

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-128**

**LABELING**

## 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](http://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

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## 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: <ul style="list-style-type: none"><li>• protease inhibitors (except tipranavir/ritonavir)</li><li>• delavirdine</li><li>• ketoconazole, itraconazole, clarithromycin,</li><li>• other strong CYP3A inhibitors (e.g., nefazadone, telithromycin)</li></ul>	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: <ul style="list-style-type: none"> <li>• efavirenz</li> <li>• rifampin</li> <li>• carbamazepine, phenobarbital, and phenytoin</li> </ul>	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  $\geq 2\%$  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)**  
**( $\geq 2\%$  on SELZENTRY and at a higher rate compared to placebo)**

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

	SELZENTRY Twice Daily*	Exposure- adjusted rate (per 100 pt-yrs) PYE=267**	Placebo	Exposure- adjusted rate (per 100 pt-yrs) PYE=99**
	N=426 (%)		N=209 (%)	
<b>GASTROINTESTINAL DISORDERS</b>				
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
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>				
Pyrexia	12.0	20.9	8.1	18.1
Pain and discomfort	3.5	5.8	2.9	6.1
<b>INFECTIONS AND INFESTATIONS ***</b>				
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
<b>METABOLISM AND NUTRITION DISORDERS</b>				
Appetite disorders	7.3	12.5	6.2	13.7
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>				
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
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED</b>				
Skin neoplasms benign	2.6	4.2	1.4	3.0
<b>NERVOUS SYSTEM DISORDERS</b>				
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
<b>PSYCHIATRIC DISORDERS</b>				
Disturbances in initiating and maintaining sleep	7.0	11.9	4.3	9.4
Depressive disorders	3.5	5.7	2.9	6.1
<b>RENAL AND URINARY DISORDERS</b>				
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
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>				
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
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>				
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
<b>VASCULAR DISORDERS</b>				
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  $\geq$ 2% of Grade 3-4 Abnormalities (ACTG Criteria)

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

Laboratory Parameter Preferred Term, %	Limit	SELZENTRY	Placebo + OBT
		Twice daily + OBT  N = 421* %	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 <sup>3</sup>	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.

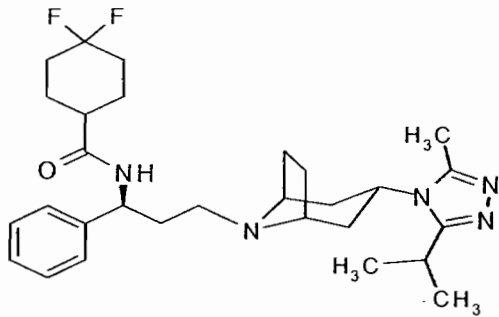
## 11 DESCRIPTION

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

The molecular formula is C<sub>29</sub>H<sub>41</sub>F<sub>2</sub>N<sub>5</sub>O 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<sup>+</sup> 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  $\geq 60$  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 <sub>12</sub> (ng·h/mL)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (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<sub>max</sub> 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 [<sup>14</sup>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 <sup>14</sup>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).

