National PBM Drug Monograph
Maraviroc (Selzentry)
November 2007
VHA Pharmacy Benefits Management Strategic Healthcare Group, the Medical Advisory Panel, and the Public Health Strategic Healthcare Group

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Maraviroc, a CCR5 co-receptor antagonist, is the first agent in this new class of antiretrovirals to receive FDA approval in the US.
- Maraviroc, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.
- Maraviroc selectively binds to human chemokine receptor CCR5 and inhibits the interaction of the envelope glycoprotein (gp120) from CCR5-tropic HIV-1 strains with CCR5. It demonstrated in vitro activity against CCR5-tropic HIV-1 strains including drug-resistant strains.
- The efficacy of maraviroc for the management of treatment experienced patients infected with CCR5 tropic HIV-1, has been demonstrated in two, randomized, double-blind, placebo-controlled superiority studies. In MOTIVATE 1 and MOTIVATE 2, treatment with maraviroc plus OBT consistently produced statistically significant differences favoring maraviroc over placebo plus OBT for the primary and secondary endpoints and demonstrated superiority compared with placebo. It was also demonstrated that compared to placebo, maraviroc provided greater efficacy regardless of a patient's screening HIV-1 RNA level, baseline CD4 count, and was independent of enfuvirtide use as part of OBT.
- Maraviroc was generally well tolerated in clinical trials. The most common treatment related adverse events occurring in >5% of patients treated with maraviroc were diarrhea, nausea, headache, pyrexia, and fatigue and were similar in the placebo group. Other events which occurred with more frequency in the maraviroc treated patients included elevated lipids, liver related events, infection-related adverse events, and an increase in the incidence of cardiac events related to coronary artery disease. Orthostatic hypotension can also occur, particularly in patients receiving CYP3A4 inhibitors.
- This agent is metabolized by CYP3A4 and is a P-gp substrate, therefore potential for drug interactions exist. Due to the potential for drug-drug interactions, the recommended dose of maraviroc is guided by the presence of concomitantly administered medications.
- HIV tropism switching from CCR5 to CXCR4 or D/M utilizing virus have been identified during maraviroc therapy in Phase III clinical trials. HIV tropism switch during maraviroc therapy is associated with an increased risk of maraviroc failure. Clinical resistance to maraviroc has also been detected.
- Place in therapy: Maraviroc has a role in the highly treatment-experienced HIV-infected patient who has evidence of virologic failure on their current antiretroviral regimen or documented intolerance/resistance to 3 classes of antiretrovirals and at least six months of treatment. Maraviroc should be utilized with a multi-drug regimen that includes, preferably, at least one additional active antiretroviral drug (if available) in addition to maraviroc. A tropism assay at baseline is required prior to initiation of maraviroc. The results of the tropism assay will take approximately 3 weeks and a prescription for maraviroc should not be written until results return indicating CCR5 tropism.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating maraviroc for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology[1,2]

The binding of envelope glycoprotein (gp120) to CD4 represents the first step of HIV-1 entry into the host cell. The second necessary step in viral entry requires binding of gp120 to human chemokine co-receptors. In vivo studies have identified CC chemokine receptor 5 (CCR5) and CX chemokine receptor 4 (CXCR4) as the most commonly utilized chemokine co-receptors of HIV-1. Gp-120 has the ability to bind to one or both of these receptors, which defines the tropism of the virus. Viruses that only use CCR5 as the co-receptor are referred to CCR5-tropic while viruses that only utilize CXCR4 as the co-receptor are referred as CXCR4-tropic. Patients may also have viruses that utilize both CCR5 and CXCR4 co-receptors (dual tropic) or have mixtures of virus that utilize CCR5 or CXCR4 (mixed-tropic virus). Commercially available assays do not distinguish between dual or mixed-tropic and thus report the present of dual/mixed (D/M) tropic virus. Maraviroc selectively binds to human chemokine receptor CCR5 and inhibits the interaction of the envelope glycoprotein (gp120) from CCR5-tropic HIV-1 strains with CCR5.

