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APPLICATION NUMBER:
21-822

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY DRAFT REVIEW
NDA: 21814 and 21822 SN: 000 DATE REVIEWED: 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

NDA#: 21814 (capsules) and 21822 (solution)
Reviewer's Name(s): Lisa K. Naeger, Ph.D.

Serial #: 000

Sponsor's Name and Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
Ridgefield, CT 06877

Initial Submission Dates:

Correspondence Date: 12/21/2004
CDER Receipt Date: 12/22/2004
Assigned Date: 10/19/2004
Review Complete Date: 6/15/2005
PDUFA Date: 6/22/2005

Amendments:

Related/Supporting Documents: IND51979

Product Name(s)

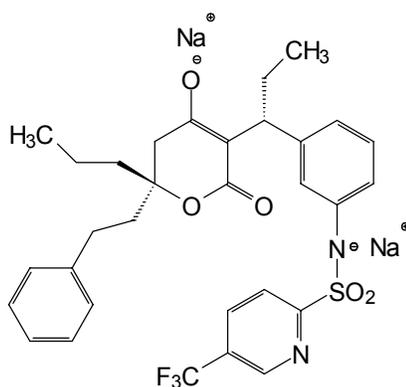
Proprietary: Aptivus
Non-Proprietary/USAN: tipranavir (TPV)
Code Name/Number: PNU-140690

Empirical formula: C₃₁H₃₁F₃N₂O₅SNa₂

Chemical Name: [R-R(*,R*)]-N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide disodium salt

Molecular mass: 646.63

Structural Formula:



TIPRANAVIR

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Drug category: antiviral

Dosage Form(s): 250-mg soft elastic capsules/Oral; co-administration of ritonavir as 100-mg soft gelatin capsules; 500 TPV/200 RTV mg BID

Route(s) of Administration: Oral

Indication(s): Combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Dispensed: Rx X OTC

Abbreviations: ABC, abacavir; APV, amprenavir; ATV, atazanavir; AZT, zidovudine; CPI, comparator protease inhibitor; ddi, didanosine; d4T, stavudine; DLV, delavirdine; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus-1; IC, inhibitory concentration; IDV, indinavir; LOCF, last observation carried forward; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; /r, ritonavir boosted; RT, reverse transcriptase; SQV, saquinavir; T20, enfuvirtide; TNF, tenofovir; TPV, tipranavir; 3TC, lamivudine;

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Executive Summary

Tipranavir (TPV), an HIV-1 protease inhibitor, has 50% inhibitory concentrations (IC₅₀ value) ranging from (b) (4) nM against laboratory HIV-1 strains grown in vitro in PBMCs and cell lines. The average IC₅₀ value for multi PI-resistant clinical HIV-1 isolates was 240 nM (range (b) (4) to (b) (4) nM). Human plasma binding resulted in a 4-fold decrease in the antiviral activity. Ninety percent (94/105) of HIV-1 isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, or SQV had ≤3-fold decreased susceptibility to TPV.

Because TPV will be administered to HIV-positive patients as part of a HAART regimen comprising several antiretroviral agents, the activity of TPV in combination with other antiviral drugs was determined in cell culture to assess the impact of potential in vitro drug interactions on overall antiviral activity. Additive to antagonistic relationships were seen with combinations of TPV with other PIs. Combinations of TPV with the NRTIs were generally additive, but additive to antagonistic for TPV in combination with ddI and 3TC. Combinations of TPV with the NNRTIs DLV and NVP were additive and with EFV were additive to antagonistic. Activity of TPV with the fusion inhibitor enfuvirtide (T20) was synergistic.

In Vitro Selection of TPV-Resistant Viruses

TPV-resistant viruses were selected in vitro when wild-type HIV-1_{NL4-3} was serially passaged in the presence of increasing concentrations of TPV in tissue culture. Amino acid substitutions L33F and I84V emerged initially at passage 16 (0.8 μM), producing a 1.7-fold decrease in TPV susceptibility. Viruses with >10-fold decreased TPV susceptibility were selected at drug concentrations of 5 μM with the accumulation of six protease mutations (I13V, V32I, L33F, K45I, V82L, I84V). After 70 serial passages (9 months), HIV-1 variants with 70-fold decreased susceptibility to TPV were selected and had 10 mutations arising in this order: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V. Mutations in the CA/P2 protease cleavage site and transframe region were also detected by passage 39. TPV-resistant viruses showed decreased susceptibility to all currently available protease inhibitors except SQV. SQV had a 2.5-fold reduced susceptibility to the TPV-resistant virus with 10 protease mutations.

