National PBM Drug Monograph

Tipranavir (Aptivus®)

July 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA Approved indication: Tipranavir, co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Dosing: The adult dose established from clinical trials for tipranavir is 500mg coadministered with ritonavir 200mg orally twice-daily with food.

Pharmacology: Tipranavir/ritonavir is an inhibitor of CYP3A4 and 2D6 resulting in a multitude of drug interactions when these agents are combined with other drugs highly dependent on CYP3A4 or 2D6.

Safety: The most common side effects and laboratory abnormalities associated with tipranavir include diarrhea, nausea, fatigue, headache, vomiting, and grade 3-4 ALT or AST elevations and triglyceride elevations. There was also an unexplained increase in rash in female patients. The tipranavir label includes a **Black Box warning** regarding hepatoxicity. Tipranavir is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency. Because TPV/r can cause serious liver toxicity, liver function tests should be performed at initiation of therapy with TPV/r and monitored frequently throughout the duration of treatment. Caution should be used when prescribing TPV/r to patients with elevated transaminases, hepatitis B or C co-infection, or other underlying hepatic impairment.

Efficacy: Tipranavir was approved on the basis of two multi-center, multi-national, randomized and controlled, open-label studies in highly treatment-experienced HIV-infected subjects with triple antiretroviral class (NRTI, NNRTI, and PI) experience and with at least two failed PI-based regimens, RESIST-1 and RESIST-2. Patients were randomized 1:1 to receive either TPV/r or a comparator PI/r along with an optimized background regimen based on genotypic resistance testing prior to randomization. The primary efficacy endpoint was the proportion of subjects with a treatment response defined as 2 consecutive viral load measurements >1 log10 below baseline at 24 weeks. Treatment response in both RESIST trials were similar and significantly higher in the TPV/r treated group versus those in the CPI/r treated group ($p<0.0001$).

Conclusion: Although the cost of tipranavir/ritonavir is higher than other PIs, tipranavir helps to address a continued unmet clinical need for new drugs to treat patients with multidrug resistant HIV-1. Tipranavir demonstrates unique resistance characteristics that offer potential therapeutic advantages to PI-experienced patients with limited treatment options. Appropriate safeguards for the use of TPV/r must be considered however, given the safety considerations and potential for drug-drug interactions. There is potential for concern in patients with HIV/HCV co-infection given the effects of TPV on liver enzymes which will require careful monitoring post-approval in VA patients.

Recommendation: The unique role of tipranavir in highly treatment experienced HIV-infected patients with few remaining treatment options support the addition of tipranavir to the National formulary in a limited capacity based on patients meeting Criteria for Use.

Introduction

Tipranavir, the ninth agent in the protease inhibitor (PI) class, was approved on June 23, 2005 for use in combination with ritonavir and with other antiretrovirals (ARVs) to treat HIV-1 infection in adults. This indication was based upon surrogate endpoint analyses of plasma HIV RNA levels for primary efficacy balanced with safety analyses in controlled studies of up to 24 weeks duration. To date, these data have only been presented at scientific meetings in oral presentations and poster formats. Information presented in this monograph includes much of this information as well as data filed with the FDA for the new drug application (NDA).

Tipranavir belongs to the Protease Inhibitor class of anti-HIV agents. There are currently 8 products from the PI class of anti-HIV agents on the VA National Formulary. Each has a unique profile that permits its use in a specific patient relative to co-administered medications, existing resistance mutations and co-morbid conditions. For this review, all drugs in the PI class will be included to permit comparisons where data are available.

Table 1: FDA Approved PIs

Generic Name	Trade Name	Manufacturer	Year Introduced
saquinavir (SQV)	Invirase Fortovase (soft gel capsule)	Roche	December 1995 November 1997 –to be discontinued in February 2006
ritonavir (RTV)	Norvir	Abbott	March 1996
indinavir (IDV)	Crixivan	Merck	March 1996
nelfinavir (NFV)	Viracept	Agouron/Pfizer	March 1997
amprenavir (APV)	Agenerase	GlaxoSmithKline	April 1999 – discontinued December 2004
lopinavir/ritonavir (LPV/r)	Kaletra	Abbott	September 2000
atazanavir (ATV)	Reyataz	*Bristol-Myers Squibb*	June 2003
fosamprenavir (fAPV)	Lexiva	GlaxoSmithKline	October 2003
tipranavir (TPV)*	Aptivus	Boehringer Ingelheim	June 2005

* drug is NOT on VA National Formulary

Prior to 1996, the standard of care was treatment with dual nucleoside reverse transcriptase inhibitors (nRTIs) but the availability of PIs soon led to a change to the current model of 3 or more drugs in an ARV regimen using multiple classes of agents. Also at this same time, the use of viral load monitoring showing significant associations between decreases in plasma viremia and improved clinical outcomes were published. Thus, CD4+ lymphocyte counts and HIV-RNA viral loads became the new surrogate markers of treatment response and predictors of disease progression thereby changing clinical trial design and becoming the new standard of clinical care. Studies using these potent PI containing triple combination regimens continued to be published, demonstrating dramatic reductions in HIV plasma viral RNA levels to undetectable levels and unprecedented increases in CD4+ lymphocyte counts and hence, the era of Highly Active Antiretroviral Therapy (HAART) began and continues today

Pharmacology/Pharmacokinetics

The PI class of anti-HIV agents functions by binding to the active site of HIV-1 protease and inhibiting the processing of viral Gag and Gag-Pol polyprotein precursors in HIV-1 infected cells, resulting in the formation of immature, noninfectious viral particles. These drugs do not require activation to an active moiety because they have intrinsic inhibitory activity against the protease enzyme.

