Effect of Food on Oral Absorption

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

Distribution

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

Metabolism

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

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

Excretion

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

Hepatic Impairment

Maraviroc is primarily metabolized and eliminated by the liver. A study compared the pharmacokinetics of a single 300 mg dose of SELZENTRY in patients with mild (Child-Pugh Class A, n=8), and moderate (Child-Pugh Class B, n=8) hepatic impairment to pharmacokinetics in healthy subjects (n=8). The mean Cmax and AUC were 11% and 25% higher, respectively, for subjects with mild hepatic impairment, and 32% and 46% higher, respectively, for subjects with moderate hepatic impairment compared to subjects with normal hepatic function. These changes do not warrant a dose adjustment. Maraviroc concentrations are higher when SELZENTRY 150 mg is administered with a strong CYP3A inhibitor compared to following administration of 300 mg without a CYP3A inhibitor, so patients with moderate hepatic impairment who receive SELZENTRY 150 mg with a strong CYP3A inhibitor should be monitored closely for maraviroc associated adverse events. The pharmacokinetics of maraviroc have not been studied in subjects with severe hepatic impairment. [*see Warnings and Precautions (5.1)*]

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. 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)		
			Cmin	AUC_{tau}	Cmax
CYP3A and/or P-gp Inhibitors					
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)
Darunavir/ritonavir 600 mg/100 mg BID	12	150 mg BID	8.00 (6.35, 10.1)	4.05 2.94, 5.59	2.29 (1.46, 3.59)
CYP3A and/or P-gp Inducers					
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)
CYP3A and/or P-gp Inhibitors and Inducers					
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. Maraviroc does not induce CYP1A2 in vitro.

In vitro results indicate that maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs.

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 6β-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 and did not cause inhibition of CYP2D6 in vitro until concentrations >100μM. 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 peripheral blood leukocyte infection. The mean EC_{50} value (50% effective concentration) for maraviroc against HIV-1 group M isolates (subtypes A to J and circulating recombinant form AE) and group O isolates ranged from 0.1 to 4.5 nM (0.05 to 2.3 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, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir). Maraviroc was additive/synergistic with the HIV fusion inhibitor enfuvirtide. Maraviroc was not active against CXCR4-tropic and dual-tropic viruses (EC_{50} value >10 μM). 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, ΔQAI (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_{50} values.

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_{50} 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.

Clinical Resistance

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). Week 48 data from treatment-experienced subjects failing maraviroc-containing regimens with CCR5-tropic virus (n=58) have identified 22 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_{50} values for maraviroc at the time of failure.

Fifteen of these viruses were sequenced in the gp120 encoding region and multiple amino acid substitutions with unique patterns in the heterogeneous V3 loop region were detected. Changes at either amino acid position 308 or 323 (HXB2 numbering) were seen in the V3 loop in 7 of the subjects with decreased maraviroc susceptibility. Substitutions outside the V3 loop of gp120 may also contribute to reduced susceptibility to maraviroc.

Tropism

In the majority of cases, treatment failure on maraviroc was associated with detection of CXCR4-using virus (i.e., CXCR4-or dual/mixed-tropic) which was not detected by the tropism assay prior to treatment. CXCR4-using virus was detected at failure in approximately 55% of subjects who failed treatment on maraviroc by Week 48, as compared to 9% 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, it was determined that 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 at Week 48 with CXCR4-using virus had a lower median increase in $CD4^+$ cell counts from baseline (+41 cells/mm^3) than those subjects failing with CCR5-tropic virus (+162 cells/mm^3). The median increase in $CD4^+$ cell count in patients failing in the placebo arm was +7 cells/mm^3.

