's Desk Reference: March 3005), 15 unique registrational trials from 13 drugs are described under subsections entitled, "treatment-experienced" population. The two TPV/r Phase 3 studies will be make 17 unique registrational trials from 14 drugs. The design and baseline characteristics of TPV/r's "treatment-experienced" studies are quite different from the other approved drugs due to the fact that this population was heavily pretreated with no treatment options while the other "treatment experienced" trials are either in populations with lesser amounts of antiretroviral pretreatment and/or with available treatment options. The design and population of TPV/r trials were in fact similar to the enfurvitide (ENF) registrational trials which were also conducted in the heavily pretreated subjects (See NDA 21-481 Team Leader Memorandum, October 2004, by this author).

Studies 1182.12 and 1182.48 are ongoing, randomized, controlled, open-label, multi-center studies in HIV-positive, triple antiretroviral class experienced subjects. All subjects were required to have previously received at least two protease inhibitor (PI)-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry with baseline HIV RNA of at least 1000 copies/mL and any CD4 cell count. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations on codons 33, 82, 84 or 90.

These studies evaluated treatment response at 24 weeks in a total of 1159 subjects receiving either TPV/r plus optimized background regimen (OBR) versus a control group receiving ritonavir-boosted PIs (lopinavir, amprenavir, saquinavir or indinavir) plus OBR. Prior to randomization, subjects were pre-assigned to either receive or not receive enfurvitide. After Week 8, subjects in the control group receiving ritonavir-boosted PIs (CPIs) who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to TPV/r in a separate roll-over study.

Demographics and baseline characteristics were balanced between the TPV arm and control arm. In both studies combined, the 1159 subjects had a median age of 43 years (range 17-80), were 88% male, 73% white, 14% black and 1% Asian. The median baseline plasma HIV RNA was 4.82 (range 2 to 6.8) log₁₀ copies/mL and median baseline CD4 cell count was 155 (range 1 to

1893) cells/mm³. Forty percent (40%) of subjects had a baseline HIV RNA of $\geq 100,000$ copies/mL, 61% had a baseline CD4 cell count <200 cells/mm³, and 57% had prior AIDS defining Class C event at baseline. Subjects had prior exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs with 12% of subjects having previously used enfurvitide. Overall at baseline, 97% of the isolates were resistant to at least one PI, 95% of the isolates were resistant to at least one NRTI, and $>75\%$ of the isolates were resistant to at least one NNRTI. The individually pre-selected protease inhibitor based on genotypic testing and the subject's medical history was lopinavir in 50%, amprenavir in 26%, saquinavir in 20% and indinavir in 4% of subjects in both studies combined. Eighty-six (86%) percent of control subjects in both studies combined were possibly resistant or resistant to the pre-selected comparator PIs.

A total of 25% of subjects in both studies used enfurvitide during study. There were differences between Studies 1182.12 and 1182.48 in investigative sites, the use of the protease inhibitors, and in the use of enfurvitide (please see Dr. Rafia Bhore's Statistical Review for complete descriptions and analyses).

Since the two pivotal clinical trials are similar in design and baseline characteristics and the resulting outcomes were also similar, the following summary outcome table is presented with pooled data. The principal analysis population was the modified intent-to-treat population (appropriate since these studies were designed as superiority trials) defined as all randomized patients (with the disease) who took at least one dose of the study and had at least one follow-up visit post baseline. The primary efficacy endpoint for week 24 was the proportion of subjects with a confirmed 1 log drop in HIV RNA without any prior evidence of treatment failure due to 1) death, 2) loss-to-follow up, 3) confirmed virologic failure, 4) permanent discontinuation of study drug, or 5) introduction of a new ARV drug for reasons other than toxicity to the background ARV. These proportions were calculated based on the FDA-defined Time to Loss of Virologic Response algorithm.

Disposition and Outcomes

TPV/r + OBR arm was superior in efficacy over the control arm of suboptimal CPI/r + OBR at 24 weeks (see Primary Outcomes Table below) with a treatment difference of 22% (95% CI, 17%, 27%). For two secondary virologic endpoints, the proportion of subjects in the TPV/r arm compared to the comparator PI/ritonavir arm with HIV RNA < 400 copies/mL was 34% and 16% respectively, and with HIV RNA < 50 copies/mL was 23% and 9% respectively.

Primary Outcomes at Week 24 (Pooled Data 1182.12 and 1182.48)

	TPV/r + OBR N (%)	CPI/r + OBR N (%)
Total treated	582 (100)	577 (100)
Treatment response at Week 24	234 (40)	103 (18)
No confirmed 1 log₁₀ drop from baseline	312 (54)	456 (79)
Initial Lack of Virologic Response by Week 8	203 (35)	340 (59)
Rebound	68 (12)	67 (11)
Never suppressed	41 (7)	49 (8)
Added ARV drug	22 (4)	9 (2)

The following table compares the treatment differences between primary and secondary virologic endpoints across the two NDAs which examined antiretroviral efficacy in heavily pretreated subjects with limited treatment options at 24 weeks. Results are slightly better for enfurvitide but consistent overall. As discussed in my enfurvitide Team Leader Memorandum, these treatment margins may be useful for cross-study comparisons and/or setting the delta for non-inferiority margins.

Virologic Outcome Treatment Differences between test drug and control arms at 24 weeks

Virologic endpoint results at 24weeks	ENF Phase 3 trials combined	TPV/r Phase 3 trials combined
Primary: 1 log↓ in viral load	26% (95% CI: 20%, 32%)	22% (95% CI: 17%, 27%)
Secondary: <400 copies/mL	21% (95% CI: 16%, 32%)	18% (95% CI: 13%, 23%)
Secondary: <50 copies/mL	14% (95% CI: 9%, 18%)	14% (95% CI: 10%, 18%)

The examination of outcome by the use of enfurvitide (representative of another virologically active compound) in the TPV/r trials was an important analysis. The justification of this subgroup analysis is that these trials demonstrated superiority in their primary outcome analysis and that enfurvitide use was a pre-specified stratification prior to randomization. Patients in the TPV/r arm achieved a significantly better virologic outcome than patients in the CPI/arm when TPV/r was combined with enfurvitide.

Proportion of Treatment Responders Through Week 24 by ENF use (pooled results)

% subjects with ENF use during study	TPV/r + OBR (N=582)	CPI/r + OBR (N=577)	Treatment Difference with CI
Yes (25%)	48%	19%	29.4% (19%, 30%)
No (75%)	29%	13%	15.6% (10%, 21%)

Issue of Early Escape Clause: Due to the heavily pretreated subjects under study, an escape clause to protect the subjects in the control arm was necessary. However, this important aspect of the study design impacted the outcome assessments of the study. The following are two examples. 1) The primary efficacy endpoint was the proportion of subjects with confirmed 1 log RNA drop from baseline at week 24 without evidence of treatment failure. The study was designed with an escape clause to allow subjects in the comparator arm who had a lack of initial virologic response at week 8 to discontinue the RESIST trial and receive TPV in a rollover safety study; lack of initial virologic response was defined as decrease in viral load < 0.5 log10 and failure to achieve a viral load of <100,000 copies/mL during the first 8 weeks of treatment despite a 0.5 log10 drop after 8 weeks of treatment. These same discontinued subjects in the comparator arm were considered as treatment failures at week 24 primarily accounting for the treatment difference in the primary efficacy endpoint. The initial virologic treatment difference (24%) between the two arms shown at week 8 explains the virologic treatment difference (22%) between the two arms at week 24. 2) Because 59% of the control arm left the study through virologic criteria at 8 weeks, assessment of the important immunologic parameter (secondary outcome of median change in CD4+ cell count from baseline) was limited. Neither the use of as-treated (AsT) analysis nor the last observation carried forward (LOCF) analyses are optimal; but, both taken together present useful information to the health care provider. If AsT analysis is used, the median change in CD4+ cell count from baseline was +40 cells/mm3 in the TPV/r arm (N=436) and +32 cells/mm3 in the CPI/r arm (N=248) at week 24. If the LOCF is used, the median

change from baseline in CD4+ cell count in patients receiving TPV/r (N=582) versus CPI/r (N=577) was +34 and +4 cells/mm³ at Week 24, respectively.

Issue of clinical endpoints in heavily pretreated subjects: The use of HIV-1 virologic suppression as the surrogate measurement of clinical outcome has been the mainstay of HIV drug trials during the last decade due to correlations between viral suppression and improved clinical outcome and since aggressive treatment of HIV has resulted in too few clinical events for adequate comparisons in short-term drug trials. The heavily pretreated population of enfurvitide drug trials and now the TPV/r drug trials are evolving populations in HIV drug trials, different from the HIV-1 clinical populations during the beginning of the epidemic. The subjects in TPV/r Phase 3 trials are clinically advanced with lower CD4 counts and high baseline viral loads with prolonged exposures to multiple drug therapeutics and subsequent multi-resistance to antiretrovirals and/or accumulation of drug toxicities. The natural history of this advanced and complicated population is unknown, but it is probable (and the accumulating data shows) that clinical events are occurring. Diligence is required to capture as much clinical information as possible in these trials so that we can better understand the relationship of clinical outcome to viral surrogates in this population. In this TPV/r Phase 3 studies, using all-cause mortality as a definitive clinical event (AIDS-defining events were captured in these trials as adverse events only and not separately captured or adjudicated and thus difficult to compare), it was noted that the number of on-treatment deaths (15 TPV/r versus 13 CPI/r) were similar between the two arms. The added virologic benefit (as measured by the surrogate of plasma HIV RNA) did not translate into any reduction in mortality at the 24 week time-point. These results may be explained by the fact that these studies were not powered for mortality and the 24 week time-point is too premature to see any clinical endpoint differences. In addition, due to the open-label nature of these RESIST trials with all the inherent bias as well as the built in escape clause for the comparator arm at 8 weeks after lack of initial virologic response, it is difficult to discern meaningful comparative clinical efficacy data beyond 8 weeks of treatment.

