Selzentry

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SELZENTRY safely and effectively. See full prescribing information.

SELZENTRY (maraviroc) tablets
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning
- **Hepatotoxicity has been reported. (5.1)**
- **May be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE). (5.1)**
- **Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. (5.1)**

----------INDICATIONS AND USAGE----------
SELZENTRY is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents (1).

Tropism and treatment history should guide the use of SELZENTRY (1).

----------DOSAGE AND ADMINISTRATION----------

When given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir), delavirdine (2, 7.1)	150 mg twice daily
With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers (2, 7.1)	300 mg twice daily
With CYP3A inducers including efavirenz (without a strong CYP3A inhibitor) (2, 7.1)	600 mg twice daily

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 150 mg and 300 mg (3).

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Use caution when administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C (5.1)
- More cardiovascular events including myocardial ischemia and/or infarction were observed in patients who received SELZENTRY. Use with caution in patients at increased risk of cardiovascular events (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>8% incidence) which occurred at a higher frequency compared to placebo are cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Coadministration with CYP3A inhibitors, including protease inhibitors (except tipranavir/ritonavir) and delavirdine, will increase the concentration of SELZENTRY (7.1)
- Coadministration with CYP3A inducers, including efavirenz may decrease the concentration of SELZENTRY (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- SELZENTRY should only be used in pregnant women if the potential benefit justifies the potential risk to the fetus (8.1)
- There are no data available in pediatric patients; therefore SELZENTRY should not be used in patients <16 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised 8/2007

FULL PRESCRIBING INFORMATION*

*Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

Hepatotoxicity has been reported with SELZENTRY use. Evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE) prior to the development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or allergic reaction following use of SELZENTRY should be evaluated immediately [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

SELZENTRY, 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.

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

The following points should be considered when initiating therapy with SELZENTRY:

- Tropism testing and treatment history should guide the use of SELZENTRY.
- Use of SELZENTRY is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group.
- The safety and efficacy of SELZENTRY have not been established in treatment-naïve adult patients or pediatric patients.

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

2 DOSAGE AND ADMINISTRATION

The recommended dose of SELZENTRY differs based on concomitant medications due to drug interactions (see Table 1). SELZENTRY can be taken with or without food. SELZENTRY must be given in combination with other antiretroviral medications.

Table 1 gives the recommended dose adjustments [*see Drug Interactions (7.1)*].

Table 1 Recommended Dosing Regimen

Concomitant Medications	SELZENTRY Dose
CYP3A inhibitors (with or without a CYP3A inducer)including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin, • other strong CYP3A inhibitors (e.g., nefazadone, telithromycin)	150 mg twice daily

Other concomitant medications, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300 mg twice daily
CYP3A inducers (without a strong CYP3A inhibitor) including: • efavirenz • rifampin • carbamazepine, phenobarbital, and phenytoin	600 mg twice daily

3 DOSAGE FORMS AND STRENGTHS

- 150 mg blue, oval film coated tablets debossed with "Pfizer" on one side and "MVC 150" on the other
- 300 mg blue, oval film coated tablets debossed with "Pfizer" on one side and "MVC 300" on the other

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

A case of possible SELZENTRY-induced hepatotoxicity with allergic features has been reported in a study of healthy volunteers. In addition, an increase in hepatic adverse events with SELZENTRY was observed during studies of treatment-experienced subjects with HIV infection, although there was no overall increase in ACTG Grade 3/4 liver function test abnormalities [*see Adverse Reactions (6)*]. Discontinuation of SELZENTRY should be considered in any patient with signs or symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms.

The safety and efficacy of SELZENTRY have not been specifically studied in patients with significant underlying liver disorders. In studies of treatment-experienced HIV-infected subjects, approximately 6% of subjects were co-infected with hepatitis B and approximately 6% were co-infected with hepatitis C. Due to the small number of co-infected subjects studied, no conclusions can be drawn regarding whether they are at an increased risk for hepatic adverse events with SELZENTRY administration. However, caution should be used when administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C.