Clinical TPV Resistance

The efficacy of ritonavir boosted tipranavir (TPV/r) was examined in treatment-experienced HIV-infected subjects in two pivotal phase III trials, study 012 (RESIST 1) and study 048 (RESIST 2). Genotypes from 1482 isolates and 454 phenotypes from both studies were submitted for review. In the comparator PI arm (CPI/r), most patients received LPV/r (n=358) followed by APV/r (n=194), SQV/r (n=162) and IDV/r (n=23). The patient populations in RESIST 1 and 2 were highly treatment-experienced with a median number of 4 (range 1-7) PIs received prior to study. In the combined RESIST trials 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 treatment arms from both studies were balanced with respect to baseline

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genotypic and phenotypic resistance. Baseline phenotypic resistance was equivalent between the TPV/r arm (n=745) and the CPI/r arm (n=737) with 30% of the isolates resistant to TPV at baseline and 80-90% of the isolates resistant to the other PIs - APV, ATV, IDV, LPV, NFV, RTV or SQV. The number of PI-resistance mutations was equivalent between the TPV/r and CPI/r arms in RESIST 1 and 2 and the median number of baseline PI, NRTI and NNRTI mutations was equivalent between arms in both studies.

Mutations Developing on TPV Treatment

TPV/r-resistant isolates were analyzed from treatment-experienced patients in the phase II study 052 (n=32) and the phase III studies RESIST 1 and 2 (n=59) who experienced virologic failure. The most common mutations that developed in greater than 20% of these TPV/r virologic failure isolates were L33V/I/F, V82T and I84V. Other mutations that developed in 10 to 20% of the TPV/r virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L and L89V/M/W. In RESIST 1 and 2, TPV/r resistance developed in the virologic failures (n=59) at an average of 38 weeks with a median decrease of >14-fold in TPV susceptibility from baseline. The resistance profile in treatment-naïve subjects has not been characterized.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

The FDA analyses of virologic outcome by baseline resistance are based on the As-Treated population from studies RESIST 1 and 2. To assess outcome, several endpoints including the primary endpoint (proportion of responders with confirmed 1 log₁₀ decrease at Week 24), DAVG24, and median change from baseline at weeks 2, 4, 8, 16, and 24 were evaluated. In addition, because subjects were stratified based on enfuvirtide (T20) use, we examined virologic outcomes in three separate groups - overall (All), subjects not receiving T20 (No T20), and subjects receiving T20 (+T20) as part of the optimized background regimen. We focused on the No T20 group in order to assess baseline resistance predictors of virologic success and failure for TPV/r without the additive effect of T20 use on the overall response.

Both the number and type of baseline PI mutations affected response rates in RESIST 1 and 2. Virologic responses were analyzed by the presence at baseline of substitutions at each of 25 different protease amino acid positions using both the primary endpoint (>1log₁₀ decrease from baseline) and DAVG24. Reduced virologic responses were seen in TPV/r-treated subjects when isolates had a baseline amino acid substitution at position I13, V32, M36, I47, Q58, D60 or I84. The reduction in virologic responses for these baseline substitutions was most prominent in the No T20 subgroup. Virologic responses were similar or greater than the overall responses for each subgroup (All, No T20, +T20) when these amino acid positions were wild-type. In addition, virologic responses to substitutions at position V82 varied depending on the amino acid substitution. Interestingly, substitutions V82S or F or I or L, but not V82A or T or C, had reduced virologic responses compared to the overall response.

Analyses were also conducted to assess virologic outcome by the number of PI mutations present at baseline. In these analyses, any changes at protease amino acid positions -

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D30, V32, M36, M46, I47, G48, I50, I54, F53, V82, I84, N88 and L90 were counted if present at baseline. These PI mutations were used based on their association with reduced susceptibility to currently approved PIs, as reported in various publications.