Issue of Bias Due to Open-Label Study Design with an Early Escape Clause: The interpretations of the data from the two Phase 3 TPV/r trials are confounded by this issue. The inevitable introduction of bias to trials where both the subjects and the investigator have knowledge of the treatment arm is particularly enhanced in a desperate population needing novel therapeutics. Subjects in the CPI/r arm know that their (HIV) virus is resistant to the control drugs and that they have TPV/r as a new treatment option if they fail early on the CPI/r drug. In contrast, subjects in the TPV/r arm do not have alternatives if they fail. This may result in different levels of compliance in the two treatment groups. There were several potential sources of open-label bias identified by the FDA review team including 1) Post-randomization changes in the Optimized Background Regimen 2) Post-randomization changes in the Randomization Strata 3) Early discontinuation of treatment arm due to initial lack of virologic response at Week 8 4) Protocol Violations 5) Potential lack of treatment compliance identified by low blood concentrations of drug level. An example to illustrate this issue is the concomitant use of enfurvitide (ENF).

Post-randomization Changes in Randomization Strata of ENF

Pre-selected ENF (No) but Actual ENF (Yes)			Pre-selected ENF (Yes) but Actual ENF (No)		
TPV/r N=427	CPI/r N=430	Total N=857	TPV/r N=155	CPI/r N=147	Total N=302
11 (3%)	4 (1%)	15 (2%)	8 (5%)	23 (16%)	31 (10%)

As shown in the table above, there were 857 subjects who were pre-assigned to not take enfurvitide. Among the subjects who were not assigned to take enfurvitide, 3% of the subjects in TPV group actually took enfurvitide, and 1% in the control group took enfurvitide. In the second type of mismatch, there were 302 subjects who were pre-assigned to use enfurvitide. Among these patients, 5% of the TPV subjects chose not to use enfurvitide, while in the comparator group 16% of the subjects did not use enfurvitide. When we compared the behavior of subjects in the comparator PI group in the first type of mismatch versus second, there is a significant difference (based on McNemar’s test for mismatches; see Statistical Review). Upon our discussion with the applicant, we found that subjects who were in the comparator PI group did not take enfurvitide even when they were assigned because they wanted to take 2 new drugs after Week 8 through the escape clause if their viral load did not drop.

Issue of baseline viral resistance impacting outcome: It is important to note that in both Phase 3 trials combined, 86% of the subjects were possibly/definitely resistant to the assigned comparator PIs. Thus, although these pivotal trials are being presented as TPV/r + Optimized background regimen (OBR) versus CPI/r + OBR, in actuality, the results should be interpreted more as TPV/r versus suboptimal control with both arms utilizing a large variety of OBR (n = 161 different drug combinations as per FDA statistical analysis). TPV/r showed significantly greater treatment effect than CPI/r when subjects were already resistant (possibly or definitely) to their treatment CPI. TPV/r did not appear to offer antiviral benefit over CPI/r for subjects in the comparator arm who were sensitive to their PIs.

Baseline HIV-1 resistance profile impacting outcome (pooled 1182.12 and 1182.48)

	TPV/r	CPI/r	
Not Resistant	23/76 (30%)	17/80 (21%)	9% (-4.6%, 22.7%)
Possibly Resistant	56/135 (41%)	23/112 (21%)	21% (9.8%, 32.1%)
Resistant	119/369 (32%)	43/385 (11%)	21.1% (15.4%, 26.8%)

Issue of baseline genotype/phenotype impact on outcome: Resistance characterization at baseline was analyzed by the FDA microbiologist (Please see Dr. Lisa Naeger’s review) to explore the impact on 24 week outcome since genotypic and/or phenotypic analysis of baseline virus may aid in determining TPV susceptibility before initiation of TPV/r therapy, particularly in heavily-pretreated subjects. Several analyses were conducted to evaluate the impact of specific mutations and mutational patterns on virologic outcome. Both the number and type of baseline PI mutations as well as concomitant enfurvitide use affected TPV/r response rates in studies 1182.12 and 1182.48 through Week 24 of treatment. Reduced virologic responses were seen in TPV/r-treated subjects when isolates had a baseline substitution at position I13, V32, M36, I47, Q58, D60, I84 or substitutions V82L/I/S/F. The reduction in virologic responses for these baseline substitutions was most prominent when subjects did not receive enfurvitide with TPV/r. In addition, subjects with substitutions at V82 including V82A or T and an I84V mutation in their HIV-1 had reduced response rates. Analyses were also conducted to assess virologic outcome by the number of PI mutations present at baseline. Response rates were reduced if five or more PI-associated mutations (at positions - D30, V32, M36, M46, I47, G48, I50, I54, F53, V82, I84, N88 or L90) were present at baseline and subjects did not receive concomitant enfurvitide with TPV.

TPV/r response rates were also assessed by baseline TPV phenotype. Analyses exploring relationships between baseline phenotypic susceptibility to TPV, the number of baseline protease mutations at amino acids 33, 82, 84 and 90, and response to TPV/r therapy at week 24 are summarized in the table below.

Response by Baseline TPV phenotype in 1182.12 and 1182.48 Trials

Baseline TPV Phenotype	Proportion of Responders^a with No ENF Use	# of Baseline Mutations at 33, 82, 84, 90	TPV Susceptibility
0-3	45% (74/163)	0-2	Susceptible
>3-10	21% (10/47)	3	Decreased Susceptibility
>10	0% (0/8)	4	Resistant

^aconfirmed 1 log₁₀ decrease at Week 24

These baseline phenotype groups do not represent definitive clinical susceptibility breakpoints for TPV/r because it is based on a selective patient population. This information represents the analyses of data from studies 1182.12 and 1182.48 to show likelihood of virologic success based on pretreatment susceptibility to TPV/r in heavily pretreated PI-experienced patients.

SAFETY

The overall safety profile is based on 3195 subjects (June 2004 data cutoff) who received at least 1 dose of TPV during various clinical trials. This includes 2430 HIV positive and 765 HIV negative subjects. In the safety update submission (September 2004 data cutoff), an additional 793 HIV positive subjects had been added to the program, predominantly from the on-going 1182.33 trial in HIV-1 infected treatment naïve population and the emergency use/expanded access programs. Specific issues relating to safety results that arose from the review of this supplemental application are briefly highlighted below. Please see Dr. Andrea James' integrated safety review for the complete discussion.

Drug-drug interaction: The drug-drug interaction potential of 500 mg of TPV in combination with 200 mg of ritonavir is extensive. TPV/r can alter plasma exposure of other drugs and other drugs can alter plasma exposure of TPV/r. Please see Dr. Derek Zhang, clinical pharmacologist's review for the complete and very complicated discussion. The known and potential interactions between TPV/r and other HIV medications as well as TPV/r potential for interactions with other classes of drugs are presented in his tables. His conclusions include the following: 1) Administration of TPV/r can increase plasma concentrations of agents that are primarily metabolized by CYP3A, because TPV/r is a net inhibitor of CYP3A. 2) The applicant did not evaluate the effect of TPV/r on substrates for enzymes other than CYP3A. In vitro studies indicate TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Due to the known effect of RTV on CYP2D6, the potential net effect of TPV/r is CYP2D6 is inhibition. The net effect of TPV/r on CYP1A2, CYP2C9 and CYP2C19 is not known. 3) In vivo data suggest that the net effect of TPV/r on P-glycoprotein is induction. Based on current data, it is difficult to predict the net effect of TPV/r on oral bioavailability and plasma exposure of drugs that are dual substrates of CYP3A and P-gp. 4) TPV is a CYP3A substrate as well as a P-gp substrate. Therefore, co-administration of TPV/r and drugs that induce CYP3A and/or P-gp may decrease

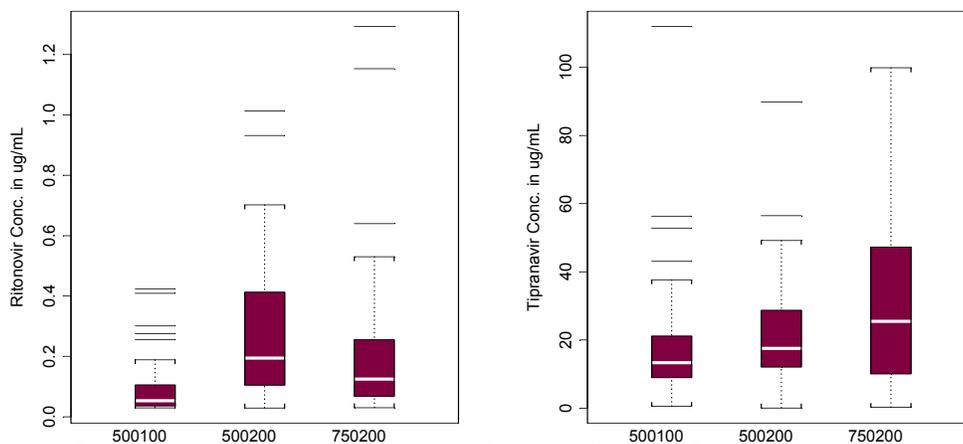
TPV plasma concentrations and reduce its therapeutic effect. Conversely, co-administration of TPV/r and drugs that inhibit P-gp may increase TPV plasma concentrations and increase or prolong its therapeutic and adverse effects. Co-administration of TPV/r and drugs that inhibit CYP3A may not further increase TPV plasma concentrations, based on the results of a submitted mass balance study.