5.2 Cardiovascular Events

Use with caution in patients at increased risk for cardiovascular events. Eleven subjects (1.3%) who received SELZENTRY had cardiovascular events including myocardial ischemia and/or infarction during the Phase 3 studies (total exposure 267 patient-years), while no subjects who received placebo had such events (total exposure 99 patient-years). These subjects generally had cardiac disease or cardiac risk factors prior to SELZENTRY use, and the relative contribution of SELZENTRY to these events is not known.

When SELZENTRY was administered to healthy volunteers at doses higher than the recommended dose, symptomatic postural hypotension was seen at a greater frequency than in placebo. However, when SELZENTRY was given at the recommended dose in HIV subjects in Phase 3 studies, postural hypotension was seen at a rate similar to placebo (approximately 0.5%). Caution should be used when administering SELZENTRY in patients with a history of postural hypotension or on concomitant medication known to lower blood pressure.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including maraviroc. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as infection with *Mycobacterium* avium, cytomegalovirus, *Pneumocystis* jirovecii, *Mycobacterium* tuberculosis, or reactivation of *Herpes* simplex and *Herpes* zoster), which may necessitate further evaluation and treatment.

5.4 Potential Risk of Infection

SELZENTRY antagonizes the CCR5 co-receptor located on some immune cells, and therefore could potentially increase the risk of developing infections. The overall incidence and severity of infection, as well as AIDS-defining category C infections, was comparable in the treatment groups during the Phase 3 studies of SELZENTRY. While there was a higher rate of certain upper respiratory tract infections reported in the SELZENTRY arm compared to placebo (20.0% versus 11.5%), there was a lower rate of pneumonia (2.1 % vs 4.8%) reported in patients receiving SELZENTRY. A higher incidence of Herpes virus infections (11.4 per 100 patient-years) was also reported in the SELZENTRY arm when adjusted for exposure compared to placebo (8.2 per 100 patient-years). Patients should be monitored closely for evidence of infections while receiving SELZENTRY.

5.5 Potential Risk of Malignancy

While no increase in malignancy has been observed with SELZENTRY, due to this drug's mechanism of action it could affect immune surveillance and lead to an increased risk of malignancy. Long-term follow-up is needed to more fully assess this risk.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety profile of SELZENTRY is primarily based on 840 HIV-infected subjects who received at least one dose of SELZENTRY during two Phase 3 trials. A total of 426 of these subjects received the indicated twice daily dosing regimen.

Assessment of treatment-emergent adverse events is based on the pooled data from two studies in subjects with CCR5-tropic HIV-1 (A4001027 and A4001028). The median duration of maraviroc therapy for subjects in these studies was 34 weeks, with the total exposure on SELZENTRY twice daily at 267 patient-years versus 99 patient-years on placebo. The population was 89% male and 84% white, with mean age of 46 years (range 17-75 years). Subjects received dose equivalents of 300 mg maraviroc once or twice daily.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse events reported with SELZENTRY twice daily therapy with frequency rates higher than placebo, regardless of causality, were cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain and dizziness. Additional adverse events that occurred with once daily dosing at a higher rate than both placebo and twice daily dosing were diarrhea, edema, influenza, esophageal candidiasis, sleep disorders, rhinitis, parasomnias, and urinary abnormalities. In these two studies, the rates of discontinuation due to adverse events were 3.8% in subjects receiving SELZENTRY twice daily + optimized background therapy (OBT) compared to 3.8% in those receiving placebo + OBT. Most of the adverse events reported were judged to be mild to moderate in severity. The data described below occurred with SELZENTRY twice daily dosing.

The total number of subjects reporting infections were 214 (50.2%) and 80 (38.3%) in the SELZENTRY twice daily and placebo groups, respectively. Correcting for the longer duration of exposure on SELZENTRY compared to placebo, the exposure-adjusted frequency (rate per 100 subject-years) of these events was similar: 126 and 118 for SELZENTRY and placebo, respectively.

Dizziness or postural dizziness occurred in 8.2% and 7.7% on SELZENTRY and placebo, respectively, with 2 subjects (0.5%) on SELZENTRY discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) discontinuing therapy due to dizziness.

Treatment-emergent adverse events, regardless of causality, from A4001027 and A4001028 are summarized in Table 2. Selected events occurring at ≥2% of subjects and at a numerically higher rate in subjects treated with SELZENTRY are included; events that occurred at a higher rate on placebo are not displayed.

