Tell your doctor if you are taking any of the following medicines:

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	bepridil (Vascor®) lidocaine (Lidoderm®) quinidine amiodarone (Cordarone®)
Anticoagulants (to prevent the clotting of red blood cells called platelets)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital phenytoin (Dilantin®, Phenytek®)
Antidepressants	trazodone (Desyrel®)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)
Antifungals (to treat fungal infections)	ketoconazole (Nizoral®) itraconazole (Sporanox®) voriconazole (Vfend®)
Antimycobacterials (to treat bacterial infections)	rifabutin (Mycobutin®) rifampin (Rifadin®, Rifater®, Rifamate®)
Calcium Channel Blockers (to treat heart disease)	felodipine (Plendil®) nifedipine (Adalat®) nicardipine (Cardene®)
Corticosteroids (to treat inflammation or asthma)	dexamethasone (Decadron®) fluticasone propionate (Advair Diskus®, Cutivate®, Flonase®, Flovent Diskus®)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor®) lovastatin (Mevacor®) pravastatin (Pravachol®) simvastatin (Zocor®)
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune®, Neoral®) tacrolimus (Prograf®) sirolimus (Rapamune®)
Narcotic Analgesics	methadone
PDE-5 Inhibitors	sildenafil (Viagra®)

Type of Drug	Examples of Generic Names (Brand Names)
(to treat erectile dysfunction)	vardenafil (Levitra®) tadalafil (Cialis®)
Selective Serotonin Reuptake Inhibitors (SSRIs) (to treat depression, anxiety, or panic disorder)	paroxetine (Paxil®) sertraline (Zoloft®)

Tell your doctor if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your doctor that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your doctors and pharmacists any time you get a new medicine. Both your doctor and your pharmacist can tell you if you can take these other medicines with PREZISTA. Do not start any new medicines while you are taking PREZISTA without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with PREZISTA.

HOW SHOULD I TAKE PREZISTA?

Take PREZISTA tablets every day exactly as prescribed by your doctor. You must take ritonavir (NORVIR®) at the same time as PREZISTA. The usual dose is 600 mg (two 300 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), twice daily *every day*. It may be easier to remember to take PREZISTA and ritonavir (NORVIR®) if you take them at the same time every day. If you have questions about when to take PREZISTA and ritonavir (NORVIR®), your doctor can help you decide which schedule works for you.

Take PREZISTA and ritonavir (NORVIR®) **with food.** The type of food is not important. Swallow the whole tablets with a drink such as water or milk. Do not chew the tablets.

Continue taking PREZISTA and ritonavir (NORVIR®) unless your doctor tells you to stop. Take the exact amount of PREZISTA and ritonavir (NORVIR®) that your doctor tells you to take, right from the very start. To help make sure you will benefit from PREZISTA and ritonavir (NORVIR®), you must not skip doses or interrupt therapy. If you don't take PREZISTA and ritonavir (NORVIR®) as prescribed, the beneficial effects of PREZISTA and ritonavir (NORVIR®) may be reduced or even lost.

If you miss a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, take your missed dose of PREZISTA and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time.

You should always take PREZISTA and ritonavir (NORVIR®) together with food.

If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, do not double the next dose. Do not take more or less than your prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PREZISTA?

Like all prescription drugs, PREZISTA can cause side effects. The following is **not** a complete list of side effects reported with PREZISTA when taken either alone or with other anti-HIV medicines. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

Mild to moderate rash has been reported in 7% of subjects receiving PREZISTA. In some patients, PREZISTA has been reported to cause a severe or life-threatening rash. Contact your healthcare provider if you develop a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether PREZISTA should be stopped.

As with other protease inhibitors, PREZISTA may cause side effects, including:

- high blood sugar (hyperglycemia) and diabetes. This can happen in patients taking PREZISTA or other protease inhibitor medicines. Some patients have diabetes before starting treatment with PREZISTA which gets worse. Some patients get diabetes during treatment with PREZISTA. Some patients will need changes in their diabetes medicine. Some patients may need new diabetes medicine.
- increased bleeding in patients with hemophilia. This may happen in patients taking PREZISTA as it has been reported with other protease inhibitor medicines.
- changes in body fat. These changes can happen in patients taking anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- immune reconstitution syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

The most common side effects include diarrhea, nausea, headache, and common cold.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

HOW SHOULD I STORE PREZISTA TABLETS?