Dose-related exposure analysis between TPV and RTV: The following excerpts are taken from various reviewers to make the point that as TPV dose increases, TPV exposure increases but RTV exposure decreases. Thus, based upon the review of the submitted data, the dose-related safety events are attributable to TPV and not to the low-dose RTV boost.

Medical Officer Review by Dr. Melissa Baylor: Phase 1 Study P & U 015 of TPV in HIV-infected subjects. She writes in her conclusion of this study review that “*TPV exposure increased with RTV boosting and with increase of TPV dose, while RTV levels decreased with increasing TPV levels. This pharmacokinetic finding allowed determination of dose response for activity and for safety. Adverse events, particularly diarrhea and nausea were common. Less common AEs of significance were increased ALT values and increases in lipid values; the frequency of these AEs was exposure related.*”

Medical Officer Review by Dr. Neville Gibbs: Phase 2 study 1182.4 of TPV in HIV-infected subjects. He writes in his conclusion of this study review that “*Pharmacokinetic analyses in this study showed that RTV concentrations in the higher dose groups (TPV/r 1250/100mg) were substantially lower when compared to the TPV/r 500/100 mg group. This decrease may be attributed to CYP3A induction by the higher dose of TPV, which results in increased metabolism of RTV. The overall safety profile of TPV co-administered with RTV was similar to that observed in previous tipranavir trials in both HIV-1-negative healthy volunteers and HIV-1-positive adults. Low dose TPV/r was easier to tolerate than high dose due to the increased frequency of GI adverse events in the high dose TPV/r group. The tolerability and safety profile of TPV/r was similar to that of SQV/r, however, there was an increased frequency of GI adverse events, rash, and hepatotoxicity in subjects receiving TPV/r compared to those receiving SQV/r.*”

Pharmacometrics Review by Dr. Jenny Zheng: Phase 2 study 1182.52, the dose finding study in HIV-infected subjects. She writes regarding the dose-related transaminase rises “*in order to understand whether ALT elevation is related to TPV or ritonavir, the exposures of both TPV and RTV were compared across treatments. The median RTVr concentration is lower (0.281 µg/mL vs. 0.217 µg/mL) and TPV concentration is higher (21.26 µg/mL vs. 30.75 µg/mL) after the 750/200 mg dose compared to the 500/200 mg dose. In spite of this, the 750/200 mg dose group had a higher proportion of subjects with grade 3/4 ALT elevations.*”



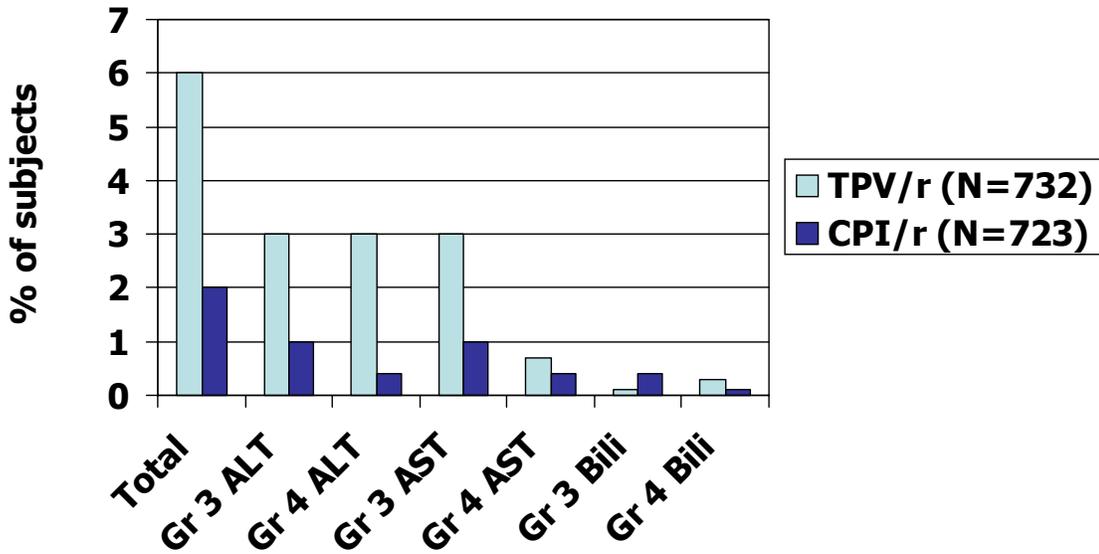
Range of trough (C_{min}) RTV and TPV concentrations at the 3 dose levels. The median concentrations of TPV are 17.46 µg/mL (n=60), 21.26 µg/mL (n=63) and 30.75 µg/mL (n=56), respectively.

Hepatotoxicity: Initial hepatotoxicity signals were observed throughout the 18 Phase 1 studies in healthy volunteers. A total of 36 (5.5%) healthy HIV-negative subjects experienced treatment emergent grade 3 or 4 liver abnormalities (rise in ALT) in the Phase 1 studies. Comparison of the 500/200 mg and 750/200 mg dose groups in Study 1182.52, the dose finding Phase 2 study, provided further strong evidence that TPV independent of, but in the presence of, ritonavir causes grade 3/4 ALT elevations in a dose dependent manner.

Proportion of subjects with grade 3/4 ALT elevations for each dose group.

Dose Group	Proportion of Subjects with Grade 3/4 ALT elevations (number/total)
500/100 mg	4.3% (3/69)
500/200 mg	11.1% (8/72)
750/200 mg	23% (16/69)

In the Phase 3 trials, 10% of subjects on the TPV/r arm compared to 3% on the CPI/r arm developed treatment emergent grade 3 or 4 ALT or AST elevations.



For 1182.12, time to first DAIDS Grade 3 or 4 ALT elevation was significantly different between the two arms with subjects in the TPV/r arm more likely to develop Grade 3 or 4 elevations in ALT and at a significantly faster rate than those in the CPI/r arm. For 1182.48, time to first Grade 3 or 4 ALT elevation was significantly shorter for subjects in the TPV/r arm compared those for subjects in the CPI/r arm (Please see Dr. Susan Zhou’s Statistical Review on Phase 2 laboratory parameters).

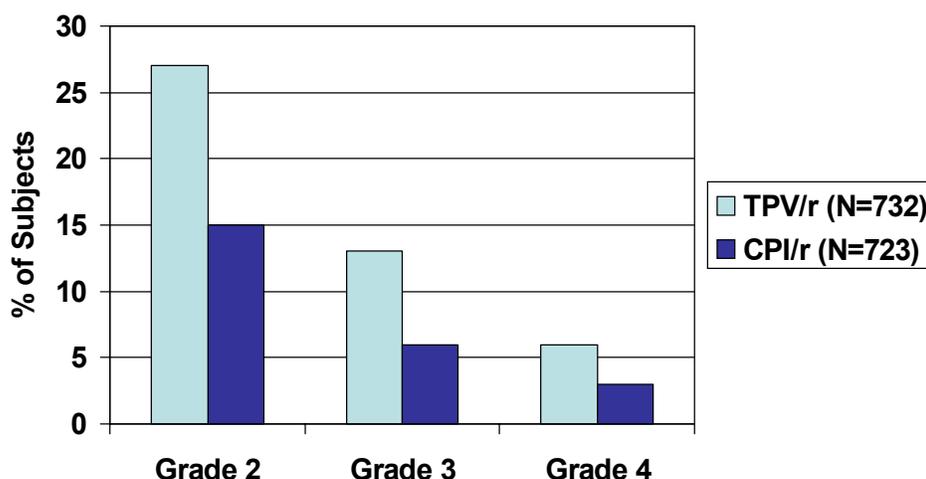
Very few subjects had documented concurrent symptoms and the following table depicts outcomes of the grade 3 and 4 ALT/AST elevations.

	TPV/r N = 732	CPI/r N = 723
Grade 3/4 ALT/AST Elevation	45 (6%)	18 (2%)
Discontinued	12 (27%)	0
Resolved	29 (64%)	17 (94%)
On tx	19 (42%)	17 (94%)
Off tx	10 (22%)	0
Unresolved	16 (35%)	1 (6%)
On tx	14 (31%)	1 (6%)
Off tx	2 (4%)	0

A possible risk factor may be baseline hepatitis. The % frequency of grade 3 and 4 ALT elevations among subjects with baseline hepatitis B or C was 9/76 (12%) in the combined TPV/r arm versus 6/113 (5%) in the CPI/r arm. Thus, the case is certainly made that LFT elevations are attributable to TPV. On the other hand, the data we have thus far does not show a clinical picture of these laboratory abnormalities resulting in acute liver injury with fulminant liver failure. However, the contributory effect of drug-induced transaminitis on subacute liver injury impacting on the ultimate negative clinical sequelae is possible, especially in the context of multiple drug-drug interactions and the medically fragile population.