Table 2
Percentage of Subjects with Selected Treatment-Emergent Adverse Events (All Causality)
(>2% on SELZENTRY and at a higher rate compared to placebo)
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Studies A4001027 and A4001028 (Pooled Analysis, Up to 48 Weeks)

	SELZENTRY Twice Daily* N=426 (%)	Exposure-adjusted rate (per 100 pt-yrs) PYE=267**	Placebo N=209 (%)	Exposure-adjusted rate (per 100 pt-yrs) PYE=99**
GASTROINTESTINAL DISORDERS				
Gastrointestinal and abdominal pains	8.2	14.1	7.7	17.1
Constipation	5.4	9.1	2.9	6.1
Dyspeptic signs/symptoms	2.8	4.6	2.4	5.2
Stomatitis, ulceration	2.6	4.2	1.4	3.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Pyrexia	12.0	20.9	8.1	18.1
Pain and discomfort	3.5	5.8	2.9	6.1
INFECTIONS AND INFESTATIONS * **				
Upper respiratory tract infection	20.0	36.9	11.5	27.1
Herpes Infection	6.8	11.4	3.8	8.2
Sinusitis	6.3	10.6	3.3	7.3
Bronchitis	5.9	9.7	4.3	9.4
Folliculitis	3.3	5.4	1.9	4.1
Condyloma acuminatum	2.1	3.4	1.0	2.0
Pneumonia	2.1	3.4	4.8	10.4
Influenza	1.6	2.7	0.5	1.0
METABOLISM AND NUTRITION DISORDERS				
Appetite disorders	7.3	12.5	6.2	13.7
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Musculoskeletal and connective tissue signs and symptoms	8.7	14.8	7.7	17.0
Joint related signs and symptoms	6.1	10.2	2.9	6.2
Muscle pains	2.8	4.6	0.5	1.0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED				
Skin neoplasms benign	2.6	4.2	1.4	3.0
NERVOUS SYSTEM DISORDERS				
Dizziness/postural dizziness	8.2	14.1	7.7	17.1
Paresthesias and dysesthesias	4.7	7.8	2.9	6.2

	SELZENTRY Twice Daily*	Exposure-adjusted rate (per 100 pt-yrs) PYE=267**	Placebo	Exposure-adjusted rate (per 100 pt-yrs) PYE=99**
Sensory abnormalities	4.0	6.6	1.4	3.1
Disturbances in consciousness	3.8	6.1	2.9	6.2
Peripheral neuropathies	3.1	5.0	2.9	6.2
PSYCHIATRIC DISORDERS				
Disturbances in initiating and maintaining sleep	7.0	11.9	4.3	9.4
Depressive disorders	3.5	5.7	2.9	6.1
RENAL AND URINARY DISORDERS				
Bladder and urethral symptoms	4.5	7.4	1.4	3.0
Urinary tract signs and symptoms	2.6	4.2	1.4	3.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Coughing and associated symptoms	12.7	22.1	4.8	10.5
Breathing abnormalities	3.3	5.3	1.9	4.1
Bronchospasm and obstruction	2.1	3.4	1.4	3.1
Paranasal sinus disorders	2.1	3.4	1.0	2.0
Respiratory tract disorders	2.1	3.4	1.4	3.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	9.6	16.5	4.8	10.7
Apocrine and eccrine gland disorders	4.5	7.4	3.8	8.4
Pruritus	3.8	6.2	1.9	4.1
Dermatitis and eczema	3.1	5.0	2.4	5.2
Lipodystrophies	2.8	4.6	0.5	1.0
VASCULAR DISORDERS				
Vascular hypertensive disorders	3.1	5.0	1.4	3.1

* 300 mg dose equivalent
** **PYE = patient years of exposure**

***MedDRA High Level Terms are shown in order to group related terms for all disorders except Infections and Infestations, which shows MedDRA Preferred Terms with the following related terms grouped:**