**Table 6: Effect of Co-administered Agents on the Pharmacokinetics of Maraviroc**

Co-administered drug and dose	N	Maraviroc Dose	Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			C <sub>min</sub>	AUC <sub>tau</sub>	C <sub>max</sub>
<b>CYP3A and/or P-gp Inhibitors</b>					
Ketoconazole 400 mg QD	12	100 mg BID	3.75 (3.01-4.69)	5.00 (3.98, 6.29)	3.38 (2.38, 4.78)
Ritonavir 100 mg BID	8	100 mg BID	4.55 (3.37-6.13)	2.61 (1.92, 3.56)	1.28 (0.79, 2.09)
Saquinavir (soft gel capsules) /ritonavir 1000 mg/100 mg BID	11	100 mg BID	11.3 (8.96-14.1)	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
Lopinavir/ritonavir 400 mg/100 mg BID	11	300 mg BID	9.24 (7.98-10.7)	3.95 (3.43, 4.56)	1.97 (1.66, 2.34)
Atazanavir 400 mg QD	12	300 mg BID	4.19 (3.65-4.80)	3.57 (3.30, 3.87)	2.09 (1.72, 2.55)
Atazanavir/ritonavir 300 mg/100 mg QD	12	300 mg BID	6.67 (5.78-7.70)	4.88 (4.40, 5.41)	2.67 (2.32, 3.08)
<b>CYP3A and/or P-gp Inducers</b>					
Efavirenz 600 mg QD	12	100 mg BID	0.55 (0.43-0.72)	0.552 (0.492, 0.620)	0.486 (0.377, 0.626)
Rifampicin 600 mg QD	12	100 mg BID	0.22 (0.17-0.28)	0.368 (0.328, 0.413)	0.335 (0.260, 0.431)
Nevirapine* 200 mg BID (+ lamivudine 150 mg BID, tenofovir 300 mg QD)	8	300 mg SD	-	1.01 (0.65, 1.55)	1.54 (0.94, 2.51)
<b>CYP3A and/or P-gp Inhibitors and Inducers</b>					
Lopinavir/ritonavir + efavirenz 400 mg/100 mg BID + 600 mg QD	11	300 mg BID	6.29 (4.72-8.39)	2.53 (2.24, 2.87)	1.25 (1.01, 1.55)
Saquinavir(soft gel capsules) /ritonavir + efavirenz 1000 mg/100 mg BID + 600 mg QD	11	100 mg BID	8.42 (6.46-10.97)	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)
Tipranavir/ritonavir 500 mg/200 mg BID	12	150 mg BID	1.80 (1.55-2.09)	1.02 (0.850, 1.23)	0.86 (0.61, 1.21)

\* Compared to historical data

*Effect of Maraviroc on the Pharmacokinetics of Concomitant Drugs*

Maraviroc is unlikely to inhibit the metabolism of co-administered drugs metabolized by the following cytochrome P enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A) because maraviroc did not inhibit activity of those enzymes at clinically relevant concentrations in vitro.

Drug interaction studies were performed with maraviroc and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions [see Table 6]. Maraviroc had no effect on the pharmacokinetics of zidovudine or lamivudine. Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinylestradiol and levonorgestrel, no effect on the urinary 6 $\beta$ -hydroxycortisol/cortisol ratio, suggesting no induction of CYP3A in vivo. Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg twice daily or less in vivo. However, there was 234% increase in debrisoquine MR on treatment compared to baseline at 600 mg once daily, suggesting potential inhibition of CYP2D6 at higher dose.

## 12.4 MICROBIOLOGY

### *Mechanism of Action*

Maraviroc is a member of a therapeutic class called CCR5 co-receptor antagonists. Maraviroc selectively binds to the human chemokine receptor CCR5 present on the cell membrane, preventing the interaction of HIV-1 gp120 and CCR5 necessary for CCR5-tropic HIV-1 to enter cells. CXCR4-tropic and dual-tropic HIV-1 entry is not inhibited by maraviroc.

### *Antiviral Activity in Cell Culture*

Maraviroc inhibits the replication of CCR5-tropic laboratory strains and primary isolates of HIV-1 in models of acute T-cell infection. The mean EC<sub>50</sub> value (50% effective concentration) for maraviroc against HIV-1 group M isolates (clades A to J) and group O isolates ranged from 0.1 to 1.25 nM (0.05 to 0.64 ng/mL) in cell culture.

When used with other antiretroviral agents in cell culture, the combination of maraviroc was not antagonistic with NNRTIs (delavirdine, efavirenz and nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine and zidovudine), or protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir). Maraviroc was additive/synergistic with the HIV fusion inhibitor enfuvirtide. Maraviroc was not active against CXCR4-tropic and dual-tropic viruses (EC<sub>50</sub> value >10  $\mu$ M). The antiviral activity of maraviroc against HIV-2 has not been evaluated.