Regardless of the endpoint used for these analyses, the response rates were greater for the TPV/r treatment arm compared to the CPI/r arm. Within each treatment arm, response rates were similar to or greater than the overall response rates for subjects with one to four PI mutations at baseline. Response rates were reduced if five or more PI-associated mutations were present at baseline. For subjects who did not use T20, 28% in the TPV/r arm and 11% in the CPI/r arm had a confirmed 1 log₁₀ decrease at Week 24 if they had five or more PI mutations in their HIV at baseline. The subjects with five or more PI mutations in their HIV at baseline and not receiving T20 in their OBT achieved a 0.86 log₁₀ median DAVG24 decrease in viral load on TPV/r treatment compared to a 0.23 log₁₀ median DAVG24 decrease in viral load on CPI/r treatment. In general, regardless of the number of baseline PI mutations or T20 use, the TPV/r arm had approximately 20% more responders by the primary endpoint (confirmed 1 log₁₀ decrease at Week 24) and greater declines in viral load by median DAVG24 than the CPI/r arm.

An examination of the median change from baseline of HIV RNA at weeks 2, 4, 8, 16 and 24 by number of baseline PI mutations (1-4 and 5+) showed the largest decline in viral load by Week 2 for all groups with the greatest decline observed in the TPV/r arms. A 1.5 log₁₀ decrease in viral load at Week 2 was observed for subjects receiving TPV/r regardless of the number of baseline PI mutations (1-4 or 5+). Sustained viral load decreases (1.5 – 2 log₁₀) through Week 24 were observed in subjects receiving TPV/r and T20. However, subjects who received TPV/r without T20 and who had five or more baseline PI mutations group began to lose antiviral response between Weeks 4 and 8.

Proportion of Responders by Baseline TPV Phenotype

TPV/r response rates were also assessed by baseline TPV phenotype. Again, we focused on the No T20 group in order to more accurately assess the effect of baseline phenotype on virologic success for TPV/r. With no T20 use, the proportion of responders was 45% if the shift in IC₅₀ value from reference of TPV susceptibility was 3-fold or less at baseline. The proportion of responders decreased to 21% when the TPV baseline phenotype values were >3- to 10-fold and 0% when TPV baseline phenotype values were >10-fold.

Conclusions

TPV is a novel protease inhibitor with antiviral activity against multi PI-resistant clinical HIV-1 isolates. The most common protease amino acid substitutions that developed in >20% of isolates from treatment-experienced subjects who failed on TPV/r treatment were L10I/V/S, I13V, L33V/I/F, M36V/I/L V82T, V82L, and I84V. The resistance profile in treatment-naïve subjects has not been characterized. Both the number and type of baseline PI mutations affected response rates to TPV/r in RESIST 1 and 2. Virologic response rates in TPV/r-treated subjects were reduced when isolates with substitutions at

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amino acid positions I13, V32, M36, I47, Q58, D60 or I84 and substitutions V82S/F/I/L were present at baseline. Virologic responses to TPV/r at week 24 decreased when the number of baseline PI mutations was 5 or more. Subjects taking enfuvirtide with TPV/r were able to achieve $>1.5 \log_{10}$ reductions in viral load from baseline out to 24 weeks even if they had 5 or more baseline PI mutations. Virologic responses to TPV/r in RESIST 1 and 2 decreased when the baseline phenotype for TPV was a >3 shift in susceptibility with respect to wild-type reference virus.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability

This NDA for is approvable with respect to microbiology for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

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

Protocol Submission: Completed

Final report Submission: September 30, 2006

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

2. Summary of OND Microbiology Assessments

2.1. Brief Overview of the Microbiological Program

2.1.1. Non-clinical

Tipranavir (TPV), a HIV-1 protease inhibitor, has 50% inhibitory concentrations (IC_{50} value) ranging from (b) (4) nM against laboratory HIV-1 strains grown in vitro in PBMCs and cell lines. The average IC_{50} value for multi PI-resistant clinical HIV-1 isolates was 240 nM (range (b) (4) to (b) (4) nM). Human plasma binding resulted in a 1.6- to 4-fold shift in the antiviral activity. Ninety percent (94/105) of HIV-1 isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, or SQV had ≤ 3 -fold decreased susceptibility to TPV.

Because TPV will be administered to HIV-positive patients as part of a HAART regimen comprising several antiretroviral agents, the activity of TPV in

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2.1.2. Clinical Microbiology

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3. Administrative

3.1. Reviewer's Signature(s)

Lisa K. Naeger, Ph.D.
Sr. Microbiologist, HFD-530

3.2. Concurrence

HFD-530/Signatory Authority _____ Signature _____ Date _____
HFD-530/Micro TL _____ Signature _____ Date _____

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

/s/

Lisa Naeger
6/22/05 10:13:31 AM
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Julian O Rear
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MICROBIOLOGIST

James Farrelly
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