Bronchitis: bronchitis, acute bronchitis, bacterial bronchitis
Herpes simplex infection: Herpes simplex, Herpes virus, Herpes ophthalmic, proctitis Herpes,
Influenza: Influenza, influenza-like illness
Pneumonia: Pneumonia, lobar pneumonia, pneumonia bacterial, bronchopneumonia
Sinusitis: sinusitis, acute sinusitis, chronic sinusitis, sinobronchitis
Upper Respiratory Infection: upper respiratory tract infection, laryngitis, laryngopharyngitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, viral respiratory tract infection

Less Common Adverse Events

The following adverse events [defined as always serious by MedDRA-Preferred -(Critical)-Terms] occurred in <2% of SELZENTRY-treated patients. These events have been included because of their seriousness and either increased frequency on SELZENTRY or are potential risks due to the mechanism of action. Events attributed to the patient's underlying HIV infection are not listed.

Cardiac Disorders: unstable angina, acute cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, myocardial ischemia

Hepatobiliary Disorders: hepatic cirrhosis, hepatic failure, cholestatic jaundice

Infections and Infestations: *Clostridium* difficile colitis, viral meningitis, pneumonia, septic shock

Musculoskeletal and Connective Tissue Disorders: myositis, osteonecrosis, rhabdomyolysis, blood CK increased

Neoplasms benign, Malignant and Unspecified (including Cysts and Polyps): abdominal neoplasm, anal cancer, basal cell carcinoma, Bowen's disease, cholangiocarcinoma, lymphoma, metastases to liver, esophageal carcinoma, squamous cell carcinoma, squamous cell carcinoma of skin, tongue neoplasm (malignant stage unspecified)

Nervous System Disorders: cerebrovascular accident

Laboratory Abnormalities

Table 3 shows the treatment-emergent Grade 3-4 laboratory abnormalities that occurred in >2% of patients receiving SELZENTRY.

Table 3
Maximum Shift in Laboratory Test Values (Without Regard to Baseline)
Incidence ≥2% of Grade 3-4 Abnormalities (ACTG Criteria)

Studies A4001027 and A4001028 (Pooled Analysis, Up to 48 Weeks)

Laboratory Parameter Preferred Term, %	Limit	SELZENTRY Twice daily + OBT N =421* %	Placebo + OBT N =207* %
Aspartate aminotransferase	>5.0x ULN	4.5	2.9
Alanine aminotransferase	>5.0x ULN	2.4	3.4
Total bilirubin	>5.0x ULN	5.7	5.3
Amylase	>2.0x ULN	5.5	5.8
Lipase	>2.0x ULN	4.9	6.3
Absolute neutrophil count	<750/mm^3	3.8	1.9

* Percentages based on total patients evaluated for each laboratory parameter

7 DRUG INTERACTIONS

7.1 Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc

Maraviroc is a substrate of CYP3A and Pgp and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters. Therefore, a dose adjustment may be required when maraviroc is coadministered with those drugs [see *Dosage and Administration (2)*].

Concomitant use of maraviroc and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of maraviroc with St. John's wort is expected to substantially decrease maraviroc concentrations and may result in suboptimal levels of maraviroc and lead to loss of virologic response and possible resistance to maraviroc.

For additional drug interaction information see *Clinical Pharmacology (12.3)*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with maraviroc in rats at exposures (AUC) approximately 20-fold higher and in rabbits at approximately 5-fold higher than human exposures at the recommended daily dose (up to 1000 mg/kg/day in rats and 75 mg/kg/day in rabbits). During the pre-and post-natal development studies in the offspring, development of the offspring, including fertility and reproductive performance, was not affected by the maternal administration of maraviroc.

However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SELZENTRY should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to SELZENTRY and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV infection. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. It is not known whether maraviroc is secreted into human milk. **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 SELZENTRY.**

8.4 PEDIATRIC USE

The pharmacokinetics, safety and efficacy of maraviroc in patients <16 years of age have not been established. Therefore, maraviroc should not be used in this patient population.

8.5 Geriatric Use

There were insufficient numbers of subjects aged 65 and over in the clinical studies to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering SELZENTRY in elderly patients, also reflecting the greater frequency of decreased hepatic and renal function, of concomitant disease and other drug therapy.