Pharmacokinetics[1,2]

Table 1. Pharmacokinetics of Maraviroc

Parameter	Maraviroc
$Cmax_{ss}$*	266 ng/mL
$Tmax_{ss}$	0.5-4 hours
AUC_{12}*	1513 ng.h/mL
$T_{1/2}$	14-18 hours
Vd	194L
Protein Binding	76% to human plasma proteins; moderate affinity for albumin and alpha-1 acid glycoprotein
Bioavailability	23% (100mg dose) and 33% (predicted for 300mg dose)
Metabolism	Metabolized by CYP3A4 to inactive metabolites
Elimination	20% in urine and 76% in feces

*PK parameters obtained in treatment-experienced HIV patients administered 300mg orally twice daily in Phase III clinical trials

Microbiology[1-3]

In vitro studies have demonstrated that maraviroc only inhibits CCR5-tropic HIV-1 replication. CXCR-4 and Dual tropic of Mixed-tropic HIV-1 virus are not inhibited by maraviroc (EC_{50} value > 10µM). Against 43 CCR5-tropic HIV-1 isolates, the IC_{50} was 0.51 nM and IC_{90} was 2.0 nM. The mean EC_{50} value for maraviroc against HIV-1 group M isolates (clades A-J) and group O isolates ranged from 0.1 to 1.25 nM. Maraviroc maintains in vitro activity against antiretroviral resistant strains including enfuvirtide-resistant strains. Against antiretroviral resistant strains (protease and reverse transcriptase inhibitors), the geometric IC_{50} n-fold change (defined as the clinical isolate IC_{50}/JRCSF reference virus IC_{50}) was 0.79 fold (95% CI 0.72-0.86) compared to 0.60 fold (95% CI, 0.55–0.65) for sensitive strains ($p<0.001$).

FDA Approved Indication[1]

Maraviroc, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

Current VA National Formulary Alternatives

Other FDA-approved formulary options for treatment-experienced patients include darunavir, enfuvirtide, and tipranavir. Each of these agents has a CFU.

Dosage and Administration[1]

Due to drug-drug interactions, the recommended dose of maraviroc in adults is guided by the presence of concomitantly administered medications (Table 2). Maraviroc may be administered with or without food.

Table 2. Recommendations for Maraviroc Dosage Regimen

Concomitant Medications	Maraviroc dosage regimen
CYP3A inhibitors (with or without CYP3A inducers) including • Protease inhibitors (except tipranavir/ritonavir) • Delavirdine • Ketoconazole, itraconazole, clarithromycin, telithromycin • Other strong CYP3A inhibitors (e.g., nefazadone)	150mg orally twice daily
Other concomitant medications including • Tipranavir/ritonavir • NRTIs, • Nevirapine • Enfuvirtide • Drugs that are not strong CYP3A inhibitors or inducers	300mg orally twice daily
CYP3A inducers including (without a strong CYP3A inhibitor) including • Efavirenz • Rifampin • Carbamazepine, phenobarbital, phenytoin	600mg orally twice daily

Hepatic Impairment: The pharmacokinetics of maraviroc has not been adequately evaluated in individuals with hepatic impairment. Since maraviroc is metabolized by the liver, concentrations may be increased in patients with hepatic impairment.

Renal Impairment: The pharmacokinetics of maraviroc has not been adequately evaluated in individuals with renal impairment. Since renal clearance accounts for ~25% of total clearance of maraviroc, concentrations may be increased in patients with renal impairment particularly with the co-administration of CYP3A4 inhibitors. These patients may experience dose-related adverse events such as dizziness and postural hypotension. The manufacturer recommends that patients with creatinine clearance of less than 50 mL/min should only receive maraviroc and CYP3A inhibitor if the potential benefit outweighs the risk. These patients should be monitored closely for adverse effects.

Pediatric: The pharmacokinetics, safety and efficacy has not be evaluated in patients <16 years of age. The manufacturer states that maraviroc should not be used in this patient population.

Efficacy[4-5]

The efficacy of maraviroc for the management of treatment experienced patients infected with CCR5 tropic HIV-1, has been demonstrated in two, randomized, double-blind, placebo-controlled superiority studies, A4001027 (MOTIVATE 1) and A4001028 (MOTIVATE 2). Twenty-four week data from these trials were presented to the FDA, ultimately leading to FDA-approval. These trials are ongoing and have only been published in abstract form.

In these studies, maraviroc 300mg QD (150mg in the presence of a protease inhibitor, except tipranavir, and delavirdine) and maraviroc 300mg BID (150mg in the presence of a protease inhibitor, except tipranavir, and delavirdine) were compared to placebo, all with an optimized background regimen (OBT). The primary objective was to confirm that maraviroc, in combination with an OBT, provided an additional reduction in plasma HIV-1 RNA level compared to OBT alone as measured by the mean changes from baseline in $\log_{10}$ plasma HIV-1 RNA level at week 24. Patients were screened four to six weeks prior to randomization to perform tropism testing and genotypic and phenotypic susceptibility. Included patients had at least six months of prior treatment with 3 of 4 antiretroviral classes, plasma HIV-RNA ≥5000 copies/mL, confirmed infection with CCR5 tropic HIV-1 at screening, and resistance testing to guide the investigators choice of OBT. Forty-four percent of patients screened did not have CCR5 tropic virus and were excluded. Patients were stratified by baseline HIV-1 RNA level (< or > 100,000 copies/mL), baseline CD4 count, and enfuvirtide use.