### *Resistance in Cell Culture*

HIV-1 variants with reduced susceptibility to maraviroc have been selected in cell culture, following serial passage of two CCR5-tropic viruses (CC1/85 and RU570). The maraviroc-resistant viruses remained CCR5-tropic with no evidence of a change from a CCR5-tropic virus to a CXCR4-using virus. Two amino acid residue substitutions in the V3-loop region of the HIV-1 envelope glycoprotein (gp160), A316T and I323V (HXB2 numbering) were shown to be necessary for the maraviroc-resistant phenotype in the HIV-1 isolate CC1/85. In the RU570 isolate a 3-amino acid residue deletion in the V3 loop,  $\Delta$ QAI (HXB2 positions 315-317), was associated with maraviroc-resistance. The relevance of the specific gp120 mutations observed in maraviroc-resistant isolates selected in cell culture to clinical maraviroc resistance is not known. Maraviroc-resistant viruses were characterized phenotypically by concentration response curves that did not reach 100% inhibition in phenotypic drug assays, rather than increases in EC<sub>50</sub> values.

### *Clinical Resistance*

The resistance profile in treatment-naïve and treatment-experienced subjects has not been fully characterized. Virologic failure on maraviroc can result from genotypic and phenotypic resistance to maraviroc or through outgrowth of undetected CXCR4-using virus present before

maraviroc treatment (see *Tropism* below). Preliminary data from a subset of treatment-experienced subjects failing maraviroc-containing regimens with CCR5-tropic virus (n=12) have identified 5 viruses that had decreased susceptibility to maraviroc characterized in phenotypic drug assays by concentration response curves that did not reach 100% inhibition. Additionally, CCR5-tropic virus from 2 of these treatment failure subjects had 3-fold shifts in EC<sub>50</sub> values for maraviroc at the time of failure.

Each of these viruses had multiple amino acid substitutions with unique patterns in the heterogeneous V3 loop region of gp120. Changes at either amino acid position 308 or 323 (HXB2 numbering) were seen in the V3 loop in all five of the subjects with decreased maraviroc susceptibility. The contribution of mutations outside the V3 loop of gp120 to maraviroc resistance has not been investigated.

#### *Cross-resistance in Cell Culture*

Maraviroc had antiviral activity against HIV-1 clinical isolates resistant to NRTIs, NNRTIs, PIs and enfuvirtide in cell culture (EC<sub>50</sub> values ranged from 0.7 to 8.9 nM (0.36 to 4.57 ng/mL)). Maraviroc-resistant viruses that emerged in cell culture remained susceptible to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.

#### *Tropism*

In the majority of cases, treatment failure on maraviroc was associated with detection of CXCR4-using (i.e., CXCR4- or dual/mixed-tropic) virus which was not detected by the tropism assay prior to treatment. CXCR4-using virus was detected at failure in approximately 60% of subjects who failed treatment on maraviroc, as compared to 6% of subjects who experienced treatment failure in the placebo arm. To investigate the likely origin of the on-treatment CXCR4-using virus, a detailed clonal analysis was conducted on virus from 20 representative subjects (16 subjects from the maraviroc arms and 4 subjects from the placebo arm) in whom CXCR4-using virus was detected at treatment failure. From analysis of amino acid sequence differences and phylogenetic data, CXCR4-using virus in these subjects emerged from a low level of pre-existing CXCR4-using virus not detected by the tropism assay (which is population-based) prior to treatment rather than from a co-receptor switch from CCR5-tropic virus to CXCR4-using virus resulting from mutation in the virus.

Detection of CXCR4-using virus prior to initiation of therapy has been associated with a reduced virological response to maraviroc. Furthermore, subjects failing maraviroc BID with CXCR4-using virus had a lower median increase in CD4<sup>+</sup> cell counts from baseline (+22 cells/mm<sup>3</sup>) than those subjects failing with CCR5-tropic virus (+149 cells/mm<sup>3</sup>). The median increase in CD4<sup>+</sup> cell count in patients failing in the placebo arm was +5 cells/mm<sup>3</sup>.