Many PIs impose a high pill burden and require frequent administration to compensate for their generally unfavorable pharmacokinetics, particularly limited oral bioavailability and short plasma half-life. All PIs have poor CSF penetration. Plasma protein binding of these agents is generally high and metabolism occurs by means of the cytochrome P450 isoenzyme system in the liver, (primarily via the CYP3A4 enzyme). All available PIs, with the exception of tipranavir, are also competitive inhibitors of CYP3A4. Tipranavir when given alone is an inducer of 3A4, however, when co-administered with ritonavir (as it has been approved), it becomes an inhibitor of 3A4. TPV also 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 on CYP2D6 is inhibition. The net effect of TPV/r on CYP1A2, CYP2C9 and CYP2C19 is not known. Relative CYP3A4 inhibition capabilities are thought to be as follows: Ritonavir > amprenavir (fosamprenavir) > lopinavir/r, indinavir > nelfinavir >saquinavir. Similarly, several of the PIs, namely ritonavir, fosamprenavir, lopinavir, tipranavir, and nelfinavir, are also CYP3A4 inducers. This makes predicting the occurrence and the magnitude of drug interactions quite complicated, particularly when dual PI boosted regimens are employed.

Coadministration of low-dose ritonavir can improve the pharmacokinetic profile of this class of agents by increasing the total area under the concentration-versus-time curve (AUC) and the C_{min} thereby minimizing suboptimal drug levels which can give rise to resistant variants due to persistent viral replication. This pharmacokinetic enhancement, also referred to as "ritonavir-boosted" or "PI boosted" regimens, often translates into improved efficacy, tolerability, and convenience. The need for PI boosting is a reflection of the suboptimal exposures and pharmacokinetics of the parent PI and as a result, several of the agents in this class have either been co-formulated with ritonavir (lopinavir/r, Kaletra®), or are approved or recommended only to be used in combination with ritonavir. Tipranavir, for example, was approved on the requirement of co-administration with low dose ritonavir, and saquinavir, though originally approved as an individual agent has new labeling which warns that it, too, must only be co-administered with ritonavir.

Ritonavir also affects the pharmacokinetics of coadministered agents through its role as an inhibitor of the transmembrane drug-transporter, P-glycoprotein (P-gp), an efflux pump which actively effluxes drugs out of the intracellular space and appears to be responsible for the low oral bioavailability and limited penetration of sanctuary sites by PIs. The PIs are, to varying degrees, both substrates and inhibitors of P-gp in vitro, but the clinical relevance of this is still being elucidated. TPV/r is a P-gp inducer at steady-state.

Table 2: Pharmacokinetic Parameters for PIs

	SQV	RTV	IDV	NFV	LPV/r	ATZ	fAPV	TPV+
Bioavailability (%)	4		65	20-80				
Plasma half-life (hr)	1-2	3-5	1.5-2	3.5-5	5-6	6.5-8.6	7.7	5.5-6
Protein Binding (%)	98	98-99	60	98	98-99	86	90	99.9
Cmax (mcg/mL)		11.2	12.6	4.0	9.8	2.3/4.4*	4.8/6.1*	77-95mM
Cmin (mcg/mL)	0.37*	3.7	0.25	0.7-2.2	5.5	0.12/0.64*	0.35/2.1*	36-42mM
AUC $_{24}$ (mcg· h/mL)	29.2*	122-129	30.6	52.8	92.6	14.8/46.0*	33/79.2*	710-851mM
Metabolism	CYP3A4	CYP3A4 / 2D6	CYP3A4	CYP3A4	CYP3A4	CYP3A4 /UGT1A1	CYP3A4 / 2C19	CYP3A4
Inducer/Inhibitor	Inhibits 3A4	Inhibits 3A4, 2D6; induces 3A4, 1A2, 2C9	Inhibits 3A4	Inhibits 3A4	Inhibits 3A4 and Induces 3A4	Inhibits 3A4, UGT1A1, 1A2, 2C9	Inhibits and induces 3A4	Induces 3A4 alone, inhibits when given with RTV, also potentially 1A2, 2C9,

								2C19, 2D6

* indicates value of parent drug in combination with low-dose ritonavir

+ molecular weight of TPV= 602.7

Virology

The development of resistance to TPV has been evaluated both in vitro and in vivo. Tipranavir (TPV) demonstrates unique resistance characteristics that offer potential therapeutic advantages to PI-experienced patients. Clinical HIV-1 strains resistant to TPV have been shown to have a high frequency of mutations V82T and I84V and, specifically, two clusters of mutation patterns were identified: V82T with I84V and I84V with L90M. In Phase II and III clinical trials, 276 patients with on-treatment genotypes have demonstrated that the predominant emerging mutations with virologic failure in PI-experienced patients receiving TPV/r are L33F/I/V, V82T/L and I84V. Combination of all three of these mutations is usually required for reduced TPV susceptibility and is associated with > 3-fold resistance to TPV/r.

