DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA: 21-814 **SN**: SE1 005 **DATE REVIEWED:** 03/17/2008
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

Reviewer's Name: Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:
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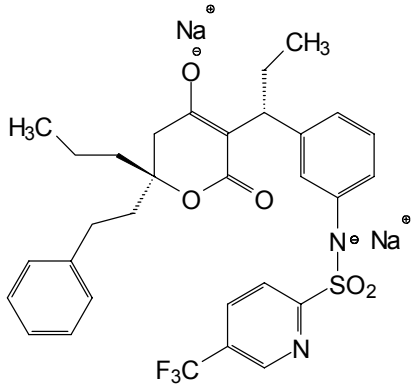
Related/Supporting Documents: IND 51,979 and NDA 21-814

Product Name(s):
Proprietary: Aptivus™
Non-Proprietary/USAN: Tipranavir (TPV)
Code Name/Number: PNU-140690

Empirical formula: $C_{31}H_{31}F_3N_2O_5SNa_2$
Chemical Name: [R-R(*,R*)]-N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-y1]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide disodium salt
Molecular mass: 646.63

Structural Formula:



TIPRANAVIR

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

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Indication(s): Combination antiretroviral treatment of HIV-1 infected adult subjects 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; ddI, didanosine; d4T, stavudine; DLV, delavirdine; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus-1; EC, effective concentration; GSS, genotypic susceptibility score; GIQ, genotypic inhibitory quotient; IAS, International AIDS Society; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PI, protease inhibitor; /r, ritonavir boosted; RT, reverse transcriptase; SQV, saquinavir; ENF, enfuvirtide; TAMs, thymidine analog mutations; TNF, tenofovir; TPV, tipranavir; 3TC, lamivudine;

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EXECUTIVE SUMMARY

This submission is a pediatric supplement to NDA 21-814 for Tipranavir (Aptivus), which received FDA approval June 22, 2005 for combination antiretroviral treatment of HIV-1 infected adult subjects who have evidence of viral replication and who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

The pediatric trial population of 115 children was predominantly ARV treatment-experienced with three children who were treatment-naïve. Patients were randomized to two dose groups of TPV/r, stratified according to age: 25 children were in the 2 to <6 year age group, 37 were 6 to <12 years and 53 were 12 to 18 years old. Major protease gene mutations were present at baseline including: D30N (10%), M46I/L (39%), I47V (10%), V82A (30%), I84V (15%), and L90M (44%). At baseline, 97% of the subjects had at least one International AIDS Society (IAS)-defined PI mutation and 57% of subjects had 6 or more IAS-defined PI mutations. The prevalence of TPV resistance-associated substitutions [L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V] at baseline was high with 51% having 3 or more TPV resistance-associated substitutions and 17% having none of these substitutions. More than half the study populations had 3 or more thymidine analog mutations (TAMs) present at baseline and had resistance mutations associated with lamivudine and tenofovir use. The M184I/V substitution was present in 14 of the 32 (44%) virologic failure subject isolates at baseline and emerged in 10 more subject isolates at failure. The higher proportion of subjects with more baseline PI and NRTI resistance mutations correlated with the high prior PI and NRTI use and a heavily treatment-experienced patient population. The number of PI and NRTI mutations was generally comparable between the high and low TPV doses.

Virologic response at Week 48 was evaluated according to genotype. Overall, 42% of children achieved a viral load of <400 copies/mL, but this response varied with age. The youngest age group of 2 to <6 year olds achieved the highest proportion of responders with 68% <400 copies/mL, as compared to 42% and 29% achieving this level in the 6 to <12 year and 12 to 18 year age groups, respectively.

Virologic response decreased with increasing baseline mutation scores. The proportion of children with 3 or more TPV-associated resistance mutations achieving <400 HIV RNA copies/mL at Week 48 was 32% compared to 52% of children with ≤2 TPV mutations. The high dose of TPV showed better virologic response with 46% of children treated with the high dose achieving viral load <400 copies/mL as compared with 38% of children treated with the low dose. Subjects with a higher number of baseline TPV resistance-associated substitutions (>5) also had better response rates if they were in the high TPV dose arm compared to the low TPV dose arm. Subjects with 5 or more TPV resistance-associated substitutions at baseline had response rates of 42% (5/12) in the high dose arm compared to 7% (1/15) in the low dose arm. Additionally, the GIQ analysis which takes into account both the trough TPV plasma concentrations and the number of TPV score mutations showed an increased rate of response with increased GIQ levels with the low dose pf TPV. Subjects in the high TPV dose group and in the

top 3 quartiles of GIQ score (>6) had response rates ≥50%, whereas the response rate was 0% for those in the bottom quartile.

Overall, response rates were lower for subjects with genotypic susceptibility score (GSS) of 0.00. In all GSS groups, a greater proportion of subjects in the youngest age group achieved <400 HIV RNA copies/mL at 48 weeks than did those in the two older age groups. Although the small numbers of subjects limit the conclusions that can be drawn, the 12 to 18 yr olds with GSS >0.25 had a better virologic response in the high TPV dose than those in the low TPV dose.

From the total study population of 115 children, there were 32 virologic failures whose isolates were analyzed genotypically and phenotypically for the emergence of resistance mutations. The most common substitutions emerged in TPV/r treated children at codon 82. Substitutions L10F/V, L33F/I/V, M36I/V/L and I84V emerged in >10% of the virologic rebounds pediatric subjects. Each of these positions has previously been reported among PI drug-experienced adults treated with TPV/r. The development of I54V in 8% of the pediatric virologic failure isolates and the associated decrease in TPV susceptibility confirms earlier findings in the original NDA review of TPV in adults. Therefore, the I54V mutations should be included in the list of mutations developing on TPV treatment in the product insert for TPV. The previously reported emergence of the V82L mutation in patients with baseline WT virus and the shift from pre-existing V82A to T was also observed in pediatric patients.

The accumulation of protease gene mutations on-treatment correlated with decreased TPV susceptibility. TPV resistance (>3-fold change in susceptibility from reference) developed on treatment in 66% (21 of the 32) virologic failure isolates with a median 22 fold-change in EC_{50} value (range 10 – 55). For the virologic failures with resistance to TPV at failure, 76% isolates were still susceptible to darunavir (<6-fold change).