### **12.5 Pharmacogenomics**

The impact of CCR5 promoter and coding sequence polymorphisms on the efficacy of maraviroc is being evaluated.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### *Carcinogenesis*

Long-term oral carcinogenicity studies of maraviroc were carried out in rasH2 transgenic mice (6 months) and in rats for up to 96 weeks (females) and 104 weeks (males). No drug-related



increases in tumor incidence were found in mice at 1500 mg/kg/day and in male and female rats at 900 mg/kg/day. The highest exposures in rats were approximately 11 times those observed in humans at the therapeutic dose of 300 mg twice daily for the treatment of HIV-1 infection.

*Mutagenesis*

Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames test in Salmonella and E. coli), a chromosome aberration test in human lymphocytes and rat bone marrow micronucleus test.

*Impairment of Fertility*

Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of treated male rats at approximately 20-fold higher exposures (AUC) than in humans given the recommended 300 mg twice daily dose.

**14 CLINICAL STUDIES**

The clinical efficacy and safety of SELZENTRY is derived from analyses of 24-week data from two ongoing studies, A4001027 (MOTIVATE-1) and A4001028 (MOTIVATE-2), in antiretroviral treatment-experienced adult subjects infected with CCR5-tropic HIV-1. These studies are supported by a 24-week study in antiretroviral treatment-experienced adult subjects infected with dual/mixed-tropic HIV-1, A4001029.

**14.1 Studies in CCR5-tropic, Treatment-Experienced Subjects**

Studies A4001027 and A4001028 are ongoing, double-blind, randomized, placebo-controlled, multicenter studies in subjects infected with CCR5-tropic HIV-1. Subjects were required to have an HIV-1 RNA of greater than 5,000 copies/mL despite at least 6 months of prior therapy with at least one agent from three of the four antiretroviral drug classes [ $\geq 1$  nucleoside reverse transcriptase inhibitors (NRTI),  $\geq 1$  non-nucleoside reverse transcriptase inhibitors (NNRTI),  $\geq 2$  protease inhibitors (PI), and/or enfuvirtide] or documented resistance or intolerance to at least one member of each class. All subjects received an optimized background regimen consisting of 3 to 6 antiretroviral agents (excluding low-dose ritonavir) selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements. In addition to the optimized background regimen, subjects were then randomized in a 2:2:1 ratio to maraviroc 300 mg once daily, maraviroc 300 mg twice daily, or placebo. Doses were adjusted based on background therapy as described in *Dosing and Administration*, Table 1.

In the pooled analysis for A4001027 and A4001028, the demographics and baseline characteristics of the treatment groups were comparable (Table 7). Of the 1043 subjects with a CCR5 tropism result at screening, 7.6% had a dual/mixed tropism result at the baseline visit 4 to 6 weeks later. This illustrates the background change from CCR5 to dual/mixed tropism result over time in this treatment-experienced population, prior to a change in antiretroviral regimen or administration of a CCR5 co-receptor antagonist.

**Table 7**  
Demographic and Baseline Characteristics of Subjects in Studies A4001027 and A4001028

	SELZENTRY BID N = 426	Placebo N = 209
Age (years) Mean (Range)	46.3 (21-73)	45.7 (29-72)
Sex		
Male	382 (89.7%)	185 (88.5%)