Store PREZISTA tablets at room temperature (77°F (25°C)). Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Ask your doctor or pharmacist if you have any questions about storing your tablets.

This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep PREZISTA and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about PREZISTA. If you have any questions or concerns about either PREZISTA or HIV, talk to your doctor.

For additional information, you may also call Tibotec Therapeutics at 1-800-325-7504.

Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

Issued: June 2006

10101700

Panretin®
(alitretinoin)
gel 0.1%
(For topical use only)

Description

Panretin® gel 0.1% contains alitretinoin and is intended for topical application only. The chemical name is 9-*cis*-retinoic acid and the structural formula is as follows:

Chemically, alitretinoin is related to vitamin A. It is a yellow powder with a molecular weight of 300.44 and a molecular formula of $C_{20}H_{28}O_2$. It is slightly soluble in ethanol (7.01 mg/g at 25°C) and insoluble in water. Panretin® gel is a clear, yellow gel containing 0.1% (w/w) alitretinoin in a base of dehydrated alcohol USP, polyethylene glycol 400 NF, hydroxypropyl cellulose NF, and butylated hydroxytoluene NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

Alitretinoin (9-*cis*-retinoic acid) is a naturally-occurring endogenous retinoid that binds to and activates all known intracellular retinoid receptor subtypes (RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ). Once activated these receptors function as transcription factors that regulate the expression of genes that control the process of cellular differentiation and proliferation in both normal and neoplastic cells. Alitretinoin inhibits the growth of Kaposi's sarcoma (KS) cells in vitro.

Pharmacokinetics

No studies have examined plasma 9-*cis*-retinoic acid concentrations before and after treatment with Panretin® gel. There is, however, indirect evidence that absorption is not extensive. Plasma concentrations of 9-*cis*-retinoic acid were evaluated during clinical studies in patients with cutaneous lesions of AIDS-related KS after repeated multiple-daily dose application of Panretin® gel for up to 60 weeks. The range of 9-*cis*-retinoic

acid plasma concentrations in these patients was similar to the range of circulating, naturally-occurring 9-*cis*-retinoic acid plasma concentrations in untreated healthy volunteers.

Although there are no detectable plasma concentrations of 9-*cis*-retinoic acid metabolites after topical application of Panretin® gel, in vitro studies indicate that the drug is metabolized to 4-hydroxy-9-*cis*-retinoic acid and 4-oxo-9-*cis*-retinoic acid by CYP 2C9, 3A4, 1A1, and 1A2 enzymes. In vivo, 4-oxo-9-*cis*-retinoic acid is the major circulating metabolite following oral administration of 9-*cis*-retinoic acid.

No formal pharmacokinetic drug interaction studies between Panretin® gel and antiretroviral agents have been conducted.

Clinical Studies

Panretin® gel is not a systemic therapy; it therefore cannot treat visceral Kaposi's sarcoma (KS) nor prevent the development of new KS lesions where it has not been applied. Visceral KS disease was not monitored in these trials, and the appearance of new KS lesions was not considered part of the response assessment in clinical trials.

Panretin® gel was evaluated in two multicenter, prospective, randomized, double-blind, vehicle-controlled studies in patients with cutaneous lesions of AIDS-related KS. In both studies the primary efficacy endpoint was the patients' cutaneous KS tumor response rate through 12 weeks of study drug treatment which was assessed by evaluating from 3 to 8 KS index lesions according to the modified AIDS Clinical Trials Group (ACTG) response criteria as applied to topical therapy (i.e., evaluation of height and area reductions of the index lesions only; progressive disease in non-index lesions and new lesions were not considered progressive disease; progressive disease was scored only in the treated index lesions). A global evaluation by physicians was also carried out. It considered all of the patient's treated lesions (index and other) compared to baseline. In this evaluation, patients with at least a 50% improvement in the KS lesions were considered responders. In addition, photographs of lesions in patients considered responders by the modified ACTG criteria were examined by the FDA for a cosmetically beneficial response, defined as at least a 50% improvement in appearance compared to baseline, considering both the KS lesions and dermal toxicity at the lesion site, in at least 50% of the index lesions and maintained for at least 3 weeks. Patients were also asked about their satisfaction with the treatment.