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 48-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 48-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 [≥1 nucleoside reverse transcriptase inhibitors (NRTI), ≥1 non-nucleoside reverse transcriptase inhibitors (NNRTI), ≥2 protease inhibitors (PI), and/or enfuvirtide] or documented resistance 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%)
Race		
White	363 (85.2%)	178 (85.2%)
Black	51 (12.0%)	26 (12.4%)
Other	12 (2.8%)	5 (2.4%)
Region		
U.S.	276 (64.8%)	135 (64.6%)
Non-U.S.	150 (35.2%)	74 (35.4%)
Subjects with Previous Enfuvirtide Use	142 (33.3%)	62 (29.7)
Subjects with Enfuvirtide as Part of OBT	182 (42.7%)	91 (43.5%)
Baseline Plasma HIV-1 RNA (log_{10} 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^3) Median (Range)	167 (2-820)	171 (1-675)
Subjects with Baseline CD4+ Cell Count ≤200 cells/mm^3)	250 (58.7%)	118 (56.5%)
Subjects with Overall Susceptibility Score (OSS):[a]		
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:[b]		
PI mutations	10	10
NNRTI mutations	1	1
NRTI mutations	6	6

[a] OSS -Sum of active drugs in OBT based on combined information from genotypic and phenotypic testing.
[b] Resistance mutations based on IAS guidelines[1]

The week 48 results for the pooled Studies A4001027 and A4001028 are shown in Table 8.

Table 8
Outcomes of Randomized Treatment at Week 48
Studies A4001027 and A4001028

Outcome	SELZENTRY BID N=426	PLACEBO N=209	Mean Difference
Mean change from Baseline to Week 48 in HIV-1 RNA (log_{10} copies/mL)	-1.84	-0.78	-1.05
<400 copies/mL at Week 48	239 (56%)	47 (22%)	34%
<50 copies/mL at Week 48	194 (46%)	35 (17%)	29%
Discontinuations			
Insufficient Clinical Response	97 (23%)	113 (54%)	
Adverse Events	19 (4%)	11 (5%)	
Other	27 (6%)	18 (9%)	
Patients with treatment-emergent CDC Category C events	22 (5%)	16 (8%)	
Deaths (during study or within 28 days of last dose)	9 (2%) [a]	1 (0.5%)	

[a] one additional subject died while receiving open-label maraviroc therapy subsequent to discontinuing double-blind placebo due to insufficient response

After 48 weeks of therapy, the proportion of subjects with HIV-1 RNA <400 copies/mL receiving maraviroc compared to placebo was 56% and 22%, respectively. The mean changes in plasma HIV-1 RNA from baseline to week 48 were -1.84 $\log_{10}$ copies/mL for subjects receiving maraviroc + OBT compared to -0.78 $\log_{10}$ copies/mL for subjects receiving OBT only. The mean increase in CD4+ counts was higher on maraviroc twice daily + OBT (124 cells/mm^3) than on placebo + OBT (60 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

[1]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-0357-3.0

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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 colds, cough, fever, rash, and 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.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SELZENTRY?

- Store SELZENTRY tablets at room temperature from 59°F to 86° (15°Cto 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.

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

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

FAX 03-3340-5448 厚生労働省エイズ治療薬研究班 班長 へ送付してください。

（1）患者登録確認書・治療薬供給申請書 （新規・継続）

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

下記の患者の治療において、日本での既承認薬による治療は困難であり、厚生労働省エイズ治療薬研究班の保有する下記の薬剤による治療研究に参加することが医学的に必要であると判断し、ここに当該患者を登録して薬剤の供給を申請します。

なお、私は当該薬剤の適切な使用法や副作用などについて熟知しており、供給された薬剤は研究班の治療研究の目的に沿って、当該患者に対して十分な説明を行い、文書による同意を得た上で、私の責任において使用し、後日、使用成績を報告します。また、研究班の薬剤は医師個人輸入として輸入するもので患者に無償で提供することを承知しており、別紙にて念書を差し入れます。

フリガナ 申請者（主治医）氏名		病院名・〒住所	
診療科名			
職　責			
電話番号	（　）	FAX番号	（　）
E-Mail			

患者氏名（イニシャル）　姓［　］. 名［　］.		男　・　女	
カルテ番号［　］		生年月日	年　月　日
最近のCD4数 年　月　日	［　］/ μl	最近のHIV-RNA量 年　月　日	［　］ ［　］×10　copies/ml