Children with greater baseline viral resistance had better 48-week virologic response rates with the high dose of TPV than with the low dose. The differences in virologic efficacy seen between 2 to <6 year olds versus the older age groups was most likely driven by baseline viral resistance. Older subjects age 6 to 18 years old in the high TPV dose groups with higher baseline viral resistance had better response rates than those in the low TPV dose group.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability

This NDA for TPV is approvable with respect to microbiology for combination antiretroviral treatment of HIV-1 infected adult and pediatric 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.

There are clinical microbiology recommendations or phase 4 commitments for this submission.

2. Summary of Clinical Microbiology Assessments

Study 1182.14 is an open-label, randomized study, in which children and adolescents were stratified according to age (2 - <6 years, 6 - <12 years, and 12 - 18 years) and randomized to one of two doses of tipranavir/ritonavir (TPV/r), with background antiretroviral (ARV) therapy chosen by their investigator according to baseline genotype results and prior ARV use history. Subjects were treated for up to 48 weeks and the trial is ongoing.

Overall, 115 subjects were entered into the study and were grouped into the following age groups: 25 (22%) subjects were 2 to <6 years old, 37 (32%) were 6 to <12 years old, and 53 (46%) were 12 to 18 years old (Table 1). The evaluation of resistance emergence is based on a subset of 32 subjects in the trial with virologic failure at Week 48, defined as never achieving a viral load <1,000 copies/mL, virologic rebound, as having an initial virologic response of viral load <400 copies/mL followed by loss of virologic suppression to an HIV RNA level above 1,000 copies/mL or discontinued before virologic suppression. An additional 3 subjects rebounded after Week 48. The age stratification of the 32 virologic failure subjects showed that the majority of virologic failures were in the older >12 age group (Table 1).

Table 1. Study 1182.14 Subject Summary

	Number of Subjects in Each Age Group (%)			
Population	**2 to <6**	**6 to <12**	**12 to ≤18**	**Total**
Baseline	25 (22%)	37 (32%)	53 (46%)	115 (100%)
Virologic Failures	3 (9%)	6 (19%)	23 (72%)	32 (100%)

All subjects in the study had baseline genotypic resistance results conducted as part of screening using the TruGene® assay conducted by Covance Central Laboratory Services, Inc., in Indianapolis, IN. The subset of subjects with virologic failure had on-treatment genotyping using the TruGene assay and both baseline and on-treatment phenotypic resistance testing using the VIRCO Antivirogram® assay.

BASELINE ANALYSIS

The majority of subjects in Study 1182.14 were treatment-experienced. There were three treatment-naïve subjects included in the study (2.6%; 3 of 115); one subject in each age group (#1081 [age group 12 to 18], 5422 [age group 6 to <12], 5413 [age group 2 to <6]). All of the treatment-naïve subjects had viral isolates with IAS-defined protease mutations. In the Rebound subgroup, only one subject (#1081) was treatment-naïve.

Subjects in the overall study group previously used a median of 5 NRTIs, 1 NNRTI, and 2 PIs. The most common previously used NRTIs were lamivudine (88.7%), didanosine and stavudine (each 77.4%) and the most commonly used PIs were nelfinavir (61.7%), treatment-dose ritonavir (48.7%), and lopinavir (41.7%). Low-dose ritonavir boosting

was also reported frequently used (50.4%). NNRTI use history included predominantly nevirapine (50.4%) and efavirenz (47.8%). Eight subjects (7%), in the two older age groups, had previously used enfuvirtide. Increasing use of ARVs was seen with increasing age.

Concomitant background ARV treatment during the study predominantly consisted of lamivudine (61.7%), abacavir (35.7%), and didanosine (33.0%), with equal use across age groups. Seventeen percent used efavirenz and 13% of subjects used enfuvirtide as part of the background regimen, all in the two older age groups.

Baseline Genotype

At baseline, 97% of the subjects had at least one IAS-defined PI resistance-associated mutation (any protease gene mutations at codons 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 63, 71, 73, 77, 82, 84, 88, and 90). Only 3 (2.6% of 115 subjects) subjects [1103, 3411, and 5214] had no IAS-defined protease gene mutations at baseline whereas 57% of subjects had 6 or more IAS-defined mutations. None of the subject viral isolates without any IAS-defined mutations were treatment-naïve. The prevalence of TPV resistance-associated substitutions [L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V] at baseline was high with 59 subjects (51%) having 3 or more TPV resistance-associated substitutions whereas 19 subjects (16.5%) had none of these substitutions. Nearly half the study population (49.6%; n=57) had lamivudine and/or tenofovir mutations (insertion at 69, K65R, M184I/V, or Q151M) and 60.0% (n=69) of the study population had 3 or more TAMs (41L, 67N/G, 70R, 210W, 215F/Y, 219Q). The higher proportion of subjects with more baseline PI and NRTI resistance-associated mutations correlated with the high prior PI and NRTI use and a heavily treatment-experienced patient population. The number of PI and NRTI mutations was generally comparable between the high and low TPV doses (Table 2 and Appendix A).

The prevalence of baseline mutations increased with increasing age, consistent with more treatment experience of the older children. As shown in Figure 1, age group C (12 to 18 year olds) had the higher percentage of ≥3 TPV RAMs, ≥6 IAS PI mutations, ≥6 NRTIs, and ≥3 TAMS with the less than six year olds having the lowest proportion of these mutation subgroups.