In Study 1, a total of 268 patients were entered from centers in the U.S. and Canada. Patients were treated topically three to four times a day with either Panretin® gel or a matching vehicle gel for a minimum of 12 weeks, followed by an open-label phase in patients who had not yet progressed on Panretin® gel. Responses during the double-blind phase are shown in Table 1. Responses to Panretin® gel were seen in both previously untreated patients and in patients with prior systemic and/or topical KS treatment. A total of 72 patients responded to Panretin® gel during the randomized or crossover portions of the study. At a median duration of monitoring of 16 weeks, only

15% of the 72 patients had relapsed. Panretin® gel would not be expected to affect development of new lesions in untreated areas and these were seen in about 50% of patients, at similar rates in treated and untreated patients, responders and non-responders. The patients' assessment of their overall satisfaction with the drug effect on all treated lesions significantly favored Panretin® gel.

Study 2 was an international study with a planned enrollment of 270 patients. Patients were treated topically twice a day with Panretin® gel or a matching vehicle for 12 weeks. The study was stopped early because of positive interim results in the initial 82 patient data set. Results of the study are shown in Table 1. Responses to Panretin® gel were seen both in previously untreated patients and in patients with prior systemic and/or topical KS treatment.

TABLE 1: Summary of Tumor Responses

	STUDY 1		STUDY 2	
	Panretin® Gel N=134	Vehicle Gel N=134	Panretin® Gel N=36	Vehicle Gel N=46
Modified ACTG Response (index lesions)	34% PR 1% CR	16% PR p=0.0012	36% PR	7% PR
Physician's Global/ Subjective Assessment (all treated lesions)	19% PR	4% PR p=0.00014	47% PR	11% PR
Beneficial Response Photographs (index lesions only)	15%	4% p=0.0026	19%	2%

In the clinical trials, responses were seen as early as two (2) weeks; most patients, however, required four (4) to eight (8) weeks of treatment, and some patients did not experience significant improvement until 14 or more weeks of treatment. The cumulative percentage of patients who achieved a response was less than 1% at 2 weeks, 10% at 4 weeks, and 28% at 8 weeks.

In both studies, responses occurred in patients with a wide range of baseline CD4+ lymphocyte counts, including patients with CD4+ lymphocyte counts less than 50 cells/mm^3. Nearly all patients received concomitant combination antiretroviral therapy.

Photographs of patients revealed a substantial erythematous and edematous response in some cases, leading to a cosmetically mixed outcome even in apparent responders. Nonetheless, in Study 1 it appeared that a cosmetically satisfactory result occurred at

about the same rate as the Physician's Global response rate and in both studies such a response was more frequent than in the vehicle control.

INDICATIONS AND USAGE

Panretin® gel is indicated for topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. Panretin® gel is not indicated when systemic anti-KS therapy is required (e.g., more than 10 new KS lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary KS, or symptomatic visceral involvement). There is no experience to date using Panretin® gel with systemic anti-KS treatment.

CONTRAINDICATIONS

Panretin® gel is contraindicated in patients with a known hypersensitivity to retinoids or to any of the ingredients of the product.

WARNINGS

Pregnancy: Panretin® gel could cause fetal harm if significant absorption were to occur in a pregnant woman. 9-*cis*-Retinoic acid has been shown to be teratogenic in rabbits and mice. An increased incidence of fused sternebrae and limb and craniofacial defects occurred in rabbits given oral doses of 0.5 mg/kg/day (about five times the estimated daily human topical dose on a mg/m^2 basis, assuming complete systemic absorption of 9-*cis*-retinoic acid, when Panretin® gel is administered as a 60 g tube over 1 month in a 60 kg human) during the period of organogenesis. Limb and craniofacial defects also occurred in mice given a single oral dose of 50 mg/kg on day eleven of gestation (about 127 times the estimated daily human topical dose on a mg/m^2 basis). Oral 9-*cis*-retinoic acid was also embryocidal, as indicated by early resorptions and post-implantation loss when it was given during the period of organogenesis to rabbits at doses of 1.5 mg/kg/day (about 15 times the estimated daily human topical dose on a mg/m^2 basis) and to rats at doses of 5 mg/kg/day (about 25 times the estimated daily human topical dose on a mg/m^2 basis). Animal reproduction studies with topical 9-*cis*-retinoic acid have not been conducted. It is not known whether topical Panretin® gel can modulate endogenous 9-*cis*-retinoic acid levels in a pregnant woman nor whether systemic exposure is increased by application to ulcerated lesions or by duration of treatment. There are no adequate and well-controlled studies in pregnant women. If Panretin® gel is used during pregnancy, or if the patient becomes pregnant while taking it, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Panretin® gel is indicated for topical treatment of Kaposi's sarcoma. Patients with cutaneous T-cell lymphoma were less tolerant of topical Panretin® gel; five of seven patients had 6 episodes of treatment-limiting toxicities—grade 3 dermal irritation—with Panretin® gel (0.01% or 0.05%).