研究班の薬剤を必要とする疾患

診断名1		診断日	年　月　日
診断名2		診断日	年　月　日
診断名3		診断日	年　月　日

希望薬剤

薬剤名1		1日投与量	［　］/日
薬剤名2		1日投与量	［　］/日
薬剤名3		1日投与量	［　］/日

希望理由（該当項目に○）

	既承認薬に必要な剤形がない。
	既承認薬による治療に障害が発生し継続出来ない。
	既承認薬による治療の効果が不十分である。
	目的とする適応症をもつ既承認薬がない。
	そのほか（具体的に記載してください。）

班長連絡先；TEL 03-3342-6111　FAX 03-3340-5448

ＦＡＸ ０３-３３４０-５４４８ 厚生労働省エイズ治療薬研究班 班長 へFAXでお送り下さい。
原本は施設長承諾書とともに事務局へ郵送してください。

（2）班員登録書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

私は厚生労働省エイズ治療薬研究班に研究協力者（班員）として参加することを承諾します。

フリガナ 氏　名	印
所属病院名 住　所	
診療科名	
職　責	
緊急連絡先 自宅住所　電話　FAX E-mail 等	

厚生労働省エイズ治療薬研究班の薬剤による治療研究を実施する医師は、当研究班の規定により研究協力者（班員）となっていただかなければなりません。厚生労働省エイズ治療薬研究班はヒューマンサイエンス振興財団のエイズ医薬品等開発推進事業からの研究費により運営されています。

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
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TEL　03-3342-6111 EXT5086　FAX　03-3340-5448
事務局連絡先　パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒104-0033 東京都中央区新川 1-17-21　茅場町ファーストビル 6F
TEL：03-3537-5902　FAX：03-3552-0452

（3）施設長承諾書の原本は（2）班員登録書とともに、厚生労働省エイズ治療薬研究班事務局へ郵便にて提出してください。

（3）施設長承諾書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

フリガナ 氏　名	
診療科名	
職　責	

上記の者が厚生労働省エイズ治療薬研究班に研究協力者（班員）として参加することを承諾します。

施　設　長　氏　名	印
職　　責	
施　設　名 住所	

厚生労働省エイズ治療薬研究班の薬剤による治療研究を実施する医師は、当研究班の規定により研究協力者（班員）となっていただかなければなりません。厚生労働省エイズ治療薬研究班はヒューマンサイエンス振興財団のエイズ医薬品等開発推進事業からの研究費により運営されています。

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
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TEL：03-3537-5902　FAX：03-3552-0452

本文書は３通作成し、１通は厚生労働省エイズ治療薬研究班事務局へ書留郵便で提出し、他は患者、主治医がそれぞれ保管してください。（同一薬剤の継続時は初回のみ必要です。）

（4）患者同意書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

フリガナ 申請者（主治医）氏名		病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）　姓［　　］. 名［　　］.			男　・　女
カルテ番号［　　］		生年月日	年　月　日

上記の患者さんに対して、以下の内容について十分に説明したうえ同意を得ました。

同意書

私は私の病気（　　）の治療のために、厚生労働省エイズ治療薬研究班から治療薬（　　）の提供を受けることに関して、上記の担当医師から下記の内容について説明を受け、また質問する機会も得て理解いたしましたので、この治療を受けることに同意いたします。

説明内容

1.この治療の目的と意義
2.予期される効果と副作用
3.他の治療法の有無とその内容
4.同意しない場合でも今後の治療に不利益を受けないこと。
5.同意した場合でも随時これを撤回でき今後の治療に不利益を受けないこと。
6.わからない点は、いつでも質問し説明を受けられること。
7.プライバシーは厳重に守られること。