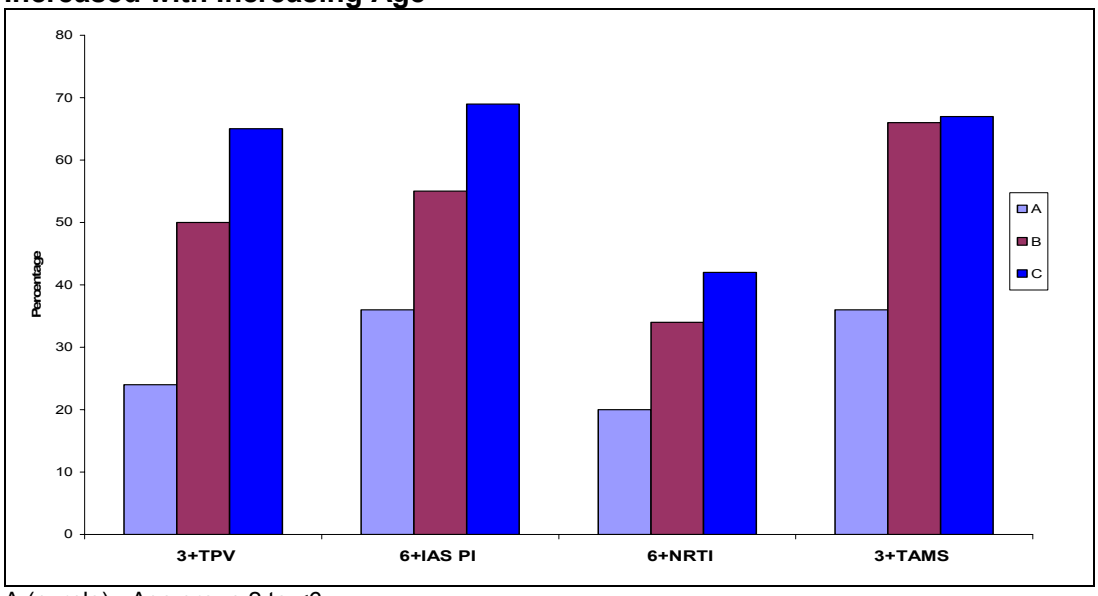
Table 2. Number of Baseline Resistance-Associated Mutations by TPV Dose

TPV Dose	**High (n=57)**	**Low (n=58)**
TPV Score…median	2	3
0	12 (21%)	7 (12%)
1-2	18 (32%)	19 (33%)
≥3	27 (47%)	32 (55%)
IAS.....median	6	7
0-2	16 (28%)	14 (24%)
3-5	9 (16%)	9 (16%)
>6	32 (56%)	34 (59%)
# NRTI median	4	5
0-2	12 (21%)	14 (24%)

3-5	27 (47%)	22 (38%)
≥6	18 (32%)	22 (38%)
# TAMs median	3	3
0	8 (14%)	11 (19%)
1-2	15 (26%)	12 (21%)
≥3	34 (60%)	35 (60%)

Tipranavir score mutations: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V.
IAS mutations: any protease gene mutations at codons 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 63, 71, 73, 77, 82, 84, 88, and 90.
Thymidine analog mutations (TAMs): RT mutations 41L, 67N/G, 70R, 210W, 215F/Y, 219Q/E/N.

Figure 1. Prevalence of Baseline PI and NRTI Resistance-Associated Mutations Increased with Increasing Age



A (purple) - Age group 2 to <6
B (maroon) – Age group 6 to <12
C (blue) – Age group 12 to 18

Baseline Phenotype

Baseline phenotypic data was not available for all subjects in the study. Phenotypes were obtained on subjects who experienced virologic failure. Six of the 35 subjects with baseline phenotypes had baseline TPV susceptibility >3-fold from reference (Table 3). All six were virologic failures with four receiving the higher dose of TPV.

Table 3. Subjects with TPV Baseline Phenotype >3

PID	AGE	TRT	TPV mutations	BL TPV Fold Change	Outcome
1095	14.69	High	4	3.8	Rebound
3331	15.87	High	9	6.6	Virologic Failure
3920	9.96	High	3	4.2	Rebound

3924	13.72	Low	6	5.7	DC for AE
4902	15.76	High	8	4.6	Never Suppressed
5509	9.34	Low	7	5.6	Never Suppressed

ANALYSES OF RESPONSE BY GENOTYPE

As the number of baseline TPV PI resistance-associated mutations, IAS-defined PI mutation, NRTI resistance-associated mutations and TAMs increased, virologic response decreased (Table 4). Furthermore, an examination of the baseline genotype of the responders and virologic failures showed that the median number of baseline TPV and IAS PI resistance-associated mutations was higher for the subjects who failed treatment than the responders (Table 5). Interestingly the median number of baseline NRTIs and TAMs was comparable between the responders and failures.

Table 4. Proportion Responders by Number of Baseline Resistance Mutations

	Proportion Responders <400 copies/mL
Overall	48/115 (42%)
TPV Mutations	
0	10/19 (53%)
1-2	19/37 (51%)
≥3	19/59 (32%)
IAS PI Mutations	
0-2	13/30 (43%)
3-5	11/19 (58%)
>6	24/66 (36%)
# NRTI mutations	
0-2	15/26 (58%)
3-5	21/49 (43%)
≥6	12/40 (30%)
# TAMs	
0	10/19 (53%)
1-2	12/27 (44%)
≥3	26/69 (38%)

Table 5. Baseline Genotype of Responders and Virologic Failures

	Responders N=48		**Virologic Failures (n=32)**	
	High (n=26)	**Low (n=22)**	**High (n=19)**	**Low (n=13)**
median # TPV mutations	1	2	4	6
median # IAS PI mutations	6	5	9	10
median # NRTI mutations	4	4.5	4	7
median # TAMs	3	2.5	3	4

The patients >6 year olds had better response rates in the high TPV dose group than the low dose group (Table 6). The response rates for the 2 to <6 years age group were similar regardless of dose group (67-69%). In addition, the 2 to <6 years age group had a better response than the older age groups (Table 6), which correlated with lower number of baseline PI and NRTI resistance mutations (See Fig. 1 above). Furthermore, the 2 to <6 years age group had better response rates than older age groups regardless of the number of baseline resistance-associated mutations, although the numbers are too small to draw firm conclusions. For example, in all the baseline mutation number subgroups, the 2 to <6 years age group had response rates of 60-70% compared to response rates of 20 to 40% for the 12-18 year old age group (Table 7).