The presence of > 6 mutations in the protease was required to confer >10- fold resistance to tipranavir. The most common amino acid substitutions that developed on 500/200mg TPV/r in greater than 20% of TPV/r virologic failure isolates were L33V/I/F, V82T, and I84V. Genotypic or phenotypic resistance testing and/or treatment history should guide the use of TPV/r as the type and number of baseline primary protease inhibitor mutations affects the virologic response to the drug. Response rates were reduced if five or more protease inhibitor associated mutations were present at baseline and subjects did not receive concomitant enfuvirtide with TPV/ritonavir. The new phenotypic cutoff using the PhenoSense assay for TPV is 4. Information presented at a recent meeting suggests that it is extremely unlikely that tipranavir will have any activity if the fold change is 4 or greater in the PhenoSense assay.

Varying degrees of cross resistance among the PIs approved for HIV therapy have been observed and have resulted in limited options for patients with PI-resistant virus. In viruses from PI-experienced patients, many of the mutations which produce resistance to TPV are different than those that produce drug resistance to other PIs. This may account for the diminished cross resistance seen between TPV and other available protease inhibitors and explain why TPV/r is virologically active against the majority of HIV-1 with broad PI resistance. Tipranavir had < 4-fold decreased susceptibility against 90% (94/105) of HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir.

This will be a very complicated drug to use by most people given its complex resistance pattern. PI resistance is a complicated and dynamic field and requires interpretation by experienced clinicians. A full discussion of TPV resistance is beyond the scope of this monograph but further up to date information can be obtained on the International Aids Society-USA website (http://www.iasusa.org/resistance_mutations).

FDA Approved Indication(s) and Off-label Uses

Tipranavir, co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of TPV/ritonavir 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.

Tipranavir has not been studied in the settings of post-exposure prophylaxis or in acute HIV seroconversion. Tipranavir is assigned Pregnancy Category C and is currently being studied in children.

Current VA National Formulary Status

There are currently 8 medications, including one coformulated product, on the VA National formulary in the PI class for the treatment of HIV infection. These medications are classified as anti-infectives, where restrictions on use may be placed at VISN and/or local facility levels. Tipranavir is currently a non-formulary item being reviewed for formulary addition.

Dosage and Administration

The adult dose established from clinical trials for tipranavir is 500mg coadministered with ritonavir 200mg orally twice-daily with food. The table below lists the FDA dosing recommendations for all PIs in the adult HIV-infected patient population with normal renal and hepatic function. Doses of agents when coadministered with ritonavir (for boosting) are also included where applicable and noted by (r). In general, ritonavir boosted PI regimens are recommended in therapy experienced patients. For additional dosing recommendations of co-administered PIs the reader is referred to the Drug Interaction Section of this monograph and the table of *Drug Effects on Concentrations of PIs*.

Table 3: FDA Approved Dosing Recommendations

Drug	Usual Dose (mg)	Schedule	# Pills per dose	Diet restrictions
saquinavir (SQV, Fortovase®)	1200	TID	6	With food
	1000 + 100r	BID	5 + 1r	
saquinavir (SQV, Invirase®)*	1000 +100r	BID	2 + 1r	Within 2 hrs of a meal
ritonavir (RTV)	600 alone	BID	6	With food
	100-200 as part of a boosted regimen+	QD-BID	1-2	Usually with food
indinavir (IDV)	800	TID	2	empty stomach or low-fat snack; increase water intake 2L/day
	800 + 100/200r+	BID	2 + 1or 2r	none
nelfinavir (NFV)	1250	BID	2	With food
lopinavir/ritonavir (LPV/r)	400/100r (co-formulated)	BID	3	With food
atazanavir (ATV)	400 (therapy naive)	QD	2	With food
	300/100r (therapy experienced)	QD	2 + 1r	
fosamprenavir (fAPV)	1400 (therapy naïve)	BID	2	none
	1400 + 200r (therapy naïve)	QD	2 + 2r	
	700 + 100r (PI-experienced)	BID	1 + 1r	
tipranavir (TPV)	500 + 200r (must be co-administered with RTV)	BID	2 + 2r	With food

*must be administered with ritonavir

+ not an FDA approved dosage in package insert, but has been studied in clinical trials

Dosing in Hepatic Insufficiency

The liver is the major organ that eliminates TPV from systemic circulation. The pharmacokinetic profiles of single-dose and steady-state TPV/r in patients with mild to moderate hepatic insufficiency were studied and the parameters AUC, Cmax, and Cmin were found to be increased, but still within the range observed in clinical trials. Based on this information, no dosing

adjustment is required in patients with mild hepatic impairment, but close clinical and laboratory monitoring of patients with impaired liver function is important. The use of TPV/r in moderate and severe hepatic insufficiency is contraindicated.