Endpoints

- The primary efficacy endpoint in MOTIVATE 1 and 2 was the change from baseline in $\log_{10}$ plasma HIV-1 RNA level at week 24.
- Secondary endpoints included the proportion of patients achieving undetectable viral loads (viral load < 400 copies/mL and <50 copies/mL), changes from baseline in CD4 cell count, and assessments of resistance and tropism shifts at baseline and at time of failure. Safety and tolerability of maraviroc, graded by severity and relation to maraviroc, was assessed by clinical and laboratory adverse events.

Summary of Efficacy Findings

Table 3. Efficacy Results at 24 weeks. Combined Analysis MOTIVATE1 and 2.

	Maraviroc QD	**Maraviroc BID**	**Placebo**	**p-value**
N	414	426	209	
Mean HIV-1 RNA change from baseline ($\log_{10}$ copies/mL) (97.5% CI, treatment difference)	-1.876 (-1.153, -0.623)	-1.960 (-1.237, -0.709)	-0.987	<0.001
VL < 50 copies/mL	44.0%	45.3%	23.0%	<0.0001
VL < 400 copies/mL	55.1%	61.0%	27.8%	<0.0001
Change in CD4 count from baseline (cells/mm3) (97.5% CI, treatment difference)	+109 (33.3, 69.2)	+106 (31.1, 66.9)	+57	
HIV RNA <50				
Baseline VL <100,000	61.3%	57.6%	34.2%	
Baseline VL >100,000	28.2%	34.7%	10.7%	

Change in CD4 count from baseline (cell/mm3)				
Patients with baseline VL <100,000	+94.8	+99.8	+58.6	
Patients with baseline VL >100,000	+128.3	+114.1	+53.5	

In MOTIVATE 1 and MOTIVATE 2, treatment with maraviroc plus OBT consistently produced statistically significant differences favoring maraviroc over placebo plus OBT for the primary and secondary endpoints (Table 3). Both dosing regimens of maraviroc demonstrated superiority compared with placebo. Furthermore, it was also demonstrated that compared to placebo, maraviroc provided greater efficacy regardless of a patient's screening HIV-1 RNA level, baseline CD4 count, and was independent of enfuvirtide use as part of OBT. There was no difference in reduction in viral load for patients receiving a 150mg dose of maraviroc (with delavirdine or any protease inhibitor except tipranavir) versus those receiving a 300mg dose and both demonstrated superiority over placebo. Lower baseline viral load, higher baseline CD4 count and greater overall susceptibility score (OSS, a measure of potentially active agents present in OBT) seemed to be predictors of improved response, by FDA analysis.

In the combined analyses, for those patients with a baseline viral load above 100,000 copies/mL, more achieved suppression to <50 copies/mL on maraviroc BID versus QD (34.7% versus 28.2%, respectively). The superiority of maraviroc over placebo for the primary endpoint analysis remained apparent across all baseline CD4 cell count strata, however, the reduction was less for patients with baseline CD4 counts < 50cells/mm3. Greater than 67% of patients in the combined analyses had an OSS≤ 2, confirming these were treatment experienced patients with few options. A treatment benefit was seen for maraviroc for all endpoints for each OSS, with the exception of an OSS ≥3. For each treatment group the proportion of patients with a viral load <50 copies/mL increased as OSS increased and the proportions of maraviroc treated patients were consistently higher than placebo. The mean change in HIV-RNA from baseline was greater in white patients than in black patients (-2.212 $\log_{10}$ copies/mL and -1.704 $\log_{10}$ copies/mL, respectively, in the BID arm) and there was less of a difference compared to placebo in the black sub-population, though the numbers in this subpopulation were small (-1.704 $\log_{10}$ copies/mL, n=50, vs. -1.515 $\log_{10}$ copies/mL, n=25).