Table 6. Proportion Responders by TPV Dose and Age Group

	Responders
High TPV Dose	26 (46%)
2 to <6	8 (67%)
6 to <12	10 (53%)
12 to 18	8 (31%)
Low TPV Dose	22 (38%)
2 to <6	9 (69%)
6 to <12	6 (32%)
12 to 18	7 (27%)

Table 7. Proportion of Responders at Week 48 by Baseline Genotype and Age

	% Responders (<400 copies/mL)			
Age	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**
TPV				
0-1	**22/40 (55%)**	**10/13 (77%)**	**7/12 (58%)**	**5/15 (33%)**
2-4	**20/48 (42%)**	**6/10 (60%)**	**9/20 (45%)**	**5/18 (28%)**
≥5	**6/27 (22%)**	**1/2 (50%)**	**0/6**	**5/19 (26%)**
IAS				
0-2	**13/30 (43%)**	**5/8 (63%)**	**6/12 (50%)**	**2/10 (20%)**
3-6	**17/28 (61%)**	**10/14 (71%)**	**3/7 (43%)**	**4/7 (40%)**
>6	**18/57 (32%)**	**2/3 (67%)**	**7/19 (37%)**	**9/35 (26%)**
NRTI				
0-2	**15/26 (58%)**	**10/14 (71%)**	**3/6 (50%)**	**2/6 (33%)**
3-5	**21/49 (43%)**	**4/6 (67%)**	**9/19 (47%)**	**8/24 (33%)**
>5	**12/40 (30%)**	**3/5 (60%)**	**4/13 (31%)**	**5/22 (23%)**

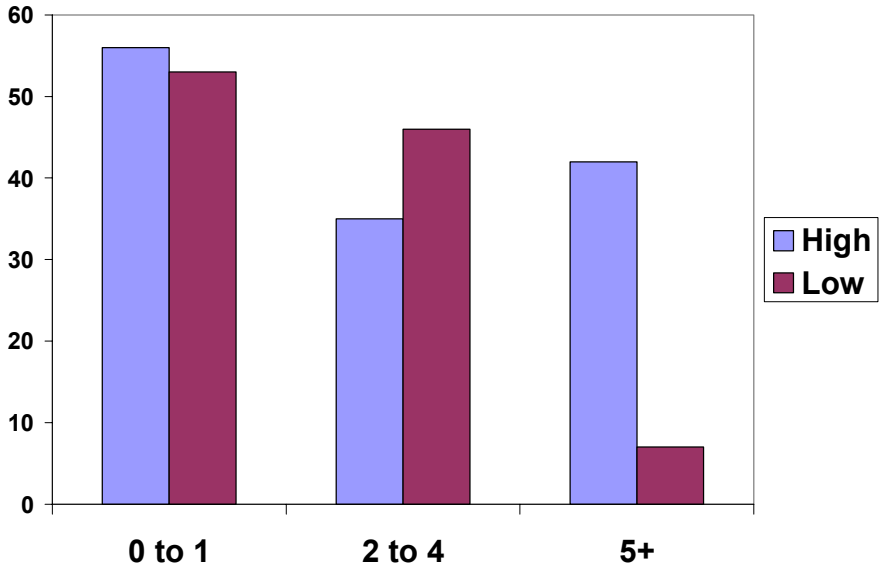
Subjects with a higher number of baseline TPV resistance-associated mutations (>5) also had better response rates if they were in the high TPV dose arm compared to the low TPV dose arm (Table 8). Subjects with 5 or more TPV resistance-associated mutations at baseline had response rates of 42% (5/12) in the high dose arm compared to 7% (1/15) in the low dose arm (Fig. 2). A breakout of the outcome by both TPV dose and age showed that the younger age groups appeared to have better response rates on the lower dose of TPV than the older age groups (Appendix B). However, the 12 to 18 year olds with ≥5 TPV PI resistance-associated mutations at baseline had response

rates of 40% (4/10) in the high TPV dose arm compared to 11% (1/9) in the low TPV dose arm (Appendix B).

Table 8. The Effect of TPV Resistance-Associated Mutations on Response (<400 copies/mL) by Dose

Dose	High	Low
#TPV Mutations		
0	4/12 (33%)	6/7 (86%)
1	10/13 (77%)	2/8 (25%)
2	2/5 (40%)	5/11 (45%)
3	4/8 (50%)	4/8 (50%)
4	1/7 (14%)	4/9 (44%)
5	2/5 (40%)	1/6 (17%)
≥6	3/7 (43%)	0/9 (0%)

Fig 2. Effect of Number of TPV Resistance-Associated Mutations on Response by Dose



Although not statistically significant, further evidence supporting using the higher TPV dose in older children was that a higher proportion of children 12-18 yrs with 3 or more TPV mutations in the low dose group were virologic failures compared to the high dose group. In the 12 to 18 year old age group, 79% (15/19) of the subjects with 3 or more baseline TPV resistance-associated mutations in the low dose arm were virologic failures compared to 67% (10/15) in the high dose arm [p=0.42].

The results in Table 9 confirm that the key TPV PI resistance-associated substitutions at amino acids L33, V82, I84 and L90 had a negative impact on response rates. Subjects

with these baseline substitutions had slightly higher response rates in the high Dose TPV arm than subjects in the low Dose TPV arm.

Table 9. Effect of TPV Resistance-Associated Mutations on Outcome by Dose

	High TPV Dose	Low TPV Dose
Overall	26/57 (46%)	22/58 (38%)
L33F	5/14 (36%)	4/14 (29%)
V82A/C/F/I/L/M/S/T	8/23 (35%)	8/24 (33%)
I84V	1/8 (13%)	0/9
L90M	10/25 (40%)	8/26 (31%)

Subjects with 2 or more TPV key mutations at baseline had response rates of 23% (5/22) in the high dose arm and 26% (6/23) in the low dose arm (Appendix C). For children older than 6 years old with 0-1 TPV key mutations, response rates were better in the high dose group. Older children 12-18 years old with 3 or more TPV key mutation had better response rates in the high dose group, further supporting using this dose for this age group (Appendix C). However, no solid conclusions for dose can be determined for the younger age children because of the limited data.

VIROLOGIC RESPONSE AT WEEK 48 BASED ON GSS

A genotypic susceptibility score (GSS) was used to measure sensitivity to the ARV background regimen. Each background ARV medication was assigned a value of 0, 0.25, or 1 based on the criteria given in Table 10, with the GSS being the sum of these values for each subject.