Female	44 (10.3%)	24 (11.5%)
<b>Race</b>		
White	363 (85.2%)	178 (85.2%)
Black	51 (12.0%)	26 (12.4%)
Other	12 (2.8%)	5 (2.4%)
<b>Region</b>		
U.S.	276 (64.8%)	135 (64.6%)
Non-U.S.	150 (35.2%)	74 (35.4%)
Subjects with Previous Enfuvirtide Use	182 (42.7%)	91 (43.5%)
Baseline Plasma HIV-1 RNA (log <sub>10</sub> copies/mL)		
Mean (Range)	4.85 (2.96-6.88)	4.86 (3.46-7.07)
Subjects with Screening Viral Load >100,000 copies/mL	179 (42.0%)	84 (40.2%)
Baseline CD4+ Cell Count (cells/mm <sup>3</sup> )		
Median (Range)	167 (2-820)	171 (1-675)
Subjects with Baseline CD4+ Cell Count ≤200 cells/mm <sup>3</sup>	250 (58.7%)	118 (56.7%)
Subjects with Overall Susceptibility Score (OSS): <sup>a</sup>		
0	57 (13.4%)	35 (16.7%)
1	136 (31.9%)	44 (21.1%)
2	104 (24.4%)	59 (28.2%)
≥3	125 (29.3%)	66 (31.6%)
Subjects with enfuvirtide resistance mutations	90 (21.2%)	45 (21.5%)
Median Number of Resistance-Associated: <sup>b</sup>		
PI mutations	10	10
NNRTI mutations	1	1
NRTI mutations	6	6

<sup>a</sup> OSS - Sum of active drugs in OBT based on combined information from genotypic and phenotypic testing.

<sup>b</sup> Resistance mutations based on IAS guidelines<sup>1</sup>

The week 24 results for the pooled Studies A4001027 and A4001028 are shown in Table 8.

**Table 8**  
**Outcomes of Randomized Treatment at Week 24**  
**Studies A4001027 and A4001028**

Outcome	SELZENTRY BID N=426	PLACEBO N=209	Mean Difference
Mean change from Baseline to Week 24 in HIV-1 RNA (log <sub>10</sub> copies/mL)	-1.96	-0.99	0.97
<400 copies/mL at Week 24	259 (60.8%)	58 (27.8%)	33.0%
<50 copies/mL at Week 24	193 (45.3%)	48 (23.0%)	22.3%
Virologic Responders <sup>b</sup>	295 (69.2%)	75 (35.9%)	33.4%
Discontinuations			
Insufficient Clinical Response	91 (21.4%)	106 (50.7%)	
Adverse Events	16 (3.8%)	8 (3.8%)	
Other	26 (6.1%)	18 (8.6%)	
Patients with treatment-emergent CDC Category C events	18 (4.2%)	14 (6.7%)	
Deaths (during study or within 28 days of last dose)	5 (1.2%)	1 (0.5%)	

<sup>b</sup> Reduction in HIV-1 RNA ≥1 log<sub>10</sub> or HIV-1 RNA <400 copies/mL at Week 24.

After 24 weeks of therapy, the proportion of subjects with HIV-1 RNA <400 copies/mL receiving maraviroc compared to placebo was 61% and 28%, respectively. The mean changes in plasma HIV-1 RNA from baseline to week 24 was -1.96 log<sub>10</sub> copies/mL for subjects receiving

maraviroc + OBT compared to  $-0.99 \log_{10}$  copies/mL for subjects receiving OBT only. The mean increase in CD4+ counts was higher on maraviroc twice daily + OBT ( $106.3 \text{ cells/mm}^3$ ) than on placebo + OBT ( $57.4 \text{ cells/mm}^3$ ).

#### **14.2 Study in Dual/Mixed-tropic, Treatment-Experienced Subjects**

Study A4001029 was an exploratory, randomized, double blind, multicenter trial to determine the safety and efficacy of maraviroc in subjects infected with dual/mixed co-receptor tropic HIV-1. The inclusion/exclusion criteria were similar to those for Studies A4001027 and A4001028 above and the subjects were randomized in a 1:1:1 ratio to SELZENTRY once daily, SELZENTRY twice daily, or placebo. No increased risk of infection or HIV disease progression was observed in the subjects who received SELZENTRY. SELZENTRY use was not associated with a significant decrease in HIV-1 RNA compared to placebo in these subjects and no adverse effect on CD4 count was noted.