Furthermore, the Applicant has submitted 7 fatal cases in their Safety Update who had a hepatic component to the fatality. Causal determination of death events to TPV hepatotoxicity cannot be determined; but, contribution of the drug toxicity to the death events also cannot be ruled out. Specific warnings, precautions, and monitoring are indicated. Since the Phase 3 trials excluded subjects with evidence of active liver disease, it will be important to request Phase IV commitments from the Sponsor to study patients with underlying liver disease including hepatitis B or C HIV-1 co-infected patients to better characterize this safety concern.

Lipid Abnormalities: More subjects in the TPV/r arm developed Grade 3 or 4 laboratory lipid abnormalities than those in the CPI/r arm and at a significantly faster rate. For combined 1182.12 and 1182.48 datasets, 21% of subjects developed treatment emergent grade 3 or 4 triglycerides compared to 11% of subjects on the CPI/r arm. The following figure depicts the % of subjects with treatment emergent rise in triglycerides.



Analyses of 1182.12 laboratory data showed that the time to first Grade 3 or 4 in total cholesterol or triglycerides were significantly different between the two arms. Analyses of 1182.48 laboratory data showed that the time to first Grade 3 or 4 elevation in total cholesterol or triglycerides were shorter for subjects in the TPV/r arm. The significant differences in the frequency of Grade 3 or 4 lipid or transaminase elevations between the TPV/r and CPI/r arms may be due to differences in follow-up between the two arms. The escape clause in these studies resulted in a differential duration of randomized treatment exposure and laboratory monitoring between the two arms. On the other hand, it is important to keep in mind many subjects randomized to the CPI/r arms (13%) already had a long duration of exposure to the CPI drug because they entered the study and continued on their current PI.

Cutaneous reaction (adverse event of “rash”): was another safety event of special interest in this review due to a substantial Phase 1 signal from an oral contraceptive study in healthy HIV negative women (Study 1182.22). Seventeen subjects (33%) developed a rash while receiving TPV. This high and unexplained incidence of rash in healthy, female volunteers raised the possibility that gender and immune status may have an impact on the frequency and types of adverse events (AEs) observed with TPV/r use. Other phase 1 trials in healthy HIV-negative volunteers showed that rash was seen in 14/390 (3.6%) males as compared to 34/265 (13%) females. In Phase 2 trials of HIV infected subjects, one large study (1182.51) showed a rash rate of 10.2% (32/315). Rash was only reported in males but the study population was 93% male. In another large phase 2 study (1182.52), 8.6% (18/216) of subjects in the study developed treatment-emergent rash. Dose relation was suggested because there were 10 subjects who developed rash in TPV/r 750/200 mg group, including one discontinuation, whereas there were 5 subjects in the TPV/r 500/200 mg group and 3 subjects in the TPV/r 500/100 mg group. Relationship of the development of rash to an intact immune system (as indicated by preserved CD4 cell counts) could not be examined in these two large Phase 2 studies because these subjects were heavily pretreated and advanced in HIV disease with median CD4 cell count of 133 (1182.51) and 178 (1182.52). Phase 2 trials enrolled predominantly males: however of the limited data available, females on the TPV/r in phase 2 trials had higher incidence of rash (15/114 or 13.2%) as compared to males (59/745 or 7.9%).

In the Phase 3 trials, the overall incidence of rash was similar in both arms (11% TPV/r versus 10% CPI/r). The severity and need for treatment were also similar between the two arms. Since the Phase 3 trial population was immunologically depleted, adequate exploration of the impact of immune competence on the frequency of rash was limited. An exploratory analysis of females in the Phase 3 trials (n=118 TPV/r; n=90 CPI/r) showed that the females on the TPV/r arm had a higher incidence of rash (14%) as compared to the females on the CPI/r arm (9%). However, the small number of women in these trials made it impossible to draw any definitive conclusions. Although BI is currently conducting a study in antiretroviral naïve subjects, the study is already fully enrolled with only about 20% of female subjects (similar to the Phase 3 trials) and based on baseline CD4+ count, viral load and AIDS defining illnesses, these naïve subjects have advanced HIV disease. Therefore, it appears unlikely that the current naïve trial will provide definitive answers to whether or not TPV/r affects women and/or immunocompetent subjects differently than the remainder of the HIV+ population. A Phase IV commitment will be requested to further explore and study this safety concern.

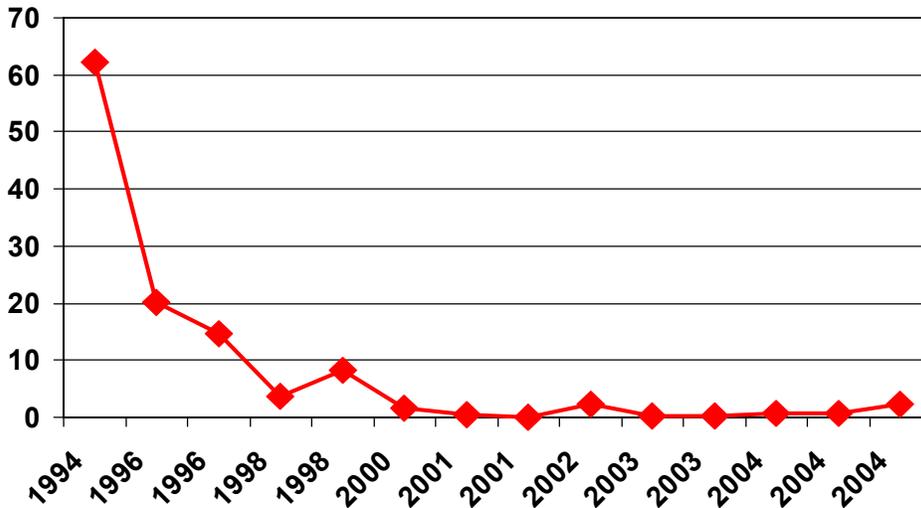
Mortality: One hundred and two subjects died during the entire TPV clinical development program up through the database lock on June 11, 2004. In total, 12 subjects died during the pretreatment phase and 90 subjects died after being exposed to at least one dose of drug (post-drug exposure). For most deaths, subjects had advanced HIV disease and multiple concomitant

medications. Three of the 90 post-drug exposure subject deaths were considered to be possibly TPV/r treatment related by the Applicant. However, FDA could not rule out relatedness or a possible contribution of the effects of TPV in most death cases. This unclear ascertainment of study drug’s relationship to mortality (and to morbidity) is due to the nature of the population under study, and in many cases, was due to the lack of available information surrounding the death cases.

Overall, there were more deaths in 1182.12 than in 1182.48 (22 versus 11), and there were more deaths on the TPV/r arms compared to the CPI/r arms (19 versus 14). The *on-treatment* deaths (15 TPV/r versus 13 CPI/r) in Phase 3 trials were similar between the two arms. AIDS defining or AIDS progression events were captured in Phase 3 trials as adverse events only and not specifically abstracted or adjudicated. The added virologic benefit of TPV/r over CPI/r (as measured by the surrogate of plasma HIV RNA) did not translate into any reduction in mortality at the 24 week time-point. However, these Phase 3 trials were not designed to assess clinical endpoints. The escape clause at 8 weeks precluded optimal evaluation of longer term clinical efficacy and safety.

Analyses of mortality rates in the NDA database of all “treatment-experienced” trials which led to approval of an antiretroviral from the archives of DAVDP were conducted to place TPV/r Phase 3 trials’ mortality rates into perspective. Fourteen unique studies from 13 registrational drug programs were found to meet our search. Mortality rate per study in 100 subject-years by year of DAVDP approval are shown in the figure below.

Mortality Rates (100 subject-years) per NDA study in “treatment-experienced” population shown by year of approval by DAVDP



Examination of subject baseline characteristics showed that the population enrolled in enfurvitide Phase 3 studies which most closely approximated the TPV Phase 3 studies was the enfurvitide trials population (http://www.fda.gov/cder/foi/nda/2003/021481_fuzeon_review.htm). All on-treatment TPV deaths were reviewed and only those deaths which occurred within the window of 24 weeks treatment + 28 days follow-up were counted as raw numbers. This was how enfurvitide deaths were counted in enfurvitide’s accelerated approval NDA review at 24 weeks. Both mortality rates (#death/100 subject-years) using data through 24 weeks were calculated for both NDAs. As shown

below, raw numbers of deaths or mortality rates between the test and control arms were similar for both the TPV and enfurvitide (ENF) NDAs at 24 weeks.

