12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Exposure Response Relationship

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

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

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

Effects on Electrocardiogram

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

12.3 Pharmacokinetics

Table 5 Mean Maraviroc Pharmacokinetic Parameters

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

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

Absorption

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

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

Effect of Food on Oral Absorption

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

Distribution

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

Metabolism

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

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

Excretion

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

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

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

ISENTRESS (raltegravir) Tablets
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------
ISENTRESS™ is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents (1).

The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients (1).

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

- 400 mg administered orally, twice daily with or without food (2.1).

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 400 mg (3).

----------CONTRAINDICATIONS ----------
None

----------WARNINGS AND PRECAUTIONS----------
Monitor for Immune Reconstitution Syndrome (5.1)

Drug Interactions

- Caution should be used when coadministering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir (5.2).

---------- ADVERSE REACTIONS----------

- The most common adverse reactions (>10%) of all intensities, reported in subjects in either the ISENTRESS or the placebo treatment group, regardless of causality were: nausea, headache, diarrhea and pyrexia (6.1).
- Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy:

- ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are encouraged to register pregnant women exposed to ISENTRESS by calling 1-800-258-4263 so that Merck can monitor maternal and fetal outcomes (8.1).

Nursing Mothers:

- Breast-feeding is not recommended while taking ISENTRESS (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ISENTRESS[1] in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients 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 up through 24 weeks in two controlled studies of ISENTRESS. These studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response *[see Clinical Studies (14)]*.

The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients.

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food.

3 DOSAGE FORMS AND STRENGTHS

400 mg pink, oval-shaped, film-coated tablets with "227" on one side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, *Mycobacterium* tuberculosis, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

5.2 Drug Interactions

Caution should be used when coadministering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS

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.

Treatment-Experienced Studies

The safety assessment of ISENTRESS in treatment-experienced subjects is based on the pooled safety data from the randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and

[1] Trademark of MERCK & CO., Inc.

BENCHMRK 2 (Protocols 018 and 019), and the randomized, double-blind, placebo-controlled, dose-ranging trial (Protocol 005) in antiretroviral treatment-experienced HIV-1 infected adult subjects reported using the recommended dose of ISENTRESS 400 mg twice daily in combination with optimized background therapy (OBT) in 507 subjects, in comparison to 282 subjects taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 332.2 patient-years in the ISENTRESS 400 mg twice daily group and 150.2 patient-years in the placebo group.

The most commonly (>10%) reported adverse reactions, of all intensities, regardless of causality in subjects treated with ISENTRESS and OBT versus placebo and OBT are presented in Table 1.

Table 1: Percentage of Subjects with the Most Commonly Reported (>10%) Adverse Reactions of All Intensities* and Regardless of Causality Occurring in Treatment-Experienced Adult Subjects

System Organ Class, Adverse Reactions	Randomized Studies P005, P018 and P019	
	ISENTRESS 400 mg twice daily + OBT (n=507)† %	Placebo + OBT (n=282)† %
Gastrointestinal Disorders		
Diarrhea	16.6	19.5
Nausea	9.9	14.2
Nervous System Disorders		
Headache	9.7	11.7
General Disorders and Administration Site Conditions		
Pyrexia	4.9	10.3

*Intensities are defined as follows: Mild (awareness of sign or symptom, but easily tolerated); Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
†n=total number of subjects per treatment group.

The clinical adverse reactions listed below were considered by investigators to be of moderate to severe intensity and causally related to any drug in the combination regimen (ISENTRESS/placebo alone or in combination with OBT, or OBT alone):

Common Adverse Reactions

Drug-related clinical adverse reactions of moderate to severe intensity occurring in ≥2% of subjects treated with ISENTRESS + OBT are presented in Table 2.

Table 2: Percentage of Subjects with Drug-Related* Adverse Reactions of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Experienced Adult Subjects

System Organ Class, Adverse Reactions	Randomized Studies P005, P018 and P019	
	ISENTRESS 400 mg Twice Daily + OBT (n = 507)‡ %	Placebo + OBT (n = 282)‡ %
Gastrointestinal Disorders		
Diarrhea	3.7	4.6
Nausea	2.2	3.2
Nervous System Disorders		
Headache	2.4	1.4

*Includes adverse reactions at least possibly, probably, or very likely related to the drug.
†Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
‡n=total number of subjects per treatment group.