All of the medications in this class are hepatically metabolized and, as a result, some require dose adjustment relative to hepatic insufficiency. There is limited pharmacokinetic information from populations with varying degrees of hepatic dysfunction. Given the substantial rate of hepatitis C co-infection in our HIV+ veteran population and the likelihood of liver disease progression in this population, it is important to understand what drugs need to be adjusted. Most dosing adjustments refer to the Child-Pugh scale which creates a score based on 5 components including encephalopathy, ascites, albumin, total bilirubin, and prothrombin time or INR. The maximum score is 15. The chart below offers specific dosing recommendations for all available PIs.

Table 4: Dosing of PIs in Hepatic Insufficiency

Drug	Child-Pugh Score/Class	Hepatic Dosing
IDV	Mild to moderate hepatic insufficiency due to cirrhosis	600mg q8h
ATZ	Class B (score 7-9)	300mg QD
	Class C (score >9)	Not recommended for use
fAPV*	C-P score 5-8	700mg BID
	C-P score 9-12	Not recommended for use
SQV, RTV, NFV, LOP/r		Use with caution in patients with underlying liver disease
TPV/r	Class B and C	Contraindicated

*ritonavir boosting is not recommended in patients with hepatic impairment

Efficacy

Efficacy Measures

Because of the possible development of resistance, drug development trials study an agent as monotherapy for only a brief period. Therefore, clinical trials of antiretroviral agents are now designed to compare an investigational regimen to current standards of care, some of which result in comparisons that provide marginal clinical utility. CD4+ lymphocyte count and HIV-RNA responses represent the clinical standard of surrogate markers of treatment response and predictors of disease progression. The relationship of plasma HIV RNA as surrogate endpoints to the actual clinical outcomes may be less well understood in studies of heavily pretreated populations.

Summary of efficacy findings

Tipranavir was approved on the basis of two multi-center, multi-national, randomized and controlled, open-label studies in highly treatment-experienced HIV-infected subjects with triple antiretroviral class (NRTI, NNRTI, and PI) experience and with at least two failed PI-based regimens, RESIST-1 and RESIST-2.

- RESIST-1 was conducted in North America and Australia, and performed 24 week interim analyses
- RESIST-2 was conducted in Europe and Latin America and performed 16 week interim analyses.

- Patients were randomized 1:1 to receive either TPV/r or a comparator PI/r (CPI/r) along with an optimized background regimen (OBR) based on genotypic resistance testing prior to randomization
- Patients in the comparator group (CPI/r) who did not show an initial virologic response by week 8 (defined as a) viral load has not dropped 0.5 log10 during the first 8 weeks of treatment and b) 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) were allowed to rollover to another study where all patients received TPV/r.

Table 5: Summary of RESIST Trials

	Study			
	RESIST-1		**RESIST-2**	
Regimen	TPV/r +OBR vs. CPI/r+OBR		TPV/r +OBR vs. CPI/r+OBR	
Randomized to	TPV/r+OBR	CPI/r +OBR	TPV/r+OBR	CPI/r +OBR
Schedule	various	various	various	various
Sample (n)	311	309	271	268
Duration	24 week data of planned 96 weeks		24 week data of planned 96 weeks	
Analysis Type	ITT		ITT	
Age (mean, years)	45	43	42	42
Sex (% male)	89	93	83	85
Race	77% white 22% black 0.6% Asian	76% white 22% black 1.6% Asian	70% white 5.5% black 0.7% Asian	67% white 4.1% black 1.1% Asian
Prior Enfuvirtide use (%)	12.5	12	11	11.6
Baseline Labs				
CD4 #	123	123	175	200
HIV RNA (log_{10} copies/ml)	4.81	4.84	4.84	4.81
HIV RNA >100,000(%)	41%		36%	
Endpoints				
CD4 change	36	6	31	1
2 consecutive VL measurements >1 log10 below baseline	41.5 *(36)**	22.3 *(16)*	41.0 *(32)*	14.9 *(13)*
HIV RNA <50	25.1	10.0	22.5	8.6
Median change in VL (log10 copies/mL) at 24wks	-0.88	-0.28	-0.72	-0.22
Virologic rebound	16.4%	12.6%	14%	9%

These data do not provide any information regarding the use of tipranavir as a first line agent in therapy-naive individuals.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials*s.