FDA Analysis of the Comparison of deaths at 24 weeks (Phase 3 data)

TPV numbers at 24 weeks		ENF numbers at 24 weeks	
TPV/r ± OBR	CPI/r ± OBR	ENF± OBR	Placebo ± OBR
12/582 (2.0%)	7/577 (1.2%)	10/663 (1.5%)	5/334 (1.5%)
Mortality rate = 4.5	Mortality rate = 2.6	Mortality rate = 3.3	Mortality rate = 3.3

These comparative mortality rates between the TPV/r and CPI/r arms, as well as between two different drug programs (ENF and TPV/r), reassured us at this point in the review (24 week analyses) that the death rates observed in the TPV drug program were within similar range to the already reviewed ENF trials’ death rates.

Special Populations: Pediatrics – Based upon the preliminary results of study 1182.14, Dr.Melisse Baylor’s conclusions are as follows: *“The applicant has proposed the inclusion of dosing guidelines for children 6 years of age and older in the TPV package insert. At this time, there is insufficient efficacy data to support any treatment effect in HIV-infected children. Furthermore, very few data points were collected to support the selected dose of TPV in children. The oral solution also appears to be difficult for children to tolerate. Therefore, in this reviewer’s opinion, there are not sufficient data to support the inclusion of pediatric information in the package insert for TPV at this time.”* Further work on appropriate formulations, safety and dosing information are needed to treat this population.

Gender Difference: Females – It has been discussed above and throughout multiple reviews that females may have a higher risk of rash when taking TPV/r. It is interesting to note that PK and efficacy analysis by gender also show gender differences. Dosing with APTIVUS 500 mg concomitant with 200 mg ritonavir twice daily for 2 to 4 weeks and without meal restriction produced the following PK parameters.

Pharmacokinetic parameters^a of TPV/r 500/200 mg for HIV+ patients by gender

	Females (n = 14)	Males (n = 106)
C _p trough (µM)	41.6 ± 24.3	35.6 ± 16.7
C _{max} (µM)	94.8 ± 22.8	77.6 ± 16.6
T _{max} (h)	2.9	3.0
AUC _{0-12h} (µM•h)	851 ± 309	710 ± 207
CL (L/h)	1.15	1.27
V (L)	7.7	10.2
t _{1/2} (h)	5.5	6.0

^aPopulation pharmacokinetic parameters reported as mean ± standard deviation

In Dr. Bhore's statistical analysis, she reported the following results which show that for both Phase 3 studies, response rates were higher for females.

**Subgroup Analysis by Gender on
Treatment Response through 24 weeks (confirmed 1 log₁₀ drop in viral load)**
1182.12

Gender	TPV/r + OBR	CPI/r + OBR	Treatment Effect, i.e., Difference in proportions (TPV/r – CPI/r) (95% Confidence Interval) [†]	Test for treatment by subgroup interaction p-value [‡]
1182.12				
Male (91%)	112/278 (40%)	62/287 (22%)	19% (11%, 26%)	0.378
Female (9%)	14/33 (42%)	3/22 (14%)	29% (7%, 51%)	
1182.48				
Male (84%)	79/225 (35%)	31/229 (13%)	22% (14%, 29%)	0.151
Female (16%)	29/46 (63%)	7/39 (18%)	45% (27%, 64%)	

RECOMMENDATION

This new molecular entity NDA for APTIVUS (tipranavir, TPV), co-administered with low-dose ritonavir is being recommended for accelerated regulatory approval under subpart H regulations. In the current NDA, the applicant has provided evidence of APTIVUS' antiviral effect (assessed at 24 weeks duration) when used in combination with other antiretroviral drugs for the treatment of HIV-1 infected, heavily antiretroviral treatment-experienced subjects. The two pivotal trials both demonstrated superior efficacy of APTIVUS + low dose ritonavir when compared to partially active control PI + optimized background regimen in subjects with multiple PI resistant virus and with limited therapeutic options. Experience gained from the review of this NDA should assist in better design and implementation of pivotal clinical trials in the heavily antiretroviral treatment experienced patients. Hepatotoxicity, hyperlipidemia, and cutaneous reactions, as well as extensive drug-drug interactions are the major safety concerns with this drug product. I concur with the clinical reviews prepared by Dr. Andrea James, Dr. Neville Gibbs, and Dr. Melissa Baylor (and advice from the FDA Anti-advisory Committee) that this drug should be approved awaiting 48 week confirmatory data. Further, as advised, the indications and usage should reflect the limitations of the current knowledge and communicate what is known about the risk/benefit balance at this time. A box warning regarding hepatotoxicity has been recommended by the Advisory Committee. The following is the recommended wording for the Box Warning and the Indications and Usage sections for the proposed package insert. Also in the proposed label, specific drug-drug interaction tables as well as detailed resistance information are recommended to guide the prescribing physician. As the drug is released to the market and the Applicant pursues further efficacy and safety studies, pharmacovigilance programs as well as post-marketing risk management strategies should be initiated in concert with the Applicant and the Agency's Office of Drug Safety.

Box Warning

APTIVUS CO-ADMINISTERED WITH LOW DOSE RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. SEE **WARNINGS**.

Indications

APTIVUS (tipranavir), co-administered with low-dose 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. This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of tipranavir of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

Usage

The following points should be considered when initiating therapy with APTIVUS/ritonavir:

- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response (see CLINICAL PHARMACOLOGY: Microbiology, DESCRIPTION OF CLINICAL STUDIES.)
- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/ritonavir. The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir (see CLINICAL PHARMACOLOGY: Microbiology).
- Liver function testing should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment (see WARNINGS).
- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, Hepatitis B or C co-infection or other underlying hepatic impairment (see WARNINGS).
- The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS)
- The risk-benefit of APTIVUS/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

PHASE IV COMMITMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. This commitment is listed below.

1. By September 30, 2006, please submit study reports for the 48 week data of the two ongoing Phase 3 studies, RESIST-1 (1182.12) and RESIST-2 (1182.48).

In addition, the Applicant has committed to the following postmarketing studies.

Drug-Drug Interaction Trials

2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and atazanavir.

Protocol Submission: Study completed

Final Report Submission: Submitted by December 31, 2005

3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and buprenorphine/naloxone.

Protocol Submission: July 15, 2005.

Final Report Submission: Submitted by June 30, 2006

4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and carbamazepine.

Protocol Submission: July 15, 2005

Final Report Submission: Submitted by September 30, 2006

5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and tadalafil.

Protocol Submission: August 31, 2005

Final Report Submission: Submitted by December 31, 2006

6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and ribavirin/pegylated IFN alpha 2a.

Protocol Submission: August 31, 2005.

Final Report Submission: Submitted by June 30, 2007

7. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and methadone.

Protocol Submission: Study completed.

Final Report Submission: Submitted by September 30, 2005

Pharmacology/Toxicology

8. Complete ongoing carcinogenicity study in mice and submit final report.

Protocol Submission: Completed
Final Report Submission: December 31, 2006

9. Complete ongoing carcinogenicity study in rats and submit final report.

Protocol Submission: Completed
Final Report submission: December 31, 2005

Special Populations

10. Assess the long term (48 week) antiviral efficacy and safety of tipranavir/ritonavir in ARV treatment naive patients through the conduct of study 1182.33.

Protocol Submission: Completed
Final Report Submission: September 30, 2006

Evaluate drug resistance in viruses from patients with virologic rebound on initial ART (in 1182.33), please submit data in resistance template.

Protocol Submission: Completed
Final Report Submission: September 30, 2006

Assess metabolic changes being studied in sub-study of 1182.33.

Protocol Submission: Completed
Final Report Submission: September 30, 2006

11. Conduct a 48-week prospective observational diversity cohort study with tipranavir/ritonavir twice daily stratified by race and gender in HIV-positive patients to assess efficacy and safety, including potential risk parameters such as CD4+ cell count.

Protocol Submission: March 30, 2006
Final Report Submission: September 1, 2008

12. Conduct a 48-week prospective observational cohort study with tipranavir/ritonavir twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.

Protocol Submission: March 30, 2006
Final Report Submission: July 1, 2008

13. Assess TPV/r pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease.

Protocol Submission: December 31, 2006
Final Report Submission: December 31, 2007

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring the submission of the Applicant's pediatric studies for ages 2 weeks to 2 years

until January 31, 2009. Also, we are deferring the submission of the Applicant's pediatric studies for ages 2 years to 18 years until June 30, 2006. These submissions are also postmarketing study commitments (pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments) and they are listed below.

14. Assess two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety, in ARV naive and experienced children and adolescents between 2 and 18 years of age.

Protocol Submission: Completed
Final Report Submission: June 30, 2006

15. Evaluate dose requirements and safety in pediatric patients age 2 weeks to 2 years with HIV-1 infection (after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the FDA).

Protocol Submission: September 30, 2006
Final Report Submission: January 31, 2009

Pharmacokinetics

16. Conduct a CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs.

Protocol Submission: September 30, 2005
Final Report Submission: December 31, 2006

Clinical

17. Conduct a formal QT prolongation study.

Protocol Submission: Special Protocol Assessment Complete
Final report Submission: June 30, 2006

In addition to the post-marketing commitments, the Applicant has agreed to the following studies.

Drug-Drug Interaction Trials

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and bupropion.
2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug TMC125 (NNRTI).
3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug UK-427,857 (CCRS inhibitor).

4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug GW873140 (CCR5 inhibitor).
5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug Reverset (NRTI).
6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug TMC 114 (PI).

Pharmacokinetics

7. Conduct a study to assess intracellular triphosphate levels of zidovudine and abacavir when co-administered with tipranavir/ritonavir twice daily.