Table 10. Algorithm for Calculation of GSS

Background ARV	Part of ARV history or taken at baseline		Resistant or Possibly resistant per Trugene®		Contribution to GSS
	Yes	No	Yes	No	
Enfuvirtide	X		NA	NA	0.25
		X	NA	NA	1.00
NRTI	X		X		0
	X			X	0.25
		X	X		0
		X		X	1.00
NNRTI	X		NA	NA	0
		X	X		0
		X		X	1.00

The median GSS for the pediatric population was 0.5. Forty-three subjects (37% of 115) had a GSS of 0.00, indicating resistance to all background ARVs; 40 subjects (35%) had GSS of 0.25 to 1.00; and 32 subjects (28%) had a GSS of 1.25 to 2.25. Overall, response rates were lower for subjects with GSS of 0 compared to GSS >0.25 (Table 11). In all GSS groups, a greater proportion of subjects in the youngest age group

achieved <400 HIV RNA copies/mL at 48 weeks than did those in the two older age groups. Although the small numbers of subjects limit the conclusions that can be drawn, the 12 to 18 yr olds with GSS >0.25 had a better virologic response in the high TPV dose than those in the low TPV dose.

Table 11. The Effect of GSS on Virologic Response by TPV Dose and Age Group

Dose	**High**				**Low**			
Age Group	**All**	**2 to <6**	**6 to <12**	**12 to 18**	**All**	**2 to <6**	**6 to <12**	**12 to 18**
GSS								
0	30% (6/20)	67% (2/3)	50% (4/8)	0% (0/9)	30% (7/23)	40% (2/5)	38% (3/8)	20% (2/10)
0.25-1.00	55% (12/22)	60% (3/5)	40% (2/5)	58% (7/12)	50% (9/18)	2/2	50% (4/8)	38% (3/8)
1.25-2.25	53% (8/15)	75% (3/4)	60% (3/5)	33% (2/6)	41% (7/17)	83% (5/6)	0/3	25% (2/8)

Median GSS Scores by Age group: 2 to <6 = 1.0 (n=25); 6 to <12= 0.3 (n=37); 12 to 18 = 1.0 (n=53); All = 0.5 (n=115)

VIROLOGIC RESPONSE AT WEEK 48 BASED ON GENOTYPIC INHIBITORY QUOTIENT

Genotypic inhibitory quotient (GIQ) is a reflection of both baseline genotypic resistance and TPV trough concentrations achieved during the 48 weeks of therapy. A total of 103 subjects had both TPV trough level data and baseline genotype available for GIQ calculation. GIQ values ranged from 0.48 to 215.38. Subjects were grouped according to GIQ quartile: 25 subjects were in the first quartile (GIQ 0.48-5.85), and 26 subjects each in the second (GIQ 6.05-14.2), third (GIQ 14.38-36.23), and fourth (GIQ 36.48-215.38) quartile. Overall, the proportion of subjects achieving virologic response <400 HIV RNA copies/mL at 48 weeks increased with increasing GIQ [1st quartile 8.0%, 2nd quartile 46%, 3rd quartile 54% and 4th quartile 81%. An examination of the effect of GIQ on response by dose and age group was hard to interpret because of the small sample numbers when broken out by individual groups (Table 12). Subjects in quartile 2 appeared to have better response rates in the high TPV dose group. However, subjects achieving higher concentrations of TPV in quartile 4 did not have a significant difference in response rates between dose groups.

Table 12. The Effect of GIQ on Virologic Response by TPV Dose and Age Group

Dose	**High**				**Low**			
Age Group	**All**	**2 to <6**	**6 to <12**	**12 to 18**	**All**	**2 to <6**	**6 to <12**	**12 to 18**
GIQ Quartile*								
Q1	0% (0/10)	-	0/3	0/7	13% (2/15)	0	13% (1/8)	14% (1/7)
Q2	58% (7/12)	40% (2/5)	33% (1/3)	100% (4/4)	36% (5/14)	33% (1/3)	50% (2/4)	29% (2/7)

Q3	50% (6/12)	1/1	75% (3/4)	29% (2/7)	57% (8/14)	67% (4/6)	67% (2/3)	40% (2/5)
Q4	77% (13/17)	83% (5/6)	83% (5/6)	60% (3/5)	89% (8/9)	4/4	67% (2/3)	2/2

*GIQ Quartiles: QI 0.48-5.85, Q2 6.05-14.2, Q3 14.38-36.23, Q4 36.48-215.38

ON TREATMENT RESISTANCE EMERGENCE

The substitutions that emerged on treatment were investigated in 32 virologic failure subject isolates. Six of the virologic failures were resistant to TPV at baseline with >3-fold change from reference. Although all subjects had baseline genotype results, the on-treatment specimen for 8 of the rebound patients could not be sequenced and thus, on-treatment genotype results are unavailable for subjects #1070, 1094, 1095, 1106, 3412, 3925, 5509, and 5511. Most of the virologic failures were in the older old age groups [12 to 18 years (n=23); 6 to <12 age group (n=6); 2-<6 age group (n=3)]. In the 12 to 18 year olds, there were more failures in the high TPV dose group (n=15) [7 had non-adherence indicated in the dataset] (Table 13).

Twenty-one of the virologic failure subjects developed TPV resistance (>3-fold) on TPV treatment (10 in the high dose; 11 in the low dose) with 6 having TPV resistance at baseline. Most of the virologic failures were in the 12 to 18 year old age group (n=13) [2-<6 age group (n=2) and 6 to <12 age group (n=6)], but these 13 failures were evenly divided between TPV dose groups (Table 14).

Table 13. Age Group and Dose of 32 Virologic Failure Subjects

Age Group	Dose	N
A	TPV High dose	1
A	TPV Low dose	2
B	TPV High dose	3
B	TPV Low dose	3
C	TPV High dose	15
C	TPV Low dose	8

Table 14. Age Group and Dose of 21 Virologic Failure Subjects with TPV Resistance (>3-fold) at Failure

Age Group	Dose	N
A	TPV High dose	1
A	TPV Low dose	1
B	TPV High dose	2
B	TPV Low dose	4
C	TPV High dose	7
C	TPV Low dose	6

The baseline and failure genotypes and phenotypes for the 21 subjects who experienced virologic failure and developed TPV resistance are shown in Table 15. The median fold change in TPV susceptibility of these virologic failure isolates at failure was 22 (range 10 – 55). Other subjects who experienced virologic failure but did not have evidence of

TPV resistance at failure are listed in Table 16. Many of these subject isolates (8/14; 57%) developed the M184V substitution and/or had evidence of lamivudine phenotypic resistance.