Adverse Events (Safety Data)

Because of guidelines and consensus statements on HIV treatment and standards of care at the time these agents were studied, most PIs were evaluated as part of a combination regimen and there is little, short-term exposure information on monotherapy other than that for saquinavir, ritonavir, and indinavir. Because PIs are prescribed as part of a multidrug regimen, assessment of toxicities is especially difficult as many of the agents share common side effect profiles. The current FDA model for HIV clinical trials design is to evaluate an investigational agent in ARV drug naïve and ARV drug experienced populations for at least 48 weeks duration. As with most drug development, only those toxicities of greater severity are reported. For the purposes of this review toxicity data for the non-formulary agent tipranavir are presented followed by a summary table of data published for each of the other available PIs.

Comparing toxicity data is difficult as rates of toxicities are often reported in the context of a multidrug regimen, often with more than one PI, and at various stages of disease. The table below lists the toxicity data seen during the RESIST 1 and RESIST 2 registry trials for tipranavir of highly treatment experienced patients.

Table 6: Adverse Events from RESIST Trials

	RESIST 1 and 2	
Randomized to	**TPV/r**	**CPI/r**
Subjects (n)	748	737
Study Discontinuation	30.0%	68.7%
Adverse event	10.4%	4.7%
Treatment failure	9.1%	42.9%
Other	10.4%	21.0%
Overall Incidence of AEs	84%	78%
Most Common AEs		
Diarrhea	23%	18%
Nausea	14%	7%
Vomiting	7%	7%
Pyrexia	9%	7%
Headache	9%	6%
Rash	11%	10%
Incidence of rash in females	14%	9%
Laboratory abnormality		
AST/ALT elevations (grade 3-4)	9.8%	3.6%
Triglyceride elevations (grade 3-4)	21%	11%
Grade 3-4 AEs	18%	15%
SAEs	13%	12%

In studies of TPV in healthy volunteers, there was an unexplained increase in rash in females (as high as 33%) which was supported by data from the RESIST trials, but, because of the small number of women in these trials and the relatively low CD4+ counts of the women, no definitive conclusions could be made and further investigation is planned. Tipranavir does contain a

sulfonamide component, and caution should be used in patients with a known sulfonamide allergy.

The other major safety concern throughout the TPV drug development program has been hepatotoxicity. Detailed exposure-response analyses indicate that ALT increases are associated with increased TPV exposures. In the RESIST trials, significantly more patients on the TPV/r arm developed treatment emergent grade 3 or 4 ALT or AST elevations compared to the CPI/r arm. Because TPV/r can cause serious liver toxicity, liver function tests should be performed at initiation of therapy with TPV/r and monitored frequently throughout the duration of treatment. Caution should be used when prescribing TPV/r to patients with elevated transaminases, Hepatitis B or C co-infection, or other underlying hepatic impairment.

Common Adverse Events

Toxicities and adverse reactions/events for PIs can be classified into acute and those due to chronic exposure. Many of the acute reactions are limited in scope and can be managed with OTC and/or prescription products and can be safely continued. Those adverse drug reactions which occur due to chronic exposure are generally class-related toxicities and can be potentially serious and may limit the patients' ability or willingness to remain on therapy. Class-related toxicities for PIs include hyperglycemia, fat maldistribution (peripheral fat wasting and central adiposity), possible increased bleeding and factor VIII requirements in hemophiliacs, cardiovascular effects, insulin resistance/diabetes mellitus, avascular necrosis, osteopenia, and osteoporosis. Common toxicities for individual agents are listed below.

Table 7: Common PI Toxicities

Drug	Most common side effects
atazanavir	Indirect hyperbilirubinemia, prolongation of PR interval and asymptomatic 1st degree AV block, rash, jaundice/icterus
fosamprenavir	Rash (especially in patients with sulfa allergy), diarrhea, nausea, vomiting, headache, hyperlipidemia (especially triglycerides), elevated transaminases
indinavir	Nephrolithiasis/urolithiasis (12.4%), tubulointerstitial nephritis, indirect hyperbilirubinemia, hyperlipidemia, headache, GI intolerance, alopecia, asthenia, metallic taste, hemolytic anemia, hepatic failure
Lopinavir/r	GI intolerance, asthenia, hyperlipidemia (especially hypertriglyceridemia), elevated transaminases
nelfinavir	diarrhea, bloating, hyperlipidemia
ritonavir	nausea, diarrhea, vomiting, paresthesias (circumoral and peripheral), hyperlipidemia (especially hypertriglyceridemia), elevated transaminases, asthenia, taste perversions
saquinavir	Nausea, diarrhea, headache, elevated transaminases, hyperlipidemia
tipranavir	Elevated transaminases and hepatotoxicity, hyperlipidemia, rash (particularly in women)

Precautions/Contraindications

Precautions

Most of the precautions for Tipranavir and the PI class reflect the multitude of drug interactions when these agents are combined with other drugs highly dependent on CYP3A, and side effect profiles, particularly those regarded as class effects. Drug interactions will be discussed in greater detail in the following section. Warnings that PIs have been associated with new onset or exacerbations of diabetes mellitus and hyperglycemia and precautions about using PIs in patients with hemophilia or hepatic impairment, and the association of hyperlipidemia and fat redistribution with PI use are listed for all PIs, including TPV. Patients prescribed TPV/r are at risk for the possible development of mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity. The rash has been accompanied by joint pain or stiffness, throat tightness, or generalized pruritus, and has been reported in both men and women, with an

increased frequency in women. Tipranavir should be used with caution in patients with a known sulfonamide allergy as tipranavir contains a sulfonamide moiety.