Less Common Adverse Reactions

Drug-related adverse reactions occurring in at least 1% but less than 2% of treatment-experienced subjects (n=507) receiving ISENTRESS + OBT and of moderate (discomfort enough to cause interference with usual activity) to severe (incapacitating with inability to work or do usual activity) intensity are listed below by system organ class:

Gastrointestinal Disorders: abdominal pain, vomiting
General Disorders and Administration Site Conditions: asthenia, fatigue
Nervous System Disorders: dizziness
Skin and Subcutaneous Tissue Disorders: lipodystrophy acquired

Discontinuations

In the pooled analyses for studies P005, P018 and P019, the rates of discontinuation of therapy due to adverse reactions were 2.0% in subjects receiving ISENTRESS + OBT and 1.4% in subjects receiving placebo + OBT.

Serious Events

Drug Related

The following serious drug-related reactions were reported in the clinical studies, P005, P018 and P019: hypersensitivity (hypersensitivity was seen in 2 subjects with ISENTRESS; therapy was interrupted and upon rechallenge the subjects were able to resume drug), anemia, neutropenia, myocardial infarction, gastritis, hepatitis, herpes simplex, toxic nephropathy, renal failure, chronic renal failure and renal tubular necrosis.

Regardless of Drug Relationship

Cancers were reported in treatment-experienced subjects who initiated ISENTRESS with OBT; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ cell counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The cancers included Kaposi's sarcoma, lymphoma, squamous cell carcinoma, hepatocellular carcinoma and anal cancer. Most subjects had other risk factors for cancer including tobacco use, papillomavirus and active hepatitis B virus infection. It is unknown if these cancer diagnoses were related to ISENTRESS use.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 3). Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

Patients with Co-existing Conditions

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus

In the clinical studies, P018 and P019, subjects with chronic (but not acute) active hepatitis B and/or hepatitis C virus co-infection (N = 113/699 or 16.2%) were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). The rates of AST and ALT abnormalities were somewhat higher in the subgroup of subjects with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. In general the safety profile of ISENTRESS in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to subjects without hepatitis B and/or hepatitis C virus co-infection. Grade 2 or higher laboratory abnormalities that represent a worsening from baseline of AST, ALT or total bilirubin occurred in 26%, 27% and 12%, respectively, of raltegravir-treated coinfected subjects as compared to 9%, 8% and 7% of all other raltegravir-treated subjects.

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily in P005, P018 and P019 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 3.

Table 3: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies P005, P018 and P019 ISENTRESS 400 mg Twice Daily + OBT (N = 507)	Placebo + OBT (N = 282)
Hematology			
Absolute neutrophil count ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	3.7%	7.4%
Grade 3	0.50 - 0.749	2.4%	2.5%
Grade 4	<0.50	1.0%	1.1%

Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	1.0%	2.8%
Grade 3	6.5 - 7.4	1.0%	0.4%
Grade 4	<6.5	0.0%	0.0%
Platelet count ($10^3/\mu L$)			
Grade 2	50 - 99.999	3.7%	5.7%
Grade 3	25 - 49.999	0.4%	0.4%
Grade 4	<25	0.8%	0.4%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	9.3%	6.8%
Grade 3	251 - 500	1.4%	1.4%
Grade 4	>500	0.0%	0.0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5.3%	6.7%
Grade 3	2.6 - 5.0 x ULN	3.2%	2.5%
Grade 4	>5.0 x ULN	0.8%	0.0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	9.1%	5.7%
Grade 3	5.1 - 10.0 x ULN	2.2%	2.1%
Grade 4	>10.0 x ULN	0.4%	0.7%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	6.9%	7.8%
Grade 3	5.1 - 10.0 x ULN	3.0%	1.4%
Grade 4	>10.0 x ULN	0.6%	1.1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	2.0%	0.4%
Grade 3	5.1 - 10.0 x ULN	0.4%	1.1%
Grade 4	>10.0 x ULN	0.4%	0.4%
Serum pancreatic amylase test			
Grade 2	1.6 - 2.0 x ULN	1.4%	0.7%
Grade 3	2.1 - 5.0 x ULN	3.6%	2.1%
Grade 4	>5.0 x ULN	0.2%	0.0%
Serum lipase test			
Grade 2	1.6 - 3.0 x ULN	3.4%	1.8%
Grade 3	3.1 - 5.0 x ULN	0.6%	0.4%
Grade 4	>5.0 x ULN	0.2%	0.0%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2.2%	1.4%
Grade 3	10.0 - 19.9 x ULN	2.4%	1.8%
Grade 4	≥20.0 x ULN	2.2%	0.7%

ULN = Upper limit of normal range

7 DRUG INTERACTIONS

7.1 Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents metabolized by CYP3A4 *in vivo* by demonstrating a lack of effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Similarly, raltegravir is not an inhibitor (IC_{50}>50 µM) of the UDP-glucuronosyltransferases (UGT) tested (UGT1A1, UGT2B7), and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, ISENTRESS is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors, NNRTIs, methadone, opioid analgesics, statins, azole antifungals, proton pump inhibitors, oral contraceptives, and anti-erectile dysfunction agents).