Tropism and Resistance

To evaluate the potential concern of HIV tropism switches from CCR5 to CXCR4 utilizing virus, tropism changes and resistance were monitored in the clinical trials and as-treated analyses performed. About 50% to 60% of patients failed with CXCR4 or dual/mixed (D/M) tropic virus in the maraviroc arms compared to over 80% of patients in the placebo arm who failed with CCR5 tropic virus, indicating the occurrence of tropism shifts while receiving maraviroc treatment (Table 4). A background change in tropism result between screening and baseline occurred in approximately 8% of patients. Of note, the tropism assay cannot reliably detect CXCR4 tropic virus if it is present in less than 10% of the sample and outgrowth of undetectable CXCR4 virus may contribute to future treatment failure. Patients who failed with CXCR4 or D/M virus had less of an increase in CD4 cell counts than those failing with CCR5 tropic virus. Of the patients receiving maraviroc who failed with CCR5 tropic virus, lower plateaus in the maximum percentage inhibition (MPI) to maraviroc were observed rather than changes in EC50 values. Changes in the V3 loop region of gp160, particularly substitutions at amino acid positions P13 or I26V, appeared to correlate with the presence of lower plateaus in MPI and maraviroc resistance. There was no difference between the maraviroc and placebo arms in the proportion of subjects who lost susceptibility to drugs in their OBT (43%).

Table 4. Tropism of Protocol Defined Treatment Failure and >400 copies/mL , Week 24 Combined Analyses

Tropism	Maraviroc QD (n=154)	Maraviroc BID (n=143)	Placebo (n=146)
CCR5	47%	34%	84%
CXCR4	12%	14%	0.7%
D/M	31%	43%	7.5%
Not reported/non-phenotypable	10%	10%	8%

FDA summary of the reasons for treatment failure in patients receiving maraviroc include a co-receptor "tropism switch" from CCR5 using virus to D/M or CXCR4 using virus, outgrowth of minor populations of CXCR4 using populations not detected at screening, resistance of CCR5 tropic virus to maraviroc, and development of resistance to OBT.

Adverse Events (Safety Data)[1-2, 4-5]

Adverse event reports from MOTIVATE 1 and 2 were combined to increase the probability of detecting events which could be related to maraviroc. Safety was further evaluated in A4001029, a Phase 2b safety study in treatment-experienced patients infected with non-CCR5 tropic HIV-1, which included dual/mixed tropic, CXCR4-tropic, and non-phenotypable virus.

Events were separated to those that occurred while on study drug (active) and those that occurred >7days after the active period (open-label). A slight excess of adverse events was observed in the maraviroc arms compared to placebo, but discontinuations due to adverse effects was similar between groups. Because the total duration of observed time was substantially longer in the maraviroc groups during the active period, adverse effects were also assessed by events per 100 subject-years of observation which may "enrich" events in arms with shorter treatment durations (i.e. placebo arm).

Given the mechanism of action of maraviroc and results of other CCR5 antagonist agents, particular adverse events were given extra attention. There was no evidence of an increase in malignancy with maraviroc. There appeared to be a modest increase in liver related adverse events, mostly elevated LFTs and bilirubin, in the maraviroc treated patients compared to the placebo treated patients. Similarly, a modest increase in the number of infection-related adverse events was observed in the maraviroc arm, particularly herpes virus infections, candidiasis, and influenza-like illness.

Although raised as a concern in pre-clinical trials, relative to placebo, maraviroc administered at a 300mg dose equivalent does not appear to be associated with an increased frequency of QTC prolongation, malignancy, or symptomatic postural hypotension (however this event did occur, rarely). A possible increase in the incidence of cardiac events related to coronary artery disease occurred in the maraviroc arm. More patients treated with maraviroc had elevations in cholesterol, LDL, and triglycerides than those in the placebo group.

The most common treatment related adverse events occurring in >5% of patients treated with maraviroc were diarrhea, nausea, headache, pyrexia, and fatigue and were similar in the placebo group.

Table 5. Adverse Events, Combined Analyses

	Maraviroc QD (n=414)	**Maraviroc BID (n=426)**	**Placebo (n=209)**
Total AEs	2242	2292	936
Total SAEs	13.5%	16.4%	17.2%
AEs resulting in discontinuation	3.9%	3.8%	3.8%
Treatment – related AEs (investigator determined)	1.7%	3.8%	1.0%
	Adverse events reported >2%, exceeding the rate in the placebo group by 3% or 3-fold Incidences per 100 years of patient exposure		
URI	15.8	17.7	11.6
Cough	14.3	19.4	10.5
Rash	11.1	13.5	8.5
Herpes simplex	5.6	10.2	6.1
Increased AST	2.7	5.8	1.0
Myalgia	7.6	4.6	1.0
Dysuria	2.3	4.2	1.0
Dyspnea	5.1	4.2	2.0
Increased ALT	2.7	3.8	1.0
Increased CPK	1.9	3.4	1.0
Influenza	5.5	2.3	0.0

Deaths
All deaths from all four phase 2b/3 trials were reviewed by the FDA and there was no evidence of an overall mortality imbalance in patients treated with maraviroc compared to placebo. The types of deaths observed were consistent with what would be expected in this patient population and there was no clustering of a specific cause of death in the maraviroc arms.