Contraindications
Tipranavir is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency. The tipranavir label includes a Black Box warning regarding hepatoxicity. Co-administration of TPV with low dose ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. The warning states that extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients are at an increased risk. Liver function tests should be performed prior to initiating therapy with TPV/r, and frequently thereafter throughout the duration of treatment. There are also several drugs which concomitant tipranavir administration is contraindicated and these will be discussed in the following section.

Look-alike / Sound-alike (LA / SA) Error Risk Potential (ANALYSIS PENDING)

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name <*generic name*>: <*list LA/SA names*>

LA/SA for trade name <*trade name*>: <*list LA/SA names*>

Provide a list of the generic and trade drug names that have LA/SA error risk potential.

Drug Interactions

Tipranavir has undergone pharmacokinetic analysis with a number of co-administered antiretrovirals. Unexpected interactions were found with combinations of TPV and zidovudine and abacavir which resulted in decreased systemic exposures of the NRTIs by approximately 40%. Co-administration with enteric-coated didanosine was associated with a 10-20% reduction in didanosine levels. Based on the metabolic pathways for NRTIs, an interaction with TPV/r of this magnitude was unanticipated and the mechanisms are unknown. It is possible that the drug interaction between didanosine and TPV/r was due to food and may be minimized by separating the didanosine administration by at least 2 hours from the dose of TPV/r taken with food. Currently, no dose adjustments of ZDV, abacavir, or ddI are recommended. No significant interactions occur between TPV/r and the NNRTIs nevirapine or efavirenz. Conversely, when tipranavir, lopinavir, and ritonavir were co-administered, a 55% reduction in lopinavir systemic exposure and a 70% reduction in the Cmin of lopinavir occurred. Co-administration of tipranavir, saquinavir, and ritonavir resulted in a 76% reduction in saquinavir exposure and >80% reduction in the Cmin of saquinavir. Similarly, tipranavir, amprenavir, and ritonavir co-administration led to a 45% reduction in amprenavir systemic exposure and a 55% reduction in Cmin. Because of these significant pharmacokinetic interactions and the absence of having established appropriate doses for the combination of TPV/r and LPV, SQV, or APV, these combinations are not recommended.

Table 8: Drugs that are Contraindicated with Tipranavir

Drug Category	***Drugs***
Cardiac -	bepredil, amiodarone, flecainide, propafenone, quinidine
Lipid lowering	simvastatin, lovastatin
Anti-mycobacterial	rifampin /rifapentine
GI agents	cisapride

Neuroleptics	pimozide
Psychotropic –	midazolam, triazolam
Ergot alkaloids –	dihydroergotamine, ergonovine (various forms)
Herbs	St. John's wort

Table 9: Drugs that require Dose Modification or Cautious Use with Tipranavir

Drug Category	***Drug(s)***	***Effect on TPV***	***Effect on Coadministerd drug***
Antacids and buffered medications	antacids and buffered medications	↓	↔
Anesthetic	meperidine	↔	↓
Antidepressants	bupropion, nefazadone, SSRIs, amitriptyline, imipramine, desipramine	↔	↑
Anticoagulant	warfarin	↔	↕ monitor INR
Anti-mycobacterials	clarithromycin , rifabutin	↔	↑*
Antifungal	ketoconazole, itraconazole	↑	↑
Calcium Channel Blockers	diltiazem, felodipine, nicardipine, nisoldipine, verapamil	↔	↑
Corticosteroid	dexamethasone	↔	↓
HMG-CoA reductase inhibitor	atorvastatin	↑	↑ (start with 10mg)
Immunosupressants	cyclosporine, rapamycin, tacrolimus	↔	↕ monitor levels
Narcotic analgesic	methadone	↔	↓ by 50%
Oral contraceptives	ethinyl estradiol	↔	↓ by 50%
PDE5 inhibitors	sildenafil, tadalafil, vardenafil	↔	↑+

* rifabutin: ↓ dose by 75% , claritromycin: CrCl 30-60 ↓ dose by 50%, CrCl <30 ↓ dose by 75%

\+ starting dose not to exceed : sildenafil 25mg/q48h, tadalafil 10mg/q72h, vardenafil 2.5mg/q72h

Acquisition Costs

The table below presents the FSS drug price as listed on the PBM website as of 5/23/05 and the number of unique veterans in the Clinical Case Registry (CCR) with at least one prescription fill between March 1, 2005 and May 31, 2005.