Clinical

8. Conduct a long-term cardiovascular safety evaluation of Protease Inhibitor/ritonavir (including tipranavir) from epidemiologic databases.

Microbiology

9. Evaluate cleavage site mutations in rebound samples on tipranavir.

Therapeutic Drug Monitoring

The Applicant will meet with the Division of Antiviral Drug Products (DAVDP) and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) within 6 months and develop a pilot study to assess the utility of therapeutic drug monitoring in HIV-infected patients receiving tipranavir/ritonavir. The study will be conducted and the results will be used to assess the value of conducting a larger trial to evaluate the clinical benefit of therapeutic drug monitoring for patients taking APTIVUS/ritonavir.

Concurrence

ODE IV/DepOffDir/ECox
HFD-530/DivDirector/DBirnkrant
HFD-530/DepDivDir/JMurray

Cc: NDA 21-814 and NDA 21-822

ODE IV/OfficeDirector/MGoldberger
HFD-530/MO/AJames
HFD-530/MO/MBaylor
HFD-530/MO/NGibbs
HFD-530/PM/TSinha
Stats/RBhore/SZhou

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Rosemary Johann-Liang
6/22/05 01:54:19 PM
MEDICAL OFFICER

Debra Birnkrant
6/22/05 01:57:42 PM
MEDICAL OFFICER

Edward Cox
6/22/05 04:22:41 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: October 27, 2004	DESIRED COMPLETION DATE: December 27, 2004 PDUFA DATE: June 22, 2005	ODS CONSULT #: 04-0279
TO: Debra Birnkrant, MD Director, Division of Anti-Viral Drug Products HFD-530		
THROUGH: Tanima Sinha Project Manager HFD-530		
PRODUCT NAME: Aptivus® (Tipranavir) 250 mg Capsules (NDA# 21-814) 100 mg/mL Oral Solution (NDA# 21-822) NDA# 21-814 and 21-822	NDA SPONSOR: Boehringer-Ingelheim Pharmaceuticals, Inc.	
SAFETY EVALUATOR: Linda M. Wisniewski, RN		
RECOMMENDATIONS: 1. DMETS has no objections to the use of the proprietary name, Aptivus. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document. 2. DMETS recommends implementation of the labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product. 3. DMETS suggests submitting the Proposed Patient's Instructions to the Division of Surveillance, Research, and Communication Support for review and comment. 4. DDMAC finds the proprietary name Aptivus acceptable from a promotional perspective.		
_____ Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	_____ Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 9, 2004

NDA# 21-814 and 21-822

NAME OF DRUG: **Aptivus** (Tipranavir Capsules 250 mg and Oral Solution 100 mg/mL)

NDA HOLDER: Boehringer-Ingelheim Pharmaceuticals, Inc.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530), for assessment of the proprietary name “Aptivus”, regarding potential name confusion with other proprietary or established drug names. Draft container label and carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Aptivus is the brand name for tipranavir, a non-peptidic protease inhibitor (NPPI) of HIV. It is co-administered with low-dose ritonavir, and is indicated for combination antiretroviral treatment of HIV-1 infected patients who are protease inhibitor treatment-experienced. It is supplied as a 250 mg capsule and oral solution containing 100 mg/mL. The recommended dose of Aptivus is 500 mg (two 250 mg capsules or 5 mL of oral solution), twice daily. Tipranavir is co-administered with 200 mg ritonavir (low-dose ritonavir). Aptivus capsules and oral solution should be stored at 25° C (77°F); excursions permitted to 15-30° C (59-86°F). Aptivus is packaged in HDPE unit-of-use bottles that contain 120 capsules with a child resistant closure and as an oral solution in 95 mL CRC bottles supplied with a 5 mL plastic oral dispensing syringe. Tipranavir must be used within 60 days after first opening of the bottle.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Aptivus to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, Drugs@fda, and the electronic online version of the FDA Orange Book.

Trademark Office’s Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Aptivus. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Aptivus acceptable from a promotional perspective.
2. The Expert Panel identified eight names as having potential for confusion with Aptivus. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel and Prescription Study Analysis

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Aptivus	Tipranavir Capsules 250 mg	Two 250 mg tablets twice a day.	N/A
	Tipranavir Oral Solution 100 mg/mL	5 mL twice a day.	
Optivar	Azelastine Hydrochloride, 0.05 % Ophthalmic Drops	One drop into each affected eye twice a day.	LA/SA
Optivite	Vitamins (OTC).	Once daily.	LA/SA
Optison	Human Albumin Injection 5 to 8 × 10 ⁸ human albumin microspheres, 10 mg albumin human, 0.22 ± 0.11 mg/mL octafluoropropane in 0.9% aqueous sodium chloride.	Individualized, 1 mL to 8.7 mL per study.	LA/SA
Antabuse	Disulfiram 250 mg tablet	125 mg to 500 mg per day. Maximum of 500 mg per day.	SA
Capoten	Captopril Tablet 12.5 mg, 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg, 150 mg	6.25 mg to 450 mg. Maximum of 450 mg per day.	LA
Ultiva	Remifentanyl Hydrochloride Injection: 1 mg, 2 mg, 5 mg	0.025 mcg/kg/min-4 mcg/kg/min intravenously as an adjunct to anesthesia.	LA
Raptiva***	Efalizumab 125 mg/vial Injection	0.7 mg/kg to 1 mg/kg. Subcutaneous once, and weekly.	SA
(b) (4)			
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***Identified through verbal prescription study. ****NOT FOI Releasable.			

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

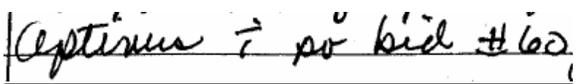
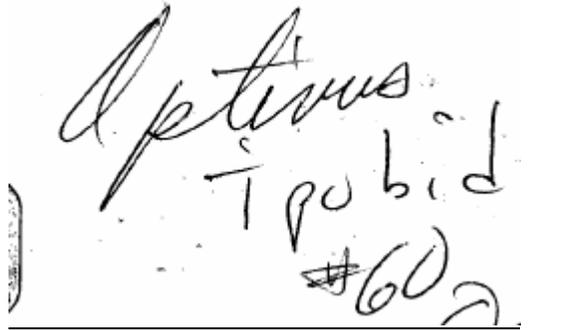
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA did not identify any other names which were considered to have significant orthographic similarities to Aptivus.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Aptivus with currently marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Aptivus (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one inpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p data-bbox="297 1186 475 1213"><u>Inpatient RX#1:</u></p> 	<p data-bbox="898 1262 995 1289">Aptivus</p>
<p data-bbox="297 1327 467 1354"><u>Outpatient RX:</u></p> 	<p data-bbox="898 1337 1125 1365">Take one PO BID</p> <p data-bbox="898 1413 946 1440">#60</p>

2. Results:

One of the respondents in the verbal study interpreted the proposed name as Aptiva, which sounds similar to the currently marketed U.S. product, Raptiva. See Appendix A for the complete listing of interpretations from the verbal and written studies.

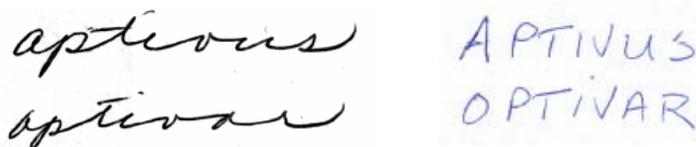
D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Aptivus, the primary concerns related to look-alike and sound-alike confusion with Optivar, Optivite, Optison, Antabuse, Capoten, Ultiva, Raptiva, and

(b) (4)

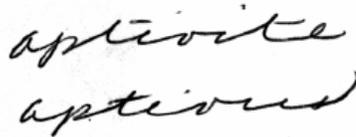
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. One respondent from the verbal study misinterpreted the proposed name as Aptiva which sounds similar to the name Raptiva. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Aptivus.

1. Optivar may look and sound similar to Aptivus when written or spoken. Optivar is a prescription ophthalmic antihistamine used for the treatment of allergic conjunctivitis. The orthographic similarities stem from the fact that both names begin and end with letters that may look similar when scripted (O vs. A and ar vs. us). The similarity in appearance of the first letter of each name (O vs. A) is most likely to occur when the name is written in cursive handwriting as opposed to a printed presentation using block letters (see below). Sixteen of the participants in the written prescription study misinterpreted the spelling of the study name as a drug name beginning with the letter 'O'. Both names also contain the same four letters in the same placement (ptiv) which may look similar in either cursive or block letters. Although the beginnings of each name sound similar (apti vs. opti), the endings (var vs. vus) are phonetically different. Although both products are dosed twice daily, there are some product characteristics that may help to differentiate them, such as dose (500 mg, 2 capsules, 5 mL, or 1 tsp. vs. one drop), dosage forms (capsules and oral solution vs. ophthalmic drops), strength (250 mg and 100 mg/mL vs. 0.05%), route of administration (oral vs. ophthalmic), indication of use (HIV vs. allergic conjunctivitis), and storage location (oral solids and oral solutions vs. ophthalmic products). Although there are similarities between the orthographic presentations of the two names, the accompanying information will help to differentiate the correct drug ordered (500 mg BID, 2 capsules BID, or 5 mL BID, vs. one drop BID). Additionally, the dosage form for an inpatient order for Aptivus will need to be identified (capsules or oral solution). Moreover, because Aptivus is supplied in more than one dosage form, the dosing amount for each form is very specific (2 capsules or 5 mL). An order for Optivar would most likely include information such as '1 drop' or 'as directed', both of which would be inappropriate for an order for either dosage form of Aptivus. Even if a prescription written for Aptivus 2 BID is misinterpreted as Optivar 2 (gtts) BID, the quantity to be dispensed will help to differentiate it. Although Aptivus is packaged in a unit-of-use container, orders are likely to say '#120' or 'XX month' or 'XX days supply.' Prescribers may not be aware that this is a unit-of-use container and will generally order the amount required to last the patient 30 days. In contrast, if Optivar 2 BID is misinterpreted as Aptivus 2 BID where #1 is interpreted to represent a bottle of Aptivus, the dose would help to differentiate the product. A dose of #2 for the oral solution would be incorrect because the dose is 1 tsp or 5 mL. Additionally, since Aptivus is supplied in two dosage forms, the identification of the dosage form would help to identify the correct product. Thus, confusion will be mitigated by the differentiating dose and dosage forms.