Photosensitivity

Retinoids as a class have been associated with photosensitivity. There were no reports of photosensitivity associated with the use of Panretin® gel in the clinical studies. Nonetheless, because in vitro data indicate that 9-*cis*-retinoic acid may have a weak photosensitizing effect, patients should be advised to minimize exposure of treated areas to sunlight and sunlamps during the use of Panretin® gel.

Drug Interactions

Patients who are applying Panretin® gel should not concurrently use products that contain DEET (N,N-diethyl-m-toluamide), a common component of insect repellent products. Animal toxicology studies showed increased DEET toxicity when DEET was included as part of the formulation.

Although there was no clinical evidence in the vehicle-controlled studies of drug interactions with systemic antiretroviral agents, including protease inhibitors, macrolide antibiotics, and azole antifungals, the effect of Panretin® gel on the steady-state concentrations of these drugs is not known. No drug interaction data are available on concomitant administration of Panretin® gel and systemic anti-KS agents.

Drug/Laboratory Test Interactions

No interference with laboratory tests has been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to assess the carcinogenic potential of 9-*cis*-retinoic acid have not been conducted. 9-*cis*-Retinoic acid was not mutagenic in vitro (bacterial assays, Chinese hamster ovary cell HGPRT mutation assay) and was not clastogenic in vitro (chromosome aberration test in human lymphocytes) nor in vivo (mouse micronucleus test).

Pregnancy Category D (see "Warnings" section)

Nursing Mothers

It is not known whether alitretinoin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions from Panretin® gel in nursing infants, mothers should discontinue nursing prior to using the drug.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Inadequate information is available to assess safety and efficacy in patients age 65 years or older.

ADVERSE REACTIONS

The safety of Panretin® gel has been assessed in clinical studies of 385 patients with AIDS-related KS. Adverse events associated with the use of Panretin® gel in patients with AIDS-related KS occurred almost exclusively at the site of application. The dermal toxicity begins as erythema; with continued application of Panretin® gel, erythema may increase and edema may develop. Dermal toxicity may become treatment-limiting, with intense erythema, edema, and vesiculation. Usually, however, adverse events are mild to moderate in severity; they led to withdrawal from the study in only 7% of the patients. Severe local (application site) skin adverse events occurred in about 10% of patients in the U.S. study (versus 0% in the vehicle control). Table 2 lists the adverse events that occurred at the application site with an incidence of at least 5% during the double-blind phase in the Panretin® gel-treated group and in the vehicle control group in either of the two controlled studies. Adverse events were reported at other sites but generally were similar in the two groups.

TABLE 2: Adverse Events with an Incidence of at Least 5% at the Application Site in Either Controlled Study in Patients Receiving Panretin® Gel or Vehicle Control

Adverse Event Term	Study 1		Study 2	
	Panretin® Gel N=134 Pts. %	Vehicle Gel N=134 Pts. %	Panretin® Gel N=36 Pts. %	Vehicle Gel N=46 Pts. %
Rash[1]	77	11	25	4
Pain[2]	34	7	0	4
Pruritus[3]	11	4	8	4
Exfoliative dermatitis[4]	9	2	3	0
Skin disorder[5]	8	1	0	0
Paresthesia[6]	3	0	22	7
Edema[7]	8	3	3	0

Includes Investigator terms:
[1] Erythema, scaling, irritation, redness, rash, dermatitis
[2] Burning, pain
[3] Itching, pruritis
[4] Flaking, peeling, desquamation, exfoliation
[5] Excoriation, cracking, scab, crusting, drainage, eschar, fissure or oozing
[6] Stinging, tingling
[7] Edema, swelling, inflammation

OVERDOSAGE

There has been no experience with acute overdose of Panretin® gel in humans. Systemic toxicity following acute overdosage with topical application of Panretin® gel is unlikely because of limited systemic plasma levels observed with normal therapeutic doses. There is no specific antidote for overdosage.