Table 15. Virologic Failures with Resistance (≥3 Fold Change) to TPV (n = 21)

PID	Age Group	TRT	Baseline Mutations	PI mutations Emerging	TPV Fold Change at Failure (BL R)
1060	C	Low	(b) (4)		25
1062	C	Low			17
1083	C	Low			22
1095	C	High			27 (3.8)
1104	C	High			20
1106	A	High			33
1210	C	High			4.2 (2.9)
1212	B	High			55
3331	C	High			17 (7)
3412	C	Low			11
3920	B	High			29 (4)
3922	C	High			42
3923	C	High			21
3924	C	Low			19 (6)

3927	B	Low	(b) (4)	18 (2.6)
4902	C	High		10 (4.6)
4903	C	Low		20
5501	B	Low		38 (2.4)
5506	B	Low		37
5509	B	Low		28 (6)
5516	A	Low		23

Table 16. Other Virologic Failures without Determined TPV Resistance at Failure (n=14)

PID	Age Group	TRT	RT Mutations Developing	PI Mutations Developing	TPV Phenotype
1020	C	Low	(b) (4)		ND
*1021**	B	Low			ND
1051	C	High			<0.5
1070	C	High			<0.5
1081	C	High			ND
*1094**	C	Low			1.9
1103	C	High			0.9
3411	C	High			ND
3921	C	High			1.0
3925	C	Low			1.9
5401	C	High			0.9
5423	C	High			ND
*5511**	A	High			0.6
5518	A	Low			ND

***Subjects 1021, 1094, and 5511 rebounded after Week 48**

The substitutions that developed on TPV/r treatment in pediatric subjects were consistent with substitutions developing in TPV/r treated adults. In adults, the most common amino acid substitutions that developed on 500/200 mg APTIVUS/ritonavir in greater than 20% of virologic failure isolates were L33V/I/F, V82T, and I84V. Other substitutions that developed in 10 to 20% of APTIVUS/ritonavir virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L, and L89V/M. In pediatric subjects, substitutions at V82 occurred most frequently in 31% of the 36 virologic rebounds subjects with about half of those developing the V82T substitution (Table 17).

Table 17. PI Substitutions Developing on TPV Treatment

PI Substitutions	Number Developing in Virologic Rebounds (%)
L10F/V	6 (17%)
L33F/I/V	6 (17%)
E35D/G	2 (6%)
M36I/V/L	6 (17%)
I47V	3 (8%)
I54V	3 (8%)
H69Q	1 (3%)
A71V/I	4 (11%)
V82L/F/T	11 (31%)
V82T	5 (14%)
I84V	5 (14%)
L89M/I	3 (8%)
L90M	2 (6%)

Substitutions L10F/V, L33F/I/V, M36I/V/L and I84V emerged in >10% of the virologic rebounds pediatric subjects. The development of substitutions at L33, I47 and L89 in the pediatric virologic failure subjects is consistent with the substitutions developing in adult virologic failure subjects. Changes at position L33 were L33I in two subjects, and L33I/V and L33V, each in one subject. The L33F substitution emerged from a baseline mixture in one subject and a L33F/L mixture emerged in another subject. The development of I54V and the associated decrease in TPV susceptibility in the pediatric virologic failure subjects confirms earlier findings in the original NDA review of TPV in adults. Therefore, the I54V mutations should be included in the list of mutations developing on TPV treatment.

Many of the substitutions associated with TPV resistance were also present at baseline. For example, the M36I mutation was very commonly present in baseline genotypes, i.e., in 68% (30 of 44) of the virologic failure subjects. Baseline isolates of the virologic failures were wild-type V82 in 22 subjects, V82A in 15 subjects, V82C in 3 subjects, V82F, V82L, V82S and a mixture of V82A/T in one subject each. In the virologic failure subjects who developed TPV resistance, 9 subjects had V82A or V82A/V mixtures at baseline and 4 of these gained an emergent V82T mutation, which was associated with a mean decrease in TPV susceptibility of 25-fold. The substitution V82L emerged in 6 subjects' isolates accompanied with a decrease in TPV susceptibility with 3 of these coming from subjects with wild-type at baseline. The observation that wild-type sequence at V82 is associated with the development of the V82L mutation and that V82A to T shifts are frequent is consistent to the observations in adult subjects treated with TPV/r.

In summary, the most common codon at which protease gene substitutions emerged with TPV/r treatment was V82. Other substitutions that commonly emerged in the virologic rebound subjects included L10F/V, L33F/I/V, M36I/V/L, I47V, I54V, I84V and L89M/I. Substitutions at these positions have been previously reported among PI drug-experienced adults treated with TPV/r. The selection of I54V mutation on TPV/r

treatment and the associated decrease in TPV susceptibility in the pediatric virologic failure subjects confirms earlier findings in the original NDA review of TPV in adults. The I54V mutation should be included in the list of mutations developing on TPV treatment. Overall, the pattern of mutation emergence in pediatric subjects on TPV/r treatment is consistent with that previously reported in adult subjects.

EMERGENCE OF REVERSE TRANSCRIPTASE MUTATIONS

Although didanosine was among the most frequent previously-used NRTIs in this pediatric subject population, there were no K65R mutations present at baseline in the total study population, and none emerged in the Rebound subgroup. Mutations at Q151 were present in 3 subjects at baseline among the total study population and each were virologic failures. The Q151M mutation is an uncommon mutation (reported frequency varies from 2.4 to 7.9% among highly treatment-experienced individuals) and is usually part of a complex with A62V, V75I, F77L and F116Y. The three subjects with the Q151M mutation at baseline, #1021 (8 years old), 3925 (15 years old), and 5423 (13 years old), each had mutations at several of the positions of the complex. No further Q151M mutations emerged.

Pre-treatment M184 mutations were common, being present in 12 subjects of the total study population, and of the 28 Rebound subgroup subjects at baseline. Emergence of the M184V mutation while on-treatment was observed in 9 subjects accompanied by the development of marked phenotypic resistance for lamivudine.

CROSS-RESISTANCE

Baseline phenotype analysis for other proteases was determined according to the clinical cutoffs reported in product labelling for each of the respective compounds: lopinavir <10 susceptible, 10-40 partially susceptible, >40 resistant; saquinavir 2.5, amprenavir 2.5, indinavir 3.0, nelfinavir 4.0, atazanavir 4.0, and darunavir 10.0. With the exception of darunavir and tipranavir, the majority of isolates (range 56.7% for saquinavir to 83.3% for nelfinavir) had reduced susceptibility to PIs (Table 18). Ten and twenty percent of the isolates were resistant at baseline to DRV and TPV, respectively, possibly reflecting that they are the newest PIs to have become available for use in treatment.