Contraindications/precautions[1]
Contraindications
None

Box warnings
- Hepatotoxicity has been reported in a patient administered maraviroc. Hepatotoxicity may be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE). Patients with signs and symptoms of hepatitis or allergic reaction should be immediately evaluated.

Warnings and Precautions

- Use with caution in patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C
- Use with caution in patients at increased risk of cardiovascular events. Cardiovascular events including myocardial ischemia and/or infarction were more commonly observed in patients who received maraviroc.
- Use caution when administering maraviroc in patients with a history of postural hypotension or on concomitant medication known to lower blood pressure.
- Immune reconstitution syndrome has been reported in patients treated with antiretroviral therapy including maraviroc.
- Patients should be monitored closely for evidence of infections while receiving maraviroc.
- Due to maraviroc's potential ability to affect immune surveillance, there may be a potential increased risk for malignancy. Long-term follow-up is needed to fully assess this risk.

Pregnancy/Nursing Mothers

- Pregnancy category B.
- Nursing mothers: Because of the potential for both HIV transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving maraviroc.

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

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 Selzentry

Celontin 150mg capsule, sildenafil citrate 20mg tablet, selsun topical lotion, symmetrel 100mg tablet, century tablet, selenium tablet, sertraline hydrochloride 150mg tablet, sulindac 150mg tablet, zantryl 150mg tablet, serevent powder inhalation, selseb topical shampoo.

LA/SA for Maraviroc

Malarone 250mg tablet, marinol 2.5mg capsule, avapro 150mg tablet, marezine 50mg tablet, miradon 50mg tablet (identified high alert drug per ISMP), mavik 1mg tablet, myrac 100mg tablet, deferasirox 125mg tablet, miradon 50mg tablet.

Drug-Drug Interactions[1]

Maraviroc is a substrate of CYP3A and p-glycoprotein (p-gp); therefore potential for drug interactions exist. A critical evaluation of potential drug-drug interactions should be conducted prior to initiation of this agent. Limited pharmacokinetic studies have been performed to date. Refer to PI for specific details of the pharmacokinetic studies.

- St. John's wort (hypericum perforatum) should NOT be co-administered with maraviroc. The co-administration of these two agents would lead to significantly decreased concentrations of maraviroc.
- Ketoconazole, ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, atazanavir and atazanavir/ritonavir have shown to increase the pharmacokinetic parameters of maraviroc.
- Efavirenz and rifampin have shown to decrease the Cmax and AUC of maraviroc.
- The combination of lopinavir/ritonavir and efavirenz as well as saquinavir/ritonavir and efavirenz has shown to increase the pharmacokinetic parameters of maraviroc.

- Tipranavir/ritonavir did not affect the pharmacokinetics of maraviroc.
- Maraviroc did not alter the pharmacokinetics of the following agents: zidovudine, lamivudine, midazolam, ethinylestradiol/levonorgestrel.

In vitro studies have shown that maraviroc is not an inhibitor of the CYP P450 isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, and 3A4). Evaluation with probe suggests that maraviroc is not an inducer of 3A4 but may have potential for inhibition of CYP2D6 at higher concentrations.

Tropism Testing[2-5]

A baseline tropism test must be obtained prior to the initiation of maraviroc to guide appropriateness of therapy. If the tropism assay indicates the presence of dual/mixed-tropic or CXCR4-tropic virus, maraviroc should not be initiated in these patients. A repeat tropism assay should only be performed if the provider is considering a change of treatment due to increasing VL and/or decreasing CD4 count. If CXCR4 or dual/mixed virus is detected during therapy, maraviroc should generally be discontinued. In failing patients who have CCR5 virus, a maraviroc resistance assay may also be necessary.

In treatment-experienced patients, studies have shown that, at baseline, 48-50% of patients have CCR5-tropic virus compared to 46-50% dual/mixed and 2-4% CXCR4. Furthermore, HIV tropism switching from CCR5 to CXCR4 or D/M utilizing virus have been identified during maraviroc therapy during Phase III clinical trials. HIV tropism switch during maraviroc therapy is associated with a greater risk of maraviroc failure (only 18% response versus 50% response). A tropism test is commercially available (Monogram Biosciences, Trofile™ co-receptor tropism assay), which costs about $1900 for a single tropism assay.

Acquisition Costs

The cost of maraviroc (one bottle of 60 tablets of 300mg or 150mg) is $649.60 (Big 4).