DOSAGE AND ADMINISTRATION

Panretin® gel should initially be applied two (2) times a day to cutaneous KS lesions. The application frequency can be gradually increased to three (3) or four (4) times a day according to individual lesion tolerance. If application site toxicity occurs, the application frequency can be reduced. Should severe irritation occur, application of drug can be temporarily discontinued for a few days until the symptoms subside.

Sufficient gel should be applied to cover the lesion with a generous coating. The gel should be allowed to dry for three to five minutes before covering with clothing. Because unaffected skin may become irritated, application of the gel to normal skin surrounding the lesions should be avoided. In addition, do not apply the gel on or near mucosal surfaces of the body.

A response of KS lesions may be seen as soon as two weeks after initiation of therapy but most patients require longer application. With continued application, further benefit may be attained. Some patients have required over 14 weeks to respond. In clinical trials, Panretin® gel was applied for up to 96 weeks. Panretin® gel should be continued as long as the patient is deriving benefit.

Occlusive dressings should not be used with Panretin® gel.

How Supplied

Panretin® gel is available in tubes containing 60 grams. Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Manufactured for: Ligand Pharmaceuticals Incorporated
San Diego, CA 92121

by: Stiefel Laboratories, Inc.
Coral Gables, FL 33134

NDC 64365-501-01

Ligand Part #3000101
Stiefel Part #80068 (Rev. 0598)

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 which may be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE).
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, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents (1).

Tropism testing is required for the appropriate use of SELZENTRY (1).

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

When given with potent CYP3A inhibitors (with or without potent 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 potent CYP3A inhibitors or CYP3A inducers (2, 7.1)	300 mg twice daily
With potent CYP3A inducers including efavirenz (without a potent CYP3A inhibitor) (2, 7.1)	600 mg twice daily

A more complete list of coadministered drugs is listed in *Dosage and Administration (2)*

----------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 upper respiratory tract infections, cough, pyrexia, rash, 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 6/2009

FULL PRESCRIBING INFORMATION*

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

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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, 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 48 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 is required for the appropriate 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.

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
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin • other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)	150 mg twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300 mg twice daily
Potent CYP3A inducers (without a potent 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 609 patient-years (300 on once daily + 309 on twice daily SELZENTRY)], while no subjects who received placebo had such events (total exposure 111 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 (23% versus 13%), there was a lower rate of pneumonia (2% vs 5%) reported in patients receiving SELZENTRY. A higher incidence of Herpes virus infections (11 per 100 patient-years) was also reported in the SELZENTRY arm when adjusted for exposure compared to placebo (8 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

The following adverse reactions are discussed in other sections of the labeling:

- Hepatotoxicity *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Cardiovascular events *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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 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 48 weeks, with the total exposure on SELZENTRY twice daily at 309 patient-years versus 111 patient-years on placebo + OBT. 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.

The most common adverse events reported with SELZENTRY twice daily therapy with frequency rates higher than placebo, regardless of causality, were upper respiratory tract infections, cough, pyrexia, rash, 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 rate of discontinuation due to adverse events was 5% for subjects who received SELZENTRY twice daily + optimized background therapy (OBT) as well as those who received 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 233 (55%) and 84 (40%) 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 133 for both SELZENTRY twice daily and placebo.

Dizziness or postural dizziness occurred in 8% of subjects on either SELZENTRY and placebo, with 2 subjects (0.5%) on SELZENTRY permanently discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) permanently 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 the same or 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)

Studies A4001027 and A4001028 (Pooled Analysis, 48 Weeks)