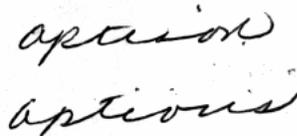


The image shows a handwritten comparison of the names 'Aptivus' and 'Optivar'. On the left, 'aptivus' is written in cursive, and 'optivar' is written in a similar cursive style. On the right, 'APTIVUS' is written in blue block letters, and 'OPTIVAR' is written in blue block letters below it. This visual comparison highlights the orthographic similarities between the two names, particularly in the first letter and the ending letters.

2. Optivite may look and sound similar to Aptivus when written or spoken. Optivite is an over-the-counter vitamin used as a nutritional supplement. The similar spelling and beginnings of each name (O vs. A and ptiv) contribute to the look-alike and sound-alike similarities of the names. Sixteen of the participants in the written prescription study misinterpreted the spelling of the study name as a drug name beginning with the letter ‘O’. However, the upstroke and crossbar required for the second ‘t’ in Optivite may help to distinguish the name when written (see below). The endings of each name are also phonetically different. There are differentiating product characteristics such as dose (500 mg , 2 capsules, or 5 mL vs. one tablet), strength (250 mg and 100 mg/mL vs. no strength), frequency of administration (twice daily vs. once daily), and indication of use (HIV infection vs. nutritional supplement). Although both products are supplied as oral solids (capsules vs. tablets), Aptivus is also supplied as an oral solution. Therefore, an order for oral solution will include the number of mL or teaspoons to be administered, which will help to distinguish the correct product ordered. Additionally, an order for Aptivus capsules would need to include the number of capsules to be administered ‘take two capsules twice daily’. An Aptivus BID prescription is unlikely to be confused as Optivite BID, because this is an uncommon frequency of administration for this nutritional supplement. The orthographic and phonetic differences along with the differentiating product characteristics will help to minimize confusion involving this name pair.



3. Optison may look and sound similar to Aptivus when scripted or spoken. Optison is used as a radiological cardiac imaging agent. The look-alike similarities stem from the fact that both names contain letters that look similar when scripted (O vs. A, pti, and son vs. vus) (see below). Sixteen of the participants in the written prescription study misinterpreted the spelling of the study name as a drug name beginning with the letter ‘O’. The similar letters at the beginning of each name contribute to the phonetic similarities, however, the endings are phonetically different. Despite some similarities in the product name, there are differentiating product characteristics such as dose (500 mg vs. 1 mL to 8.7 mL), dosage form (capsule and oral solution vs. injection), strength (250 mg and 100 mg/mL vs. 5 to 8×10^8 human albumin microspheres, 10 mg albumin human, 0.22 ± 0.11 mg/mL octafluoropropane in 0.9% aqueous sodium chloride), frequency (twice daily vs. once), route of administration (oral vs. intravenous), indication of use (HIV vs. cardiac imaging), and storage location (oral solids and oral liquids vs. injectable contrast agents). Although a 5 mL dose of Optison could be potentially confused as Aptivus 5 mL Oral Solution, the dosing intervals would help differentiate the products. The product differences will help to differentiate this name pair and minimize confusion.



4. Antabuse may sound similar to Aptivus when spoken. Antabuse is indicated as an alcohol deterrent. The endings of each name may be pronounced with a long 'u', and as a result may sound similar (buse vs. vus). However, the beginnings of each name (apti and anta) are phonetically different. Although both drugs are supplied in the same strength (250 mg), Aptivus is also supplied as an oral solution containing 100 mg/mL of tipranavir. Thus, an order for Aptivus will most likely include further information such as 'take two capsules twice daily or 5 mL twice daily', whereas an order for Antabuse would have a specific dose because it's dose ranges from 125 mg to 500 mg and is dosed on a once daily basis. The dose may overlap at 500 mg, however, the frequency of administration is different (once daily vs. twice daily). Although the frequency of administration is not a significant differentiating product characteristic, an Aptivus BID prescription is less likely to be confused as Antabuse BID, because this is an uncommon frequency of administration for Antabuse. Additionally, the maximum dosage of Antabuse is 500 mg. Therefore, a BID Aptivus order misinterpreted as 500 mg Antabuse BID would result in an Antabuse overdose. Therefore, the phonetic differences between the beginnings of each name and product differences (dose and frequency) will help to differentiate the two products and help to minimize confusion.
5. Capoten may look similar to Aptivus when scripted. Capoten is indicated in the treatment of heart failure and hypertension. Both names contain letters that look similar when scripted (Apt and Capot) (see below). However, the endings of each name are orthographically different (ivus vs. oten). Although there are some similar product characteristics such as frequency of administration (twice daily), and route of administration (oral), there are product characteristics that will help to differentiate the two when ordered. They include the dose (500 mg vs. 6.25 mg to 450 mg per day), dosage form (capsule and oral solution vs. tablet), and strength (250 mg and 100 mg/mL vs. 12.5 mg, 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg, and 150 mg). An order for Aptivus 500 mg BID misinterpreted as Capoten 500 mg BID would result in a daily dose that is two times the recommended maximum daily dose. This would serve as a potential warning that the prescriber should be contacted for clarification. The orthographic differences and the product characteristics will help to differentiate between these two products and minimize error.



A handwritten comparison of the words 'Capoten' and 'Aptivus'. The letters 'Apt' in 'Aptivus' and 'Capot' in 'Capoten' are written in a similar cursive style, making them look alike when scripted. The words are written side-by-side, with 'Capoten' on the left and 'Aptivus' on the right.

6. Ultiva may look similar to Aptivus when scripted. Ultiva is indicated as an adjunct to anesthesia. Both names contain letters that may look similar when scripted (apti vs. ulti) (see below) which contribute to the look-alike similarities of the name pair. Despite this similarity, there are differentiating product characteristics, such as dose (500 mg vs. 0.025 mcg/kg/min to 4 mcg/kg/min), dosage form (capsule and oral solution vs. injection), strength (250 mg and 100 mg/mL vs. 1 mg, 2 mg, and 5 mg), frequency of administration (twice daily vs. continuously), route of administration (oral vs. intravenous), indication of use (HIV vs. adjunct to anesthesia), and storage location (oral solids vs. injectable narcotics). Although, there are orthographic similarities, the product characteristics will help to minimize confusion.



A handwritten comparison of the words 'Ultiva' and 'Aptivus'. The letters 'Apti' in 'Aptivus' and 'Ulti' in 'Ultiva' are written in a similar cursive style, making them look alike when scripted. The words are written side-by-side, with 'Ultiva' on the left and 'Aptivus' on the right.

7. One respondent from the verbal prescription study interpreted the proposed name as Aptiva, which sounds similar to Raptiva. Thus, we will evaluate the sound-alike similarity to Aptivus. Raptiva is indicated in the treatment of psoriasis. Both names contain five of the same letters (aptiv) which contributes to the sound-alike similarities of this name pair. The last 'a' in Raptiva may sound similar to 'us' particularly if a short 'u' is utilized such as in 'bus' and the letter 's' is not clearly enunciated. Despite the phonetic similarities, there are differentiating product characteristics, such as dose (500 mg vs. 0.7 mg/kg to 1 mg/kg up to a maximum dose of 200 mg), dosage form (capsule and oral solution vs. injection), strength (250 mg and 100 mg/mL vs. 125 mg), frequency of administration (twice daily vs. once and weekly), route of administration (oral vs. subcutaneous), indication of use (HIV vs. psoriasis), and storage location (oral solids and oral liquids vs. injection) that will help to minimize confusion involving Raptiva and Aptivus.

8.



(b) (4)

Aptivus
Aptivus



(b) (4)

E. INDEPENDENT NAME ANALYSIS (b) (4)

On the 27th of February, 2002, Boehringer Ingelheim commissioned (b) (4) the marketing research subsidiary of (b) (4), to conduct a name validation study using its proprietary (b) (4) for tipranavir, a new non-peptidic protease inhibitor. Although the scope of the tipranavir name validation study was global, for the purpose of this report, the specific findings and conclusions will be limited to the candidate 'Aptivus' and the U.S. market. The assessment, dated August 10, 2004 is based on the dispensing-specific data of the (b) (4)

NOTE: This review contains proprietary and confidential information that should not be released to the public.