Table 10: PI Acquisition Costs

Drug	$ per UOU	Qty	Cost / day	Cost/30Day	Cost/Year	Unique Patients* 3/05 - 5/05
atazanavir	482.73	60	$16.09	482.73	$5793	2142
fosamprenavir	372.07	60	$12.40	372.07	$4465	422
indinavir	318.17	180	$10.60	318.17	$3818	637
Lopinavir/r	403.57	180	$13.45	403.57	$4843	2603
Nelfinavir **(250mg)**	429.19	300	$14.30	429.19	$5150	1186
ritonavir	33.00	30	$2.20-$4.40	66.00-132.00	$792-$1584	2259
saquinavir	447.31	120	$14.91	447.31	$5368	359
Enfuvirtide*	1222.82	60	$40.76	1222.82	$14,674	212

tipranavir	669.18	120	$22.31	669.18	$8030	na

*fusion inhibitor but included for comparisons sake

Although the acquisition cost of tipranavir is high relative to other agents in this class, the addition of tipranavir to the formulary may result in a minimal overall increase to the overall formulary budget as the predicted use of tipranavir is expected to be limited. The price of tipranavir is expected to be $669.18, however as this agent must be administered with 200mg of ritonavir, the realized cost will be $801 ($669 for tipranavir + $132 for ritonavir). This is considerably higher than other PIs, yet lower than enfuvirtide, which is also used in highly experienced patients. In most clinical situations patients would already be on a different PI, so costs resulting from tipranavir initiation would really be the difference in shifting (from one PI to tipranavir). There would be some situations i.e. patients with highly resistant virus and limited options) where tipranavir might be added to an existing PI regimen. Many clinicians may not be inclined to prescribe tipranavir until more prospective clinical trials and safety data are available.

In the most recently completed quarter (FY05/Q1), there were over 14,000 veterans receiving non-investigational ARV therapy according to the National Clinical Case Registry (CCR). Sixty-nine percent of these patients are receiving at least one drug from the PI class. As only those antiretroviral experienced patients who have been on 2 prior PI regimens and have documented resistance to other PIs will be candidates for tipranavir, the number of patients meeting this criteria is much lower. Furthermore, considering that a proportion of these patients likely have moderate or severe hepatic insufficiency (thus tipranavir use is contraindicated), the number of potentially eligible patients will be even less. In some situations VA clinicians may be inclined to use tipranavir in conjunction with or in place of the fusion inhibitor, enfuvirtide, which is also indicated for highly experienced patients, so it is worth looking at use of that medication. Enfuvirtide was prescribed to 1.5% of all patients receiving ARVs in this past quarter. It is difficult to estimate how many of these patients would be initiated or switched to tipranavir in place of enfuvirtide, however, since the indications of these two drugs are similar, it may provide a rough estimation of potential patients. Because tipranavir is less expensive and easier to administer compared enfuvirtide, one might expect slightly higher use.

Conclusions

Tipranavir is a PI class antiretroviral approved for use in HIV positive treatment experienced patients. Tipranavir must be coadministered with ritonavir (200mg) to exert its therapeutic effect. Tipranavir helps to address a continued unmet clinical need for new drugs to treat patients with multidrug resistant HIV-1, and demonstrates unique resistance characteristics that offer potential therapeutic advantages to PI-experienced patients. Data for its use comes from 2 trials in highly experienced patients with triple antiretroviral class (NRTI, NNRTI, and PI) experience and with at least two failed PI-based regimens. Appropriate safeguards for the use of TPV/r must be considered however, given the limited inclusion criteria and open-label nature of the RESIST trials, TPV/r drug-drug interactions, safety considerations, and the impact of resistance on response. Particular attention will need to be paid to the monitoring and management of hepatotoxicity and rash. There is potential for concern in patients with HIV/HCV co-infection given the effects of TPV on liver enzymes and cautious use is warranted in patients with elevated transaminases, Hepatitis B or C coinfection or other underlying liver disease. There are no published data on the use of tipranavir in treatment naïve patients and therefore its use in this population is not recommended. Providers should be aware of the potential for drug interactions as the TPV/r combination inhibits CYP3A4 and 2D6.

Although clinical experience with tipranavir is limited, its favorable genetic profile may make it a useful agent for VA HIV clinicians in treating those highly ARV-experienced patients, resistant to all other PIs, particularly LPV/r. Treatment responses were significantly higher for TPV treated patients compared to those patients receiving a comparator PI. Conversely, its place in the DHHS guidelines remains undetermined, and serious side effects, particularly hepatotoxicity in this at risk population are of concern and will require diligent monitoring. The high price of

TPV+ritonavir reflects its unique role, however, also may necessitate specific criteria for clinical situations of when the drug should be used.

Recommendations

The unique role of tipranavir in highly treatment experienced HIV-infected patients with few remaining treatment options support the addition of tipranavir to the National formulary in a limited capacity fulfilling the great need for treatment for patients who are resistant to all other agents.