Table 10. Cost of Antiretroviral Agents for Treatment-Experienced Patients

Drug & Strength	Dosage Regimen	Cost Dose ($)	Cost/Year/patient ($)
Maraviroc 150mg, 300mg	150mg orally twice daily 300mg orally twice daily 600mg orally twice daily	$10.83 (Big 4) $10.83 (Big 4) $21.66 (Big 4)	$7905.90 $7905.90 $15,811.80
Enfuvirtide 90mg/mL	90mg subcutaneously twice daily	$21.00 (Big 4)	$15,330.00
Darunavir 300mg	600mg darunavir + 100mg ritonavir orally twice daily	$9.04 (FSS) + $1.16 (FSS)	$7,774.50
Tipranavir 250mg	500mg tipranavir + 200 ritonavir orally twice daily	$10.59 (FSS) + $2.32 (FSS)	$9,424.30

Conclusions[1-5]

Maraviroc, a CCR5 co-receptor antagonist, is the first agent in this new class of antiretrovirals to receive FDA approval in the US. The FDA has approved maraviroc for treatment-experienced adults infected with only CCR5–tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Maraviroc selectively binds to human chemokine receptor CCR5 and inhibits the interaction of the envelope glycoprotein (gp120) from CCR5-tropic HIV-1 strains with CCR5. This is the first antiretroviral that targets a human cellular receptor rather than a viral target such as protease enzyme or reverse transcriptase enzyme. Maraviroc has in vitro activity against CCR5-tropic HIV-1 strains including drug-resistant strains. Maraviroc should only be utilized in patients with CCR5-tropic HIV-1 strains; therefore, a baseline tropism test must be obtained to guide initiation of therapy (Note: only about 50% of patients will have CCR5-tropic virus at baseline and will be candidates to receive maraviroc; this should be factored into the overall cost of maraviroc treatment). HIV tropism switching from CCR5 to CXCR4 or D/M utilizing virus have been identified during maraviroc therapy in Phase III clinical trials. HIV tropism switch during maraviroc therapy is associated with maraviroc failure. Clinical resistance to maraviroc has also been detected. In MOTIVATE 1 and MOTIVATE 2, treatment with maraviroc plus OBT consistently produced statistically significant differences favoring maraviroc over placebo plus OBT for the primary endpoint (change from baseline in $\log_{10}$ plasma HIV-1 RNA level at week 24), secondary endpoints (viral load < 400 copies/mL, <50 copies/mL, and changes from baseline in CD4 cell count), and demonstrated superiority compared with placebo. Maraviroc was generally well tolerated in clinical trials. The most common treatment related adverse events were diarrhea, nausea, headache, pyrexia, and fatigue. Other events which occurred with more frequency in the maraviroc treated patients included elevated lipids, liver related events, infection-related adverse events, and an increase in the incidence of cardiac events related to coronary artery disease. Orthostatic hypotension can also occur, particularly in patients receiving CYP3A4 inhibitors. Labeling includes a box warning for hepatotoxicity.

Recommendations

Maraviroc has a role in the highly treatment-experienced HIV-infected patient who has evidence of virologic failure on their current antiretroviral regimen or documented intolerance/resistance to 3 classes of antiretrovirals and at least six months of treatment. Maraviroc should be utilized with a multi-drug regimen that includes, preferably, at least one additional active antiretroviral drug (if available) in addition to maraviroc. A tropism assay at baseline is required prior to initiation of maraviroc. The results of the tropism assay will take approximately 3 weeks and a prescription for maraviroc should not be written until results return indicating CCR5 tropism.

References:

1. Selzentry (Maraviroc) package insert, Pfizer Inc. August 2007.
2. FDA product review transcripts. April 24, 2007.
3. Dorr P, Westby M, Dobbs S. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrob Agents Chemother. 2005;49: 4721–4732.
4 Lalezari J, Goodrich J, DeJesus E. et al. Efficacy and safety of maraviroc plus optimized background therapy in viremia ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a Phase 2b/3 study in the US and Canada. Poster presented at the 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25-28; Los Angeles, CA, USA.
5. Nelson M, Fatkenheuer G, Konourina I. et al. Efficacy and safety of maraviroc plus optimized background therapy in viremia ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-week results. Poster presented at the 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25-28; Los Angeles, CA, USA.