#### **15 REFERENCES**

<sup>1</sup>IAS-USA Drug Resistance Mutations Figures  
<http://www.iasusa.org/pub/topics/2006/issue3/125.pdf>

#### **16 HOW SUPPLIED/STORAGE AND HANDLING**

SELZENTRY film-coated tablets are available as follows:

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

Bottle packs 150 mg tablets

- 60 tablets (NDC 0069-0807-60)

Bottle packs 300 mg tablets

- 60 tablets (NDC 0069-0808-60)

SELZENTRY film-coated tablets should be stored at 25°C (77°F); excursions permitted between 15° and 30°C (59°-86°F) [see USP Controlled Room Temperature].

Shelf life is 24 months.

#### **17 PATIENT COUNSELING INFORMATION**

*See Medication Guide.*

Patients should be informed that if they develop signs or symptoms of hepatitis or allergic reaction following use of SELZENTRY (rash, skin or eyes look yellow, dark urine, vomiting, abdominal pain), they should stop SELZENTRY and seek medical evaluation immediately [see *Warnings and Precautions (5.1)*].

Patients should be informed that SELZENTRY is not a cure for HIV infection and patients may still develop illnesses associated with HIV infection, including opportunistic infections. The use of SELZENTRY has not been shown to reduce the risk of transmission of HIV to others through sexual contact, sharing needles or blood contamination.

Patients should be advised that it is important to:

- remain under the care of a physician when using SELZENTRY;
- take SELZENTRY every day as prescribed and in combination with other antiretroviral drugs;
  - report to their physician the use of any other prescription or nonprescription medication or herbal products;
  - inform their physician if they are pregnant, plan to become pregnant or become pregnant while taking SELZENTRY;
  - not change the dose or dosing schedule of SELZENTRY or any antiretroviral medication without consulting their physician.

Patients should be advised that if they forget to take a dose, they should take the next dose of SELZENTRY as soon as possible and then take their next scheduled dose at its regular time. If it is less than 6 hours before their next scheduled dose, they should not take the missed dose and should instead wait and take the next dose at the regular time.

Caution should be used when administering SELZENTRY in patients with a history of postural hypotension or on concomitant medication known to lower blood pressure. Patients should be advised that if they experience dizziness while taking SELZENTRY, they should avoid driving or operating machinery.

LAB-0357-0.1

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## MEDICATION GUIDE

### SELZENTRY® (sell-ZEN-tree) Tablets (maraviroc)

Read the Medication Guide that comes with SELZENTRY before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

#### What is the most important information I should know about SELZENTRY?

##### Liver problems

**Liver problems (liver toxicity) have happened in patients taking SELZENTRY.** An allergic reaction may happen before liver problems occur. Stop taking SELZENTRY and call your doctor right away if you get any of the following symptoms:

- an itchy rash on your body (allergic reaction)
- Your skin or eyes look yellow and/or dark (tea-colored) urine
- vomiting and/or upper right stomach area (abdominal) pain

You should see your doctor right away but continue taking SELZENTRY if you have any of the following other symptoms: nausea, fever, flu-like symptoms, fatigue

#### What is SELZENTRY?

SELZENTRY is an anti-HIV medicine called a CCR5 antagonist. HIV (Human Immunodeficiency Virus) is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

SELZENTRY is used with other anti-HIV medicines in adults with CCR5-tropic HIV-1 infection who are already taking anti-HIV medicines and the medicines are not controlling their HIV infection.

- SELZENTRY will not cure HIV infection.
- People taking SELZENTRY may still develop infections, including opportunistic infections or other conditions that happen with HIV infection.
- It is very important that you stay under the care of your doctor during treatment with SELZENTRY.
- The long-term effects of SELZENTRY are not known at this time.
- SELZENTRY has not been studied in children less than 16 years of age.

#### Does SELZENTRY lower the risk of passing HIV to other people?

**No, SELZENTRY does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.**

- Continue to practice safer sex.
- Use latex or polyurethane condoms or other barrier methods to lower the chance of

sexual contact with any body fluids. This includes semen from a man, vaginal secretions from a woman, or blood.