The study included 100 primary research respondents of which included 50 U.S. physicians, comprising of HIV specialists (40), and Primary Care physicians (10), and 50 U.S. pharmacists comprising of hospital pharmacists (25) and retail pharmacists (25).

1. (b) (4) Verbal Assessment – U. S. Pharmacists

25 Hospital-based pharmacists and 25 Retail-based pharmacists were asked to rate the ability (*unaided*) of the candidate to be communicated clearly when spoken as well as when written, to identify (*unaided*) first their immediate associations then specific pharmaceutical associations with existing pharmaceutical brand (trade/invented) as well as generic names. Respondents were finally asked to provide an overall assessment (*aided by product description/context*) of the candidate as a pharmaceutical brand name, potentially including a determination as unsuitable due to the risk of mis-prescription with presently marketed brand names, to rate their level of personal consideration, and vote for their most preferred/least preferred candidates. There were no exact matches to currently marketed U.S. drug products

DMETS Response:

Although (b) (4) included pharmacists in the verbal interpretations, nurses were not included as participants in this study. Quite often, nurses are called upon to receive and interpret verbal orders. This leaves open the possibility of additional information concerning the interpretation of the pronunciation of the proposed name being omitted in the evaluation process. DMETS notes that several respondents provided spelling variations that begin with the letter ‘O’. These include Octivus, Optavos, Optivious, Optivos, and Optivus. DMETS notes that these responses confirm the possibility that the candidate drug name may be mispronounced and subsequently misinterpreted using the vowel “O” rather than ‘A’. Additionally, after a verbal order were transcribed, it may be written as a name beginning with the letter ‘O’. However, despite this finding DMETS agrees with (b) (4) in that this name does not pose a significant safety risk.

2. (b) (4) Written Assessment – U. S. Pharmacists

25 Hospital-based pharmacists and 25 Retail-based pharmacists were asked to identify [spell] (*unaided*) the candidate when written by a prescriber using a representative set of sample written orders communicated by fax. Due to the wide variations present in prescriber handwriting, a sampling of four written orders was provided. The representative set of sample written orders provide a reasonable facsimile of what a dispenser is likely to encounter during the first week of availability post-launch. There were no exact spelling matches with the candidate name.

DMETS Response:

DMETS acknowledges the results and agree that the none of the misspelling variations identified in this study are orthographically or phonetically similar to currently marketed drug products.

3. (b) (4) Verbal Assessment – U. S. Physicians

The following research findings were identified related to the interpretation of a simulated verbal order using 50 physicians in the U.S., comprising of 40 HIV specialists and 10 Primary Care physicians. As noted by the listing of spelling variations, there were no citations for presently marketed brand or generic names as well as known investigational drugs.

DMETS Response:

DMETS acknowledges the results and agree that the none of the misspelling variations identified in this study are orthographically or phonetically similar to currently marketed drug products.

4. Error Index Dispensing Assessment –Aptivus

Potential conflicts identified during the fieldwork are included for further assessment and a side-by-side comparison of dispensing factors is conducted with the anticipated dispensing profile for tipranavir. No citations were derived from the Error Index Verbal Assessment or Error Index Visual Assessment.

DMETS Response:

(b) (4) refers to the “unaided immediate associations assessment” and to the ‘aided overall assessment’. However, these sections (e.g. methodology) are not included in the report. Thus, DMETS did not have the opportunity to evaluate and comment on the summary analysis.

Additionally, (b) (4) listed three citations with error index ratings and respondent type. The three products are Activella, Actifed, and Optivar. Of note is that one respondent who misinterpreted the name as Optivar, an ophthalmic drug, is an HIV specialist. This is interesting since an HIV specialist would be the same type of practitioner who would prescribe Aptivus. However, without the methodology, DMETS is unable to determine how the name Aptivus was misinterpreted as Optivar. In particular, DMETS questions what “aided overall assessment” refers to (e.g. scripted order for Aptivus, information as to the class of drug, indication of use, dosage and administration information, etc.). Without the actual methodology, DMETS is unable to evaluate and comment further.

However, despite this finding, DMETS evaluated Optivar in section II-D above and found the potential for confusion to be minimal. Additionally, after evaluation of the additional two products, Activella and Actifed, DMETS agrees with (b) (4) that due to differentiating product characteristics, they do not pose a significant safety risk.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Aptivus, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. DMETS notes that the draft container label for the capsules was submitted in black and white. However, the container label for the oral solution was submitted in color. It appears that the fonts, graphics, etc of these two samples are similar. Therefore, DMETS will make comments relating to the capsules with the assumption that the color, fonts, graphics, etc. will be the same as the oral solution.
2. The proprietary and established names should be the most prominent information on the primary display panel. In the current presentation, the purple and orange rectangles are most prominent. Increase the font on the proprietary and established names so that they are more prominent than the orange and purple rectangles. We refer you to 21 CFR201.1(a)(1).
3. In the current presentation, the dosage form (oral solution and capsules), strength, and the proprietary name have equal prominence. The proprietary and established names should be the most prominent information on the label. Increase the font size of the proprietary name so that it is more prominent than the dosage form and strength.

B. CONTAINER LABEL Capsules (120 count)

1. See GENERAL COMMENTS A1 through A3.
2. Relocate the net quantity so that it does not appear in close proximity to the strength.
3. Include a usual dose statement such as “Usual dose is 500 mg BID”.
4. Increase the size and prominence of the statement “Must be used within 60 days after first opening”.

C. CONTAINER LABEL Oral Solution (95 mL)

1. See GENERAL COMMENTS A2 and A3 and comments B2 through B4.
2. The oral solution container is labeled as “unit of use container”. The dose of tipranavir is 5 mL twice daily for a total daily dose of 10 mL. The container holds 95 mL. This would be a 9 ½ day supply. Even if three bottles are dispensed, it will not be sufficient for a 30-day supply. DMETS questions why the container only holds 95 mL as this amount is mismatched with the duration of therapy.

D. CARTON LABELING (Oral Solution)

1. See GENERAL COMMENTS A2 and A3, B2, B3, and B4.
2. DMETS notes that the Insert Labeling states that a 5 mL plastic oral dispensing syringe is packaged with the oral solution. However, this device or a picture of it was not provided for review and comment. Ensure that the markings on this syringe are clear and legible. Ensure that the syringe is an oral syringe and that an injection needle will not be able to be attached to it. Additionally, DMETS notes the possibility that the pharmacy label may include directions to ‘take one tsp’ and the syringe is labeled in mL, or vice versa. To prevent dosing errors, we recommend that the plastic oral dispensing syringe also contain clear markings in teaspoons, in addition to mL.

E. INSERT LABELING

1. DOSAGE AND ADMINISTRATION section:

This section states that “Aptivus Capsules, co-administered with low-dose ritonavir, should be administered with food”. However, the patient instructions sheet states “Take Aptivus with food at all times to improve tolerability”. Revise to provide consistency between these two documents.

2. HOW SUPPLIED SECTION:

This section states that ‘ [REDACTED] (b) (4) [REDACTED] The wording is confusing and DMETS questions whether there are two different packaging configuration for this product, one with a child resistant closure and one with 120 capsules. DMETS suggest revising this section to state something similar to “They are packaged in 120-count HDPE unit-of-use bottles that have a child resistant closure”.

F. PATIENT INSTRUCTIONS FOR USE

1. The use of trailing zeros, such as 5.0 mL, has historically been associated with a ten-fold overdose of some medications. Therefore, delete all references to trailing zeros.
2. The statement ‘Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternative contraceptive measures should be used during therapy with Aptivus’ is found in the precautions section of the insert labeling. However, this information is not included in the Patient Instructions for Use. Revise to provide consistency between these two documents.
3. PRECAUTIONS section, Information for Patients subsection:

This section states that ‘*patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time*’. However, the PROPOSED PATIENT’S INSTRUCTIONS FOR USE state: [REDACTED] (b) (4) [REDACTED]

Revise to provide consistent wording between these two documents. Additionally, this wording seems complex and difficult to follow. DMETS recommends that the Division of Surveillance, Research, and Communication Support be consulted for review and comment.

III. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Aptivus. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DMETS suggests submitting the Proposed Patient's Instructions to the Division of Surveillance, Research, and Communication Support for review and comment.
4. DDMAC finds the proprietary name Aptivus acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

Verbal	Written Inpatient	Written Outpatient
Activist	Aptimus	Aptivus
Activis	Aptimus	Aptivus
Activis	Aptimus	Optivus
Activis	Aptinus	Optivus
Activis	Aptinus	Optivus
Activis	Aptinus	Optivus
Activist	Aptinus	Optivus
Activos	Aptinus	Optivus
Activus	Aptinus	Optivus
Activus	Aptisucs	Optivus
Activus	Aptisurs	Optivus
Activus	Aptivus	Optivus
Aptiva	Ceptirius	Optivus
	Optimis	Optivus
	Optimus	Optivus
	Optinus	

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this page is the manifestation of the electronic signature.**

/s/

Linda Wisniewski
4/19/05 08:04:22 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/19/05 12:36:06 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, R.Ph., Director of DMETS