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Citation	A4001027 (MOTIVATE 1) Lalezari J, Goodrich J, DeJesus E. et al. Efficacy and safety of maraviroc plus optimized background therapy in viremia ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a Phase 2b/3 study in the US and Canada. Poster presented at the 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25-28; Los Angeles, CA, USA.
Study Goals	To evaluate the safety and efficacy of maraviroc in triple-class antiretroviral treatment-experienced patients with HIV-1 infection.
Methods	**Study Design** The MOTIVATE-1 study is an ongoing randomized, placebo-controlled, double-blind, phase 2b/3, multicenter study in patients with CCR5-tropic virus at screening. Included subjects were randomized 1:2:2 to receive placebo, maraviroc qd+ an optimized background regimen (OBR), or maraviroc bid + OBR. The optimized background regimen included 3 to 6 antiretroviral drugs +/- low-dose ritonavir and was administered as open-label therapy. Maraviroc was dosed at 150mg once or twice daily in the presence of a protease inhibitor (except tipranavir) or delavirdine; otherwise a dose of 300mg once or twice daily was used. Patients were stratified by enfuvirtide use and baseline viral load (< or > 100,000 copies/mL). These are results of the 24 week interim analysis. The primary endpoint was the change from baseline in $\log_{10}$ HIV-RNA level at week 24. Other efficacy endpoints were the proportion of patients achieving viral suppression (defined as < 50 HIV copies/mL, and <400 HIV copies/mL), the portion of patients achieving ≥ 1 $\log_{10}$ reduction in HIV copies/mL by week 24, and difference and magnitude of change in CD4 cell count from baseline to week 24. Additionally, HIV-1 tropism was assessed at baseline and at the time of failure. **Data Analysis** The Full Analysis Set (FAS) population consisted of all randomized patients who received at least 1 study drug dose, both as randomized and as treated, both of which were used to analyze the primary endpoint. The FAS-as treated population was used for the analysis of all secondary endpoints. Analysis of percent responders was performed using the time to loss of virologic response (TLOVR) algorithm. Change in HIV-1 RNA from baseline was performed using a noncompleter equal failure (NC = F) analysis and immunologic response was measured using a last observation carried forward (LOCF) analysis.
Criteria	**Inclusion criteria** Male and female subjects were included in the study if they were 18 years of age or older who had received at least 6 months of prior treatment with at least 1 agent (2 agents for PIs) from 3 of 4 antiretroviral drug classes and or documented resistance to 3 of the 4 drug classes. Their plasma HIV-1 RNA had to be > 5,000 copies/mL. Patients with confirmed CCR5 tropic HIV-1 at screening were randomized. Patients with Hepatitis B or C were allowed to enter the study, although the numbers were small. **Exclusion criteria** Patients who were found to harbour dual/mixed (D/M) tropic virus, CXCR4-using virus, or patients whose virus was non-phenotypable.
Results	Of 601 patients randomized, 585 received ≥1 dose of study drug. Baseline characteristics were similar across treatment arms.

	<u>Baseline Characteristics</u>: *Median CD4 count and mean HIV-1 RNA:* • Placebo: 163 cells/mm3, and 4.84 $\log_{10}$ • Maraviroc QD: 168 cells/mm3, and 4.85 $\log_{10}$ • Maraviroc BID: 150 cells/mm3, and 4.86 $\log_{10}$ *OBT contained ≤2 active drugs:* • Placebo: 66.1% • Maraviroc QD: 68.5% • Maraviroc BID: 75.7% **<u>Primary Endpoint</u>:** *Mean change from baseline in $\log_{10}$ HIV-RNA level at week 24:* • Placebo + OBR (n=118): -1.03 • Maraviroc QD + OBR (n=232): -1.82 (97.5% CI, -1.14, -0.44) • Maraviroc BID + OBR (n=235): -1.95 (97.5% CI, -1.28, -0.57) **<u>Other Endpoints</u>:** *Mean CD4 increase from baseline (cells/mm^3):* • Placebo + OBR (n=118): +52 • Maraviroc QD + OBR (n=232): +107 (p<0.0001) • Maraviroc BID + OBR (n=235): +111 (p<0.0001) *Proportion of patients with viral load < 50 copies/mL:* • Placebo + OBR (n=118): 24.6% • Maraviroc QD + OBR (n=232): 42.2% (p=0.0006) • Maraviroc BID + OBR (n=235): 48.5% (p<0.0001) *Proportion of patients with viral load < 400 copies/mL:* • Placebo + OBR (n=118): 31.4% • Maraviroc QD + OBR (n=232): 54.7% (p<0.0001) • Maraviroc BID + OBR (n=235): 60.4% (p<0.0001)
Conclusions	The authors concluded that in this treatment-experienced population, maraviroc + OBR provided significantly superior virologic control and increases in CD4 cell counts compared with placebo + OBR.