- Never re-use or share needles.
- Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

### **How does SELZENTRY work?**

HIV enters cells in your blood by attaching itself to structures on the surface of the cell called receptors. SELZENTRY blocks a specific receptor called CCR5 that CCR5-tropic HIV-1 uses to enter CD4 or T-cells in your blood. Your doctor will do a blood test to see if you have been infected with CCR5-tropic HIV-1 before prescribing SELZENTRY for you.

- When used with other anti-HIV medicines, SELZENTRY may:
  - reduce the amount of HIV in your blood. This is called “viral load”.
  - increase the number of white blood cells called T (CD4) cells.

Both of these may keep your immune system healthy, so it can help fight infection.

SELZENTRY does not work in all patients with CCR5-tropic HIV-1 infection.

### **What should I tell my doctor before taking SELZENTRY?**

**Tell your doctor about all of your medical conditions, including if you:**

- have any allergies
- have liver problems including a history of hepatitis B or C
- have heart problems
- have kidney problems
- have low blood pressure or take medicines to lower blood pressure
- are pregnant or planning to become pregnant. It is not known if SELZENTRY may harm your unborn baby. If you take SELZENTRY while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breast-feeding or planning to breast-feed. It is recommended that HIV-positive women should not breastfeed their babies. This is because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain other medicines may affect the levels of SELZENTRY in your blood. Your doctor may need to change your dose of SELZENTRY when you take it with certain medicines.

**Do not take products that contain St. John’s Wort (*hypericum perforatum*). St. John’s Wort may lower the levels of SELZENTRY in your blood so that it will not work to treat your CCR5-tropic HIV infection.**

**Know the medicines you take.** Keep a list of your medicines. Show the list to your doctor and pharmacist when you get a new medicine.

### **How should I take SELZENTRY?**

**Take SELZENTRY exactly as prescribed by your doctor.** SELZENTRY comes in 150 mg and 300 mg tablets. Your doctor will prescribe the dose that is right for you.

- Take SELZENTRY twice a day.
- Swallow SELZENTRY tablets whole. Do not chew the tablets.
- Take SELZENTRY tablets with or without food.
- Always take SELZENTRY with the other anti-HIV drugs prescribed by your doctor.

**Do not change your dose or stop taking SELZENTRY or your other anti-HIV medicines without first talking with your doctor.**

- If you take too much SELZENTRY, call your doctor or the poison control center right away.
- If you forget to take SELZENTRY, take the next dose of SELZENTRY as soon as possible and then take your next scheduled dose at its regular time. If it is less than 6 hours before your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a missed dose.
- It is very important to take all your anti-HIV medicines as prescribed and at the same time each day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your SELZENTRY supply starts to run low, ask your doctor or pharmacist for a refill. This is very important because the amount of virus in your blood may increase and SELZENTRY could stop working if it is stopped for even a short period of time.

### **What are the possible side effects of SELZENTRY?**

**When SELZENTRY has been given with other anti-HIV drugs, there have been serious side effects including:**

- **Liver problems.** See "What is the most important information I should know about SELZENTRY?"
- **Heart problems** including heart attack
- **Low blood pressure when standing up (postural hypotension).** Low blood pressure when standing up can cause dizziness or fainting. Do not drive a car or operate heavy machinery if you have dizziness while taking SELZENTRY.
- **Changes in your immune system.** A condition called Immune Reconstitution Syndrome can happen when you start taking HIV medicines. Your immune system may get stronger and could begin to fight infections that have been hidden in your body such as pneumonia, herpes virus or tuberculosis. Tell your doctor if you develop new symptoms after starting your HIV medicines.
- **Possible chance of infection or cancer.** SELZENTRY affects other immune system cells and therefore may possibly increase your chance for getting other infections or cancer, although there is no evidence from the clinical trials of an increase in serious infections or cancer.