8.6 Renal Impairment

The safety and efficacy of maraviroc have not been specifically studied in patients with renal impairment, therefore maraviroc should be used with caution in this population. In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc. Maraviroc concentrations may be increased in patients with renal impairment, especially when CYP3A inhibitors are coadministered. Patients with a creatinine clearance of less than 50 mL/min who receive maraviroc and a CYP3A inhibitor may be at an increased risk of adverse effects related to increased maraviroc concentrations, such as dizziness and postural hypotension. Thus, patients with a creatinine clearance of less than 50 mL/min should receive maraviroc and a CYP3A inhibitor only if the potential benefit is felt to outweigh the risk, and they should be monitored for adverse effects.

8.7 Hepatic Impairment

The pharmacokinetics of maraviroc have not been sufficiently studied in patients with hepatic impairment. Because maraviroc is metabolized by the liver, concentrations are likely to be increased in these patients [*see Warnings and Precautions (5.1)*].

8.8 Gender

Population pharmacokinetic analysis of pooled Phase 1/2a data indicated gender (female: n=96, 23.2% of the total population) does not affect maraviroc concentrations. Dosage adjustment based on gender is not necessary

8.9 Race

Population pharmacokinetic analysis of pooled Phase 1/2a data indicated exposure was 26.5% higher in Asians (N=95) as compared to non-Asians (n=318). However, a study designed to evaluate pharmacokinetic differences between Caucasians (n=12) and Singaporeans (n=12) showed no difference between these two populations. Only 14 Black subjects were included in the population pharmacokinetic analysis. No dosage adjustment based on race is needed.

10 OVERDOSAGE

The highest dose administered in clinical studies was 1200 mg. The dose limiting adverse event was postural hypotension, which was observed at 600 mg. While the recommended dose for SELZENTRY in patients receiving a CYP3A inducer without a CYP3A inhibitor is 600 mg twice daily, this dose is appropriate due to enhanced metabolism.

Prolongation of the QT interval was seen in dogs and monkeys at plasma concentrations 6 and 12 times, respectively, those expected in humans at the intended exposure of 300 mg equivalents twice daily. However, no significant QT prolongation was seen in the studies in treatment-experienced patients with HIV using the recommended doses of maraviroc or in a specific pharmacokinetic study to evaluate the potential of maraviroc to prolong the QT interval [*see Clinical Pharmacology (12.3)]*

There is no specific antidote for overdose with maraviroc. Treatment of overdose should consist of general supportive measures including keeping the patient in a supine position, careful assessment of patient vital signs, blood pressure and ECG.

If indicated, elimination of unabsorbed active maraviroc should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since maraviroc is moderately protein bound, dialysis may be beneficial in removal of this medicine.

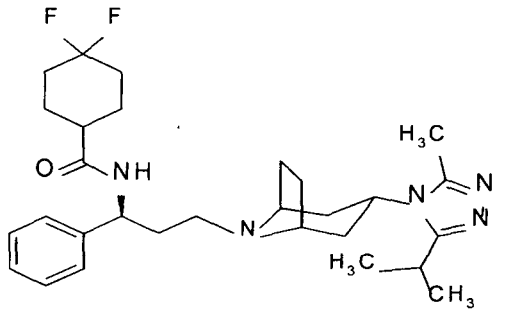
11 DESCRIPTION

SELZENTRY (maraviroc) is a selective, slowly reversible, small molecule antagonist of the interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells.

SELZENTRY is available as film-coated tablets for oral administration containing either 150 or 300 mg of maraviroc and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate (anhydrous), sodium starch glycolate, and magnesium stearate. The film-coat [Opadry® II Blue (85G20583)] contains FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc and titanium dioxide.

Maraviroc is chemically described as 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide.

The molecular formula is $C_{29}H_{41}F_2N_5O$ and the structural formula is:



Maraviroc is a white to pale colored powder with a molecular weight of 513.67. It is highly soluble across the physiological pH range (pH 1.0 to 7.5).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Maraviroc is an antiviral drug. [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Exposure Response Relationship

The relationship between maraviroc mean predicted plasma trough concentration (C_{min}) (1-9 samples per patient taken on up to 7 visits) and virologic response was evaluated in 973 treatment-experienced HIV-1-infected subjects in studies A4001027 and A4001028. The C_{min}, baseline viral load, baseline $CD4^+$ cell count and overall sensitivity score (OSS) were found to be important predictors of virologic success (defined as viral load < 400 copies/mL at 24 weeks). Table 4 illustrates the proportion of patients with virologic success (%) within each C_{min} quartile for 150 mg twice daily and 300 mg twice daily groups.