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: lamivudine, tenofovir.

7.2 Effect of Other Agents on the Pharmacokinetics of Raltegravir

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes. Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway.

Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, caution should be used when coadministering ISENTRESS with rifampin or other strong inducers of UGT1A1 *[see Warnings and Precautions (5.2)]*. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less strong inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used with the recommended dose of ISENTRESS.

Similar to rifampin, tipranavir/ritonavir reduces plasma concentrations of ISENTRESS. However, approximately 100 subjects received raltegravir in combination with tipranavir/ritonavir in Protocols 018 and 019. Comparable efficacy was observed in this subgroup relative to subjects not receiving tipranavir/ritonavir. Based on these data, tipranavir/ritonavir may be coadministered with ISENTRESS without dose adjustment of ISENTRESS.

Atazanavir, a strong inhibitor of UGT1A1, and atazanavir/ritonavir increase plasma concentrations of raltegravir. However, concomitant use of ISENTRESS and atazanavir/ritonavir did not result in a unique safety signal in Protocol 005 and Protocols 018 and 019. Based on these data, atazanavir/ritonavir may be coadministered with ISENTRESS without dose adjustment of ISENTRESS.

Coadministration of ISENTRESS with other drugs that inhibit UGT1A1 may increase plasma levels of raltegravir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients.

Developmental toxicity studies were performed in rabbits (at oral doses up to 1000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The reproductive toxicity study in rats was performed with pre-, peri-, and postnatal evaluation. The highest doses in these studies produced systemic exposures in these species approximately 3- to 4-fold the exposure at the recommended human dose. In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal changes were observed in rabbits. However, treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 3-fold the exposure at the recommended human dose).

Placenta transfer of drug was demonstrated in both rats and rabbits. At a maternal dose of 600 mg/kg/day in rats, mean drug concentrations in fetal plasma were approximately 1.5- to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours postdose, respectively. Mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose at a maternal dose of 1000 mg/kg/day in rabbits.

Antiretroviral Pregnancy Registry

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

8.3 Nursing Mothers

Breast-feeding is not recommended while taking ISENTRESS. In addition, it is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. Mean drug concentrations in milk were approximately 3-fold greater than those in maternal plasma at a maternal dose of 600 mg/kg/day in rats. There were no effects in rat offspring attributable to exposure of ISENTRESS through the milk.

8.4 Pediatric Use

Safety and effectiveness of ISENTRESS in pediatric patients less than 16 years of age have not been established.

8.5 Geriatric Use

Clinical studies of ISENTRESS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied *[see Clinical Pharmacology (12.3)]*.

8.7 Use in Patients with Renal Impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects were observed. No dosage adjustment is necessary *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

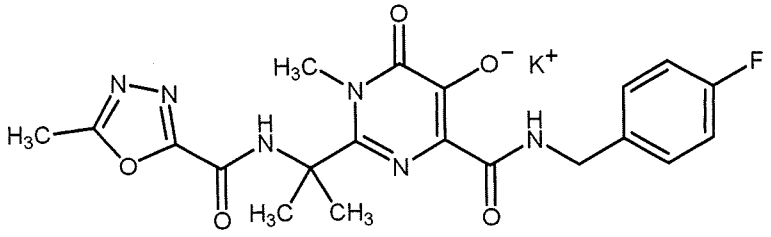
No specific information is available on the treatment of overdosage with ISENTRESS. Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. Occasional doses of up to 1800 mg per day were taken in the P005/P018 & P019 studies without evidence of toxicity.

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. The extent to which ISENTRESS may be dialyzable is unknown.

11 DESCRIPTION

ISENTRESS contains raltegravir potassium, a human immunodeficiency virus integrase strand transfer inhibitor. The chemical name for raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt.

The empirical formula is $C_{20}H_{20}FKN_6O_5$ and the molecular weight is 482.51. The structural formula is:



Raltegravir potassium is a white to off-white powder. It is soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and acetonitrile and insoluble in isopropanol.

Each film-coated tablet of ISENTRESS for oral administration contains 434.4 mg of raltegravir potassium (as salt), equivalent to 400 mg of raltegravir (free phenol) and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.