Ongoing Safety/Quality Issues to be Addressed

- The risk/benefit assessment of TPV/r given the data provided for safety and efficacy in the treatment of "heavily pretreated" HIV-infected individuals, especially those with underlying liver disease including Hepatitis B/C.
- Monitoring and management of hepatotoxicity during clinical use of TPV/r given the transaminase elevations data in healthy volunteers and HIV-infected patients in the development program
- Further investigation and characterization of rash in females receiving TPV/r given the limited available data in HIV-infected females.

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Appendix: Clinical Trials

TPV/r 500mg/200mg was compared to other ritonavir boosted PI regimens which were genotypically determined, through 24 weeks of a planned 96 week study. The randomizations were stratified according to both the pre-selected PI and on whether or not investigators intended to use enfuvirtide. In RESIST-1, 630 patients were randomized of which 620 were treated. In the comparator PI arm, 61% of patients were receiving LPV/r and 57% had genotypic resistance to their pre-selected PI. In RESIST-2, 880 patients were randomized, 863 patients were treated and 539 patients reached 24 weeks and were included in the analyses. Forty percent of patients were receiving amprenavir, 38% lopinavir/r, and 20% saquinavir in the comparator PI arm, and 74% had genotypic resistance to their pre-selected PI.

Patients in the RESIST trials were highly experienced having received a median of 12 prior antiretroviral agents and a median of 4 prior PIs. In both RESIST trials, because so many of the patients had genotypic and phenotypic resistance to their pre-selected PI, the comparator arm could be viewed as a sub-optimal control arm and results should be reviewed as TPV/r vs. suboptimal control. Because patients in the CPI/r arm had few active options to use with enfuvirtide, enfuvirtide was actually used as part of an OBR in only 22% of the CPI/r subjects compared to 28% of subjects in the TPV/r arm.

The primary efficacy endpoint in the RESIST trials is the proportion of subjects with a treatment response at 48 weeks (=1 log10 reduction from baseline HIV RNA in two consecutive measurements without prior evidence of treatment failure), however, the efficacy endpoint for the data submitted to the FDA is the proportion of subjects with a treatment response at 24 weeks. Treatment response in both RESIST trials were similar and significantly higher in the TPV/r treated group versus those in the CPI/r treated group ($p<0.0001$). For patients receiving TPV/r who also received ENF response rates were 58.2% compared to 25.8% in those receiving a CPI/r with enfuvirtide. For the FDA analysis, comparing changes in CD4 counts between the TPV/r and CPI/r groups at week 24 in both RESIST groups combined, the mean increase in CD4 cell counts were +58 and +40 cells/mm 3, respectively.

In regards to pre-selected PI resistance, TPV/r showed significantly greater treatment response than CPIs/r only when subjects were possibly or definitely resistant to their CPI/r. Both the type and number of baseline protease inhibitor mutations as well as use of additional active agents (e.g., enfuvirtide) affected TPV/r response rates. Change in viral load from baseline was greatest in those subjects receiving TPV/r and who had less than 5 baseline PI mutations. Subjects who had five or more baseline PI mutations and who received TPV/r without ENF began to lose antiviral activity between Weeks 4 and 8 with their HIV RNA trending back toward baseline by week 24. Those patients who received ENF and TPV/r, however, were able to sustain 1.5-2 log10 HIV RNA decreases through week 24. Of note, subjects in the CPI/r arm who also received enfuvirtide were also able to maintain 1.5 log10 decreases at week 24. When evaluating the proportion of responders by baseline phenotype, there was a 45% response with a 3-fold or less change in TPV IC50 at baseline compared to a 21% when the TPV baseline phenotype values were >3 to 10-fold and 0% when TPV baseline phenotype values were >10-fold.

One must interpret these data cautiously. Although treatment response for patients receiving TPV/r was greater than the treatment response for those receiving LPV/r, SQV/r, or APV/r, the comparator PI being used was not always “new” and was not always considered “genotypically available” on the baseline resistance report. For example, in the LPV/r stratum, if the LPV/r was “new” the treatment response was 45.3% in the TPV/r arm and 36.1% in the CPI/r arm (p=NS), however, if the LPV/r was “ongoing” the treatment response was 35.2% in the TPV/r arm and 10.7% in the CPI/r arm, a statistically significant result. Thus, in patients with other active PI options, TPV may not offer a significant benefit. Although there were some flaws in the design of the RESIST studies, virologic responses (defined as a confirmed 1 log10 or greater decrease in HIV RNA from baseline) were better in the tipranavir group and particularly in patients with less than 5 baseline PI mutations. The added virologic benefit of TPV/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 studies were not powered for mortality. The 24 week time-point may be too

premature to see any clinical endpoint differences, and the comparator arm's escape option at week 8 may have salvaged patients before being subjected to prolonged virologic failure and also resulted in a diminishing comparator arm. This escape clause and the open-label design of the RESIST trials make it somewhat difficult to discern treatment differences in some efficacy and safety parameters beyond 8 weeks of treatment.