**The most common side effects of SELZENTRY include** cough, fever, colds, rash, muscle and joint pain, stomach pain, dizziness. Tell your doctor about any side effect that bothers you or does not go away.

These are not all of the side effects with SELZENTRY. For more information, ask your doctor or pharmacist.

**How should I store SELZENTRY?**

- Store SELZENTRY tablets at room temperature from 59°F to 86° (15°C to 30°C)
- Safely throw away medicine that is out of date or that you no longer need.
- **Keep SELZENTRY and all medicines out of the reach of children.**

**General information about SELZENTRY**

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use SELZENTRY for a condition for which it was not prescribed. Do not give SELZENTRY to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about SELZENTRY. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for more information about SELZENTRY that is written for health professionals. For more information go to [www.selzentry.com](http://www.selzentry.com).

**What are the ingredients in SELZENTRY?**

**Active Ingredient:** maraviroc

**Inactive Ingredients:**

**Tablet core:** microcrystalline cellulose, dibasic calcium phosphate (anhydrous), sodium starch glycolate, magnesium stearate

**Film-coat:** FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc and titanium dioxide

**Issued August 2007**

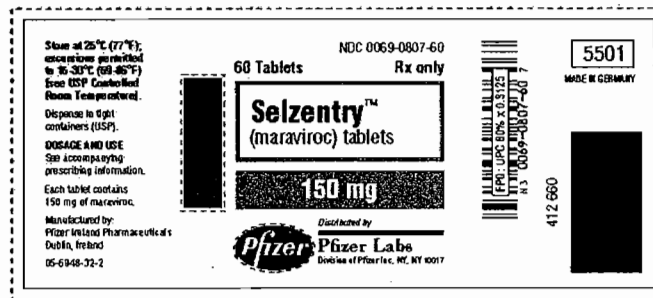
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LAB-0357-0.1

This Medication Guide has been approved by the US Food and Drug Administration



07-045.0B 05-6948-32-2 Selzentry 150 mg (3-1/2" x 1-1/2")



PACKAGE DESIGN & DEVELOPMENT PHARMACEUTICAL PROMOTED PRODUCTS  <b>07-045.0B</b> JOB #	F-09 COVERT VARNISH			N/A NOTES
	05-6948-32-2 SPEC #	PRODUCT  Selzentry Tablets 150mg x 60 TRADE	IMAGE PRINTS OUT AT 100% 3-1/2" (89mm) x 1-1/2" (38mm) SIZE	
60 cc Freiburg DRAWING #	Label ITEM			

07-045.0B 05-6950-32-2 Selzentry 300 mg (4-3/4" x 1-1/2")

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in light containers (USP).

**DOSE AND USE**  
See accompanying prescribing information.

Each tablet contains 300 mg of maraviroc.

Manufactured by  
Pfizer Ireland Pharmaceuticals  
Dublin, Ireland  
05-6950-32-2

60 Tablets  
**Selzentry™**  
(maraviroc) tablets  
**300 mg**

NDC 0069-0808-60  
Rx only

FPO (80% x 11.8mm)  
N 0069-0808-60 4  
412661

5502  
MADE IN GERMANY

**Pfizer**  
Pfizer Labs  
Division of Pfizer Inc, NY, NY 10017



PACKAGING  
DESIGN &  
DEVELOPMENT  
PHARMACEUTICAL  
PROMOTIONAL  
PRODUCTS

BLACK

PMS  
166

VEL METAL  
B-87

F-09  
COVERT

VARNISH

JOB # SPEC # PRODUCT SIZE

05-6950-32-2

Version 19 02Aug07

Pfizer Confidential

Selzentry Tablets 300mg x 60 TRADE

4-3/4"(120mm) x  
1-1/2"(38mm)

DRAWING # ITEM NOTES

**07-045.0B**

**IMAGE  
PRINTS  
OUT AT  
100%**

N/A

120 cc (Freiburg) Label

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/s/

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Debra Birnkrant  
8/6/2007 11:49:52 AM  
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