Table 4 Patients with Virologic Success by C_{min} Quartile

	150 mg BID (with CYP3A inhibitors)			300 mg BID (without CYP3A inhibitors)		
	n	Median C_{min}	% patients with virologic success	n	Median C_{min}	% patients with virologic success
Placebo	160		30.6	35		28.6
Q1	78	33	52.6	22	13	50.0
Q2	77	87	63.6	22	29	68.2
Q3	78	166	78.2	22	46	63.6
Q4	78	279	74.4	22	97	68.2

Effects on Electrocardiogram

A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female volunteers was conducted with three single oral doses of maraviroc and moxifloxacin. The placebo-adjusted mean maximum (upper 1-sided 95% CI) increases in QTc from baseline after 100, 300 and 900 mg of maraviroc were –2 (0), -1 (1), and 1 (3) msec, respectively, and 13 (15) msec for moxifloxacin 400 mg. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

12.3 Pharmacokinetics

Table 5 Mean Maraviroc Pharmacokinetic Parameters

	Maraviroc dose	N	AUC_{12} (ng.h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Healthy volunteers (phase 1)	300 mg twice daily	64	2908	888	43.1
Asymptomatic HIV patients (phase 2a)	300 mg twice daily	8	2550	618	33.6
Treatment-experienced HIV patients (phase 3)*	300 mg twice daily	94	1513	266	37.2
	150 mg twice daily (+ CYP3A inhibitor)	375	2463	332	101

* the estimated exposure is lower compared to other studies possibly due to food effect, compliance and concomitant medications.

Absorption

Peak maraviroc plasma concentrations are attained 0.5-4h following single oral doses of 1-1200 mg administered to uninfected volunteers. The pharmacokinetics of oral maraviroc are not dose proportional over the dose range.

The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg. Maraviroc is a substrate for the efflux transporter P-glycoprotein.

Effect of Food on Oral Absorption

Coadministration of a 300mg tablet with a high fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers. There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc [*see Clinical Studies (14)*]. Therefore, maraviroc can be taken with or without food at the recommended dose [*See Dosage and Administration (2)*].

Distribution

Maraviroc is bound (approximately 76%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. The volume of distribution of maraviroc is approximately 194L.

Metabolism

Studies in humans and in vitro studies using human liver microsomes and expressed enzymes have demonstrated that maraviroc is principally metabolized by the cytochrome P450 system to metabolites that are essentially inactive against HIV-1. In vitro studies indicate that CYP3A is the major enzyme responsible for maraviroc metabolism. In vitro studies also indicate that polymorphic enzymes CYP2C9, CYP2D6 and CYP2C19 do not contribute significantly to the metabolism of maraviroc.

Maraviroc is the major circulating component (~42% drug related radioactivity) following a single oral dose of 300 mg [^{14}C]-maraviroc. The most significant circulating metabolite in humans is a secondary amine (~22% radioactivity) formed by N-dealkylation. This polar metabolite has no significant pharmacological activity. Other metabolites are products of mono-oxidation and are only minor components of plasma drug related radioactivity.

Excretion

The terminal half-life of maraviroc following oral dosing to steady-state in healthy subjects was 14-18 hours. A mass balance/excretion study was conducted using a single 300mg dose of ^{14}C-labeled maraviroc. Approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the feces over 168 hours. Maraviroc was the major component present in urine (mean of 8% dose) and feces (mean of 25% dose). The remainder was excreted as metabolites.

Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc

Maraviroc is a substrate of CYP3A and Pgp and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters. The CYP3A/Pgp inhibitors

ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir and atazanavir all increased the C_{max} and AUC of maraviroc [see Table 6]. The CYP3A inducers rifampin and efavirenz decreased the C_{max} and AUC of maraviroc [see Table 6].

Tipranavir/ritonavir (net CYP3A inhibitor/Pgp inducer) did not affect the steady state pharmacokinetics of maraviroc. Co-trimoxazole and tenofovir did not affect the pharmacokinetics of maraviroc (see Table 6).