For the virologic failures with resistance to TPV (>3-fold change) at failure (Table 18), 5/21 (24%) isolates were also resistant to DRV (>10 fold change). The remaining 16 (76%) had fold changes in DRV susceptibility of less than 6-fold.

Table 18. Phenotypic Data of Approved PIs for Study 1182.14

	Baseline			Last On-Treatment		
PI	**Median**	**Range**	**% Resistant**	**Median**	**Range**	**% Resistant**
TPV	1.2	0.5 - 6.6	20	18.1	0.5 - 55	70
DRV	1.5	0.2 - 44	10	1.4	0.2 - 16	13.3
LPV	39.6	0.2 - 55.2	60	26.7	0.2 - 53	66.7
SQV	9.6	0.4 - 70.8	56.7	9.5	0.3 - 113	73.3
APV	8.3	0.4 - 100	65.5	8.5	0.5 – 86	76.7
IDV	6.8	0.3 - 85	66.7	7.3	0.5 – 98	73.3

NFV	27	0.6 - 96	83.3	28	0.7 - 96	83.3
ATV	18	0.3 - 170	72.4	23	0.5 - 149	80

CONCLUSIONS

- A high proportion of 115 pediatric subjects in Study 1182.14 had baseline PI and NRTI resistance mutations consistent with the high prior PI and NRTI use and a heavily treatment-experienced patient population.
- The youngest age group of 2 to <6 year olds had the best response with 68% <400 copies/mL, compared to 42% and 29% achieving this level in the 6 to <12 year and 12 to 18 year age groups, respectively.
- Virologic response decreased with increasing baseline mutation scores.
- Subjects with a higher number of baseline TPV resistance-associated mutations (>5) also had better response rates if they were in the high TPV dose arm compared to the low TPV dose arm.
- The most common protease substitutions developing in the virologic failures analyzed emerged at codon 82 in TPV/r treatment in children. Substitutions L10F/V, L33F/I/V, M36I/V/L and I84V emerged in >10% of the virologic rebounds pediatric subjects. Each of these positions has previously been reported among PI-experienced adults treated with TPV/r.
- The development of I54V in 8% of the pediatric virologic failure isolates and the associated decrease in TPV susceptibility confirms earlier findings in the original NDA review of TPV in adults. Therefore, the I54V mutations should be included in the list of mutations developing on TPV treatment in the product insert for TPV.
- TPV resistance developed on treatment in 66% of the virologic failure isolates with a median 22 fold-change in EC_{50} value (range 10 – 55). For the virologic failures with resistance to TPV at failure, 76% were susceptible to darunavir.
- Children with greater viral resistance had better 48 week virologic response with the high dose than with the low dose. Older subjects age 6 to 18 years old in the high TPV dose groups with higher baseline resistance had better response rates than those in the low TPV dose group.

This supplemental NDA is approvable with respect to microbiology for the treatment of HIV-1 in PI-experienced pediatric patients. It is indicated for use as combination antiretroviral treatment of HIV-1 infected adult and pediatric patients with evidence of viral replication, who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA: 21-814 **SN**: SE1 005 **DATE REVIEWED:** 03/17/2008
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

CHANGES TO PROPOSED TIPRANAVIR USPI

The I54V/A/M substitutions were included in the list of mutations developing on TPV treatment in 10-20% of failure isolates.

TIPRANAVIR US PRODUCT INSERT

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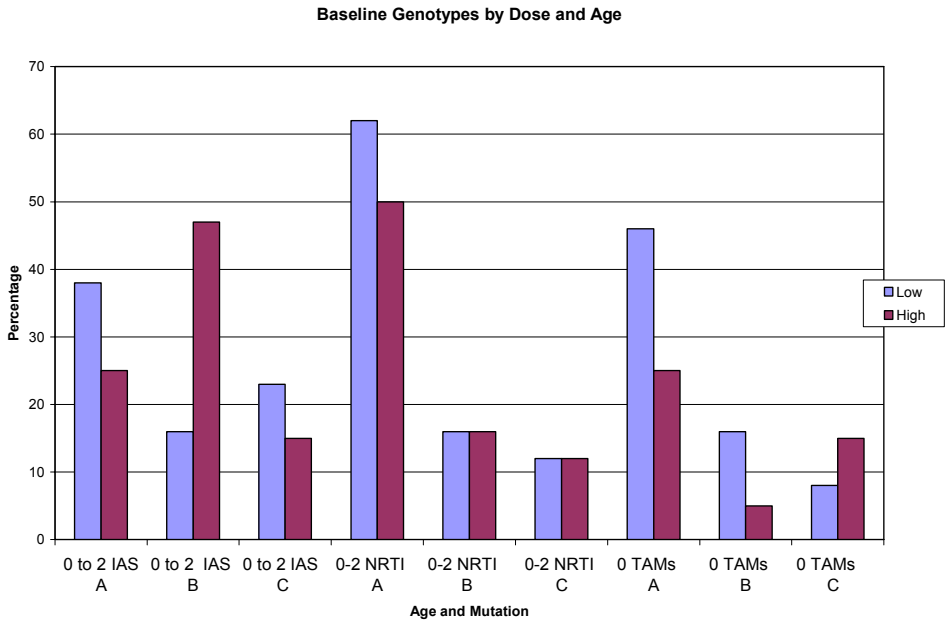
APPENDIX A:

Number of Baseline Mutations in Each TPV Dose Group by Age

TPV Dose	High (n=57)			Low (n=58)		
Age Group	**2 to <6 (n=12)**	**6 to <12 (n=19)**	**12 to 18 (n=26)**	**2 to <6 (n=13)**	**6 to <12 (n=19)**	**12 to 18 (n=26)**
TPV Score						
0	3 (25%)	3 (16%)	6 (23%)	5 (38%)	1 (5%)	1 (4%)
1-2	5 (42%)	8 (42%)	5 (19%)	6 (46%)	7 (37%)	6 (23%)
≥3	4 (33%)	8 (42%)	15 (58%)	2 (15%)	11 (58%)	19 (73%)
IAS						
0-2	3 (25%)	9 (47%)	4 (15%)	5 (38%)	3 (16%)	6 (23%)
3-5	3 (25%)	1 (5%)	5 (19%)	4 (31%)	4 (21%)	1 (4%)
>6	6 (50%)	9 (47%)	17 (65%)	3 (23%)	12 (63%)	19 (73%)
# NRTI						
0-2	6 (50%)	3 (16%)	3 (12%)	8 (62%)	3 (16%)	3 (12%)
3-5	4 (33%)	10 (53%)	13 (50%)	2 (15%)	9 (47%)	11 (42%)
≥6	2 (17%)	6 (32%)	10 (38%)	3 (23%)	7 (37%)	12 (46%)
# TAMs						
0	3 (25%)	1 (5%)	4 (15%)	6 (46%)	3 (16%)	2 (8%)
1-2	5 (42%)	5 (26%)	5 (19%)	2 (15%)	4 (21%)	6 (23%)
≥3	4 (33%)	13 (68%)	17 (65%)	5 (38%)	12 (63%)	18 (69%)

TPV Score median = 3
IAS median = 6
NRTI median = 5
TAMs median = 3



A - Age group 2 to <6
B – Age group 6 to <12
C – Age group 12 to 18

APPENDIX B:

Proportion of Responders at Week 48 by Baseline Genotype, Dose and Age

TPV Dose	High				Low			
Age	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**
TPV PI								
0-1	14/25 (56%)	5/7 (71%)	7/10 (70%)	2/8 (25%)	8/15 (53%)	5/6 (83%)	0/2	3/7 (43%)
2-4	7/20 (35%)	2/4 (50%)	3/8 (38%)	2/8 (25%)	13/28 (46%)	4/6 (67%)	6/12 (50%)	3/10 (30%)
≥5	5/12 (42%)	1/1	0/1	4/10 (40%)	1/15 (7%)	0/1	0/5	1/9 (11%)
IAS PI								
0-2	7/16 (44%)	1/3 (33%)	6/9 (67%)	0/4	6/14 (43%)	4/5 (80%)	0/3	2/6 (33%)
3-6	9/14 (64%)	5/7 (71%)	2/2	2/5 (40%)	8/14 (57%)	5/7 (71%)	1/5 (20%)	2/2
>6	10/27 (37%)	2/2	2/8 (25%)	6/17 (35%)	8/30 (27%)	0/1	5/11 (45%)	3/18 (17%)
NRTI								
0-2	7/12 (58%)	3/6 (50%)	3/3	1/3 (33%)	8/14 (57%)	7/8 (88%)	0/3	1/3 (33%)
3-5	13/27 (48%)	¾ (75%)	6/10 (60%)	4/13 (31%)	8/22 (36%)	1/2	3/9 (33%)	4/11 (36%)
>5	6/18 (33%)	2/2	1/6 (17%)	3/10 (30%)	6/22 (27%)	1/3 (33%)	3/7 (43%)	2/12 (17%)

APPENDIX C:

Effect of # Key Mutations by Dose and Age Group

TPV Dose	High				Low			
Age	ALL	2 to <6	6 to <12	12 to 18	ALL	2 to <6	6 to <12	12 to 18
TPV Key PI								
0	50% (11/22)	71% (5/7)	63% (5/8)	14% (1/7)	53% (10/19)	88% (7/8)	0/4	43% (3/7)
1	77% (10/13)	75% (3/4)	100% (5/5)	50% (2/5)	38% (6/16)	50% (2/4)	33% (3/9)	33% (1/3)
2	11% (1/9)	0/1	0/3	20% (1/5)	36% (4/11)	-	50% (1/2)	33% (3/9)
3	25% (3/12)	-	0/3	33% (3/9)	17% (2/12)	0/1	50% (2/4)	0/7
4	1/1			1/1				
≥2	23% (5/22)	0/1	0/6	33% (5/15)	26% (6/23)	0/1	50% (3/6)	19% (3/16)

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/s/

Lisa Naeger
6/18/2008 01:57:42 PM
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clinical virology review

Julian O Rear
6/18/2008 03:50:39 PM
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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) **Serial #:** 000
Reviewer's Name(s): Lisa K. Naeger, Ph.D.

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

Initial Submission Dates:

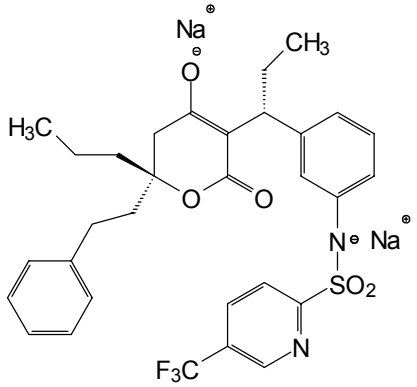
Correspondence Date:	12/21/2004
CDER Receipt Date:	12/22/2004
Assigned Date:	10/19/2004
Review Complete Date:	6/15/2005
PDUFA Date:	6/22/2005

Amendments:
Related/Supporting Documents: IND51979

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

Empirical formula: $C_{31}H_{31}F_3N_2O_5SNa_2$
Chemical Name: [R-R(*,R*)]-N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-y1]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide disodium salt
Molecular mass: 646.63

Structural Formula:



TIPRANAVIR

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.

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;

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.

Executive Summary

Tipranavir (TPV), an 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-l isolates was 240 nM (range (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-l_{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

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-naive 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 $\log_{10}$ 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 (>1$\log_{10}$ 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 -

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 $\log_{10}$ 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 $\log_{10}$ median DAVG24 decrease in viral load on TPV/r treatment compared to a 0.23 $\log_{10}$ 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 $\log_{10}$ 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 $\log_{10}$ 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 $\log_{10}$) 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 IC_{50} 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-l 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-naive 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

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-l isolates was 240 nM (range (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 $\leq$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.

TPV-resistant viruses were selected in vitro when wild-type HIV-l_{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 reduction in susceptibility to the TPV-resistant virus with 10 protease mutations.

2.1.2. Clinical Microbiology

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 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 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.

TPV/r-resistant isolates were analyzed from treatment-experienced patients in the phase II study 052 (n=32) and 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-naive subjects has not been characterized.

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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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