Citation	A4001028 (MOTIVATE 2) Nelson M, Fatkenheuer G, Konourina I. et al. Efficacy and safety of maraviroc plus optimized background therapy in viremia ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-week results. Poster presented at the 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25-28; Los Angeles, CA, USA.
Study Goals	To evaluate the safety and efficacy of maraviroc in triple-class antiretroviral treatment-experienced patients with HIV-1 infection.
Methods	**Study Design** The MOTIVATE-2 study is an ongoing randomized, placebo-controlled, double-blind, phase 2b/3, multicenter, international study in patients with CCR5-tropic virus at screening. Included subjects were randomized 1:2:2 to receive placebo, maraviroc qd+ an optimized background regimen (OBR), or maraviroc bid + OBR. The optimized background regimen included 3 to 6 antiretroviral drugs +/- low-dose ritonavir and was administered as open-label therapy. Maraviroc was dosed at 150mg once or twice daily in the presence of a protease inhibitor (except tipranavir) or delavirdine; otherwise a dose of 300mg once or twice daily was used. Patients were stratified by enfuvirtide use and baseline viral load (< or > 100,000 copies/mL). These are results of the 24 week interim analysis. The primary endpoint was the change from baseline in $\log_{10}$ HIV-RNA level at week 24. Other efficacy endpoints were the proportion of patients achieving viral suppression (defined as < 50 HIV copies/mL, and <400 HIV copies/mL), the portion of patients achieving ≥ 1 $\log_{10}$ reduction in HIV copies/mL by week 24, and difference and magnitude of change in CD4 cell count from baseline to week 24. Additionally, HIV-1 tropism was assessed at baseline and at the time of failure. **Data Analysis** The Full Analysis Set (FAS) population consisted of all randomized patients who received at least 1 study drug dose, both as randomized and as treated, both of which were used to analyze the primary endpoint. The FAS-as treated population was used for the analysis of all secondary endpoints. Analysis of percent responders was performed using the time to loss of virologic response (TLOVR) algorithm. Change in HIV-1 RNA from baseline was performed using a noncompleter equal failure (NC = F) analysis and immunologic response was measured using a last observation carried forward (LOCF) analysis.
Criteria	**Inclusion criteria** Male and female subjects were included in the study if they were 18 years of age or older who had received at least 6 months of prior treatment with at least 1 agent (2 agents for PIs) fro 3 of 4 antiretroviral drug classes and or documented resistance to 3 of the 4 drug classes. Their plasma HIV-1 RNA had to be > 5,000 copies/mL. Patients with confirmed CCR5 tropic HIV-1 at screening were randomized. Patients with Hepatitis B or C were allowed to enter the study, although the numbers were small. **Exclusion criteria** Patients who were found to harbour dual/mixed (D/M) tropic virus, CXCR4-using virus, or patients whose virus was non-phenotypable.
Results	Of 475 patients randomized, 464 received ≥1 dose of study drug. Baseline characteristics were similar across treatment arms. **<u>Baseline Characteristics</u>:** *Median CD4 count and mean HIV-1 RNA:*

	• Placebo: 174 cells/mm3, and 4.89 log_{10} • Maraviroc QD: 174 cells/mm3, and 4.87 log_{10} • Maraviroc BID: 182 cells/mm3, and 4.84 log_{10} *OBT contained ≤2 active drugs:* • Placebo: 66.0% • Maraviroc QD: 62.6% • Maraviroc BID: 62.3% **<u>Primary Endpoint</u>:** *Mean change from baseline in log_{10} HIV-RNA level at week 24:* • Placebo + OBR (n=91): -0.93 • Maraviroc QD + OBR (n=182): -1.95 (97.5% CI, -1.43, -0.62) • Maraviroc BID + OBR (n=191): -1.97 (97.5% CI, -1.44, -0.64) **<u>Other Endpoints</u>:** *Mean CD4 increase from baseline (cells/mm^3):* • Placebo + OBR (n=91): +64 • Maraviroc QD + OBR (n=182): +112 (p<0.0001) • Maraviroc BID + OBR (n=191): +102 (p<0.0001) *Proportion of patients with viral load < 50 copies/mL:* • Placebo + OBR (n=91): 20.9% • Maraviroc QD + OBR (n=182): 45.6% (p<0.0001) • Maraviroc BID + OBR (n=191): 40.8% (p=0.0005) *Proportion of patients with viral load < 400 copies/mL:* • Placebo + OBR (n=91): 23.1% • Maraviroc QD + OBR (n=182): 55.5% (p<0.0001) • Maraviroc BID + OBR (n=191): 61.3% (p<0.0001)
Conclusions	The authors concluded that in this treatment-experienced population, maraviroc + OBR provided significantly superior virologic control and increases in CD4 cell counts compared with placebo + OBR.