同意取得日	年　月　日			
フリガナ 患者氏名 （自署）	印	フリガナ 代諾者氏名 （自署）	印	続柄
生年月日	年　月　日			
住所		代諾者住所		

本文書は薬剤を受け取り次第、念書とともに厚生労働省エイズ治療薬研究班事務局へ郵便で提出してください。

（5）薬剤受領書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

薬剤名	数量

上記の薬剤を確かに受領いたしました。

フリガナ 受領者（主治医） 氏名	印
診療科名	
職責	
病院名・〒住所	

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
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(6) 臨床研究使用成績調査票 (1)

臨床経過と検査値の推移を各ポイント記載する毎に本表のコピーも事務局へお送り下さい

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
電話番号	(　　)	FAX番号	(　　)
E - Mail			

患者氏名（イニシャル）　姓 [　　]. 名 [　　].		男 ・ 女	身長　　cm
カルテ番号 [　　　　　　]	生年月日	年　　月　　日	
合併症 1. 無し 2. 慢性肝炎 3. 肝硬変 4. 腎障害 5. 糖尿病 6. 高脂血症 7. 血友病 8. その他 (　　　　)			

今回使用した研究班の薬（研究班の薬剤を全てを記載して下さい。）

薬剤名	含有量・剤形	1日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /

研究班の薬剤を投与中に使用した併用薬を全て記載してください。

薬剤名	剤形	1日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
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		/日　回/日	/ / - / /
		/日　回/日	/ / - / /
		/日　回/日	/ / - / /

(7) 臨床研究使用成績調査票 (2)

臨床経過と臨床検査値の推移　　ポイント毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　　責			
患者氏名（イニシャル）　姓 [　　]. 名 [　　].		男 ・ 女	
カルテ番号 [　　]		生年月日	年　　月　　日

検査ポイント	投与前	開始後　　ヶ月	開始後　　ヶ月	開始後　　ヶ月
検査日	年　月　日	年　月　日	年　月　日	年　月　日
外来・入院	外来・入院	外来・入院	外来・入院	外来・入院
体重	Kg	Kg	Kg	Kg
体温	℃	℃	℃	℃
血圧	/　mmHg	/　mmHg	/　mmHg	/　mmHg
症状の程度	3+・2+・1+・-	3+・2+・1+・-	3+・2+・1+・-	3+・2+・1+・-
CD4細胞数	/μl	/μl	/μl	/μl
HIV-RNA量	×10　/ml	×10　/ml	×10　/ml	×10　/ml
白血球数 WBC	/μl	/μl	/μl	/μl
赤血球数 RBC	/μl	/μl	/μl	/μl
Hb	g/dl	g/dl	g/dl	g/dl
Htc	%	%	%	%
血小板数	/μl	/μl	/μl	/μl
好中球%	%	%	%	%
好酸球%	%	%	%	%
好塩基球%	%	%	%	%
リンパ球%	%	%	%	%
単球%	%	%	%	%
TP	g/dl	g/dl	g/dl	g/dl
T-Bil	mg/dl	mg/dl	mg/dl	mg/dl
GOT	IU/L	IU/L	IU/L	IU/L
GPT	IU/L	IU/L	IU/L	IU/L
γGTP	IU/L	IU/L	IU/L	IU/L
BUN	mg/dl	mg/dl	mg/dl	mg/dl
クレアチニン	mg/dl	mg/dl	mg/dl	mg/dl
尿酸	mg/dl	mg/dl	mg/dl	mg/dl
総コレステロール	mg/dl	mg/dl	mg/dl	mg/dl
中性脂肪	mg/dl	mg/dl	mg/dl	mg/dl
グルコース	mg/dl	mg/dl	mg/dl	mg/dl
尿蛋白	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿糖	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿潜血反応	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿沈さ異常と内容	無・(　　)	無・(　　)	無・(　　)	無・(　　)

(8) 臨床研究使用成績調査票 (3)

その他の重要な臨床検査成績
XP，CT，MRI，シンチグラム等

検査毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　　責			
患者氏名（イニシャル）　姓［　　］. 名［　　］.		男 ・ 女	
カルテ番号［　　］		生年月日	年　　月　　日