	SELZENTRY Twice Daily*	Exposure-adjusted rate (per 100 pt-yrs) PYE=309**	Placebo	Exposure-adjusted rate (per 100 pt-yrs) PYE=111**
	N=426 (%)		N=209 (%)	
EYE DISORDERS				
Conjunctivitis	2	3	1	3
Ocular infections, inflammations and associated manifestations	2	3	1	2
GASTROINTESTINAL DISORDERS				
Constipation	6	9	3	6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Pyrexia	13	20	9	17
Pain and discomfort	4	5	3	5
INFECTIONS AND INFESTATIONS				
Upper respiratory tract infection	23	37	13	27
Herpes Infection	8	11	4	8
Sinusitis	7	10	3	6
Bronchitis	7	9	5	9
Folliculitis	4	5	2	4
Pneumonia	2	3	5	10
Anogenital warts	2	3	1	3
Influenza	2	3	0.5	1
Otitis media	2	3	0.5	1
METABOLISM AND NUTRITION DISORDERS				
Appetite disorders	8	11	7	13
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Joint related signs and symptoms	7	10	3	5
Muscle pains	3	4	0.5	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED				
Skin neoplasms benign	3	4	1	3
NERVOUS SYSTEM DISORDERS				
Dizziness/postural dizziness	9	13	8	17
Paresthesias and dysesthesias	5	7	3	6
Sensory abnormalities	4	6	1	3
Disturbances in consciousness	4	5	3	6
Peripheral neuropathies	4	5	3	6

	SELZENTRY Twice Daily*	Exposure-adjusted rate (per 100 pt-yrs) PYE=309**	Placebo	Exposure-adjusted rate (per 100 pt-yrs) PYE=111**
PSYCHIATRIC DISORDERS				
Disturbances in initiating and maintaining sleep	8	11	5	10
Depressive disorders	4	6	3	5
Anxiety symptoms	4	5	3	7
RENAL AND URINARY DISORDERS				
Bladder and urethral symptoms	5	7	1	3
Urinary tract signs and symptoms	3	4	1	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Coughing and associated symptoms	14	21	5	10
Upper respiratory tract signs and symptoms	6	9	3	6
Nasal congestion and inflammations	4	6	3	5
Breathing abnormalities	4	5	2	5
Paranasal sinus disorders	3	4	0.5	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	11	16	5	11
Apocrine and eccrine gland disorders	5	7	4	7.5
Pruritus	4	5	2	4
Lipodystrophies	3	5	0.5	1
Erythemas	2	3	1	2
VASCULAR DISORDERS				
Vascular hypertensive disorders	3	4	2	4

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

Less Common Adverse Events
The following adverse events 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.

Blood and Lymphatic System: Marrow depression and hypoplastic anemia

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, portal vein thrombosis

Infections and Infestations: endocarditis, infective myositis, viral meningitis, pneumonia, treponema infections, septic shock

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

Neoplasms benign, malignant and Unspecified (incl Cysts and Polyps): anal cancer, anaplastic large cell lymphomas T- and null-cell types, bile duct neoplasms malignant, endocrine neoplasms malignant and unspecified, basal cell carcinoma, lymphoma, metastases to liver, esophageal carcinoma, squamous cell carcinoma, tongue neoplasm (malignant stage unspecified)

Nervous System Disorders: cerebrovascular accident, convulsions and epilepsy, tremor (excluding congenital)

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, 48 Weeks)

Laboratory Parameter Preferred Term, %	Limit	SELZENTRY Twice daily + OBT N =421* %	Placebo + OBT N =207* %
Aspartate aminotransferase	>5.0x ULN	4.8	2.9
Alanine aminotransferase	>5.0x ULN	2.6	3.4
Total bilirubin	>5.0x ULN	5.5	5.3
Amylase	>2.0x ULN	5.7	5.8
Lipase	>2.0x ULN	4.9	6.3
Absolute neutrophil count	<750/mm^3	4.3	2.4

* 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 breastfeed 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 breastfeed 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 23% 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

Maraviroc is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because maraviroc concentrations may be increased. Maraviroc has not been studied in subjects with severe hepatic impairment. [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

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.

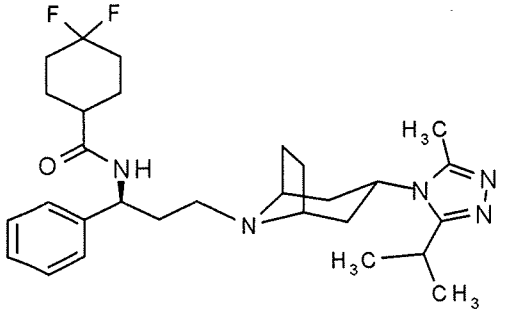
11 DESCRIPTION

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).