

DATA SHEET

CELSENTRI[®] (maraviroc)

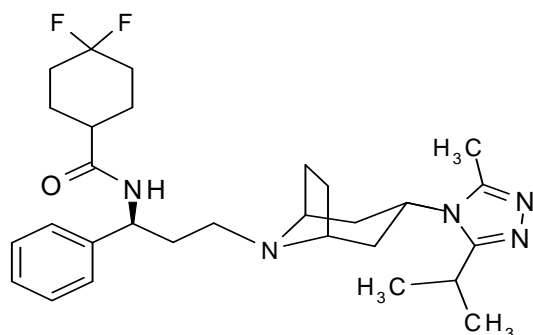
NAME OF THE MEDICINE

CELSENTRI[®] 150 mg and 300 mg film-coated tablets.

DESCRIPTION

Maraviroc is a white to pale coloured powder with a molecular weight of 513.67. It is highly soluble across the physiological pH range (pH 1.0 to 7.5). 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 C₂₉H₄₁F₂N₅O and the structural formula is:



CAS no.: 376348-65-1

CELSENTRI is supplied for oral administration in two strengths: 150 and 300 mg blue, biconvex, oval film-coated tablets debossed with “MVC 150” or “MVC 300” on one side. Each film-coated tablet contains either 150 or 300 mg of maraviroc and the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), sodium starch glycolate, magnesium stearate. The film-coat [Opadry[®] II Blue (85G20583)] contains indigo carmine CI73015, soya lecithin, macrogol 3350, polyvinyl alcohol, talc and titanium dioxide.

PHARMACOLOGY

Pharmacological actions

Pharmacotherapeutic group: Antivirals for systemic use, Other Antivirals

ATC code: J05AX09

Mechanism of action:

Maraviroc is a member of a therapeutic class called CCR5 antagonists. Maraviroc selectively binds to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells.

Antiviral activity in vitro:

Maraviroc inhibits the entry and replication of CCR5-tropic laboratory strains and clinical isolates of HIV-1 in models of acute T-cell infection. The in vitro IC₅₀ (50% inhibitory concentration) for maraviroc against the replication of 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). HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and enfuvirtide were all susceptible to maraviroc in cell culture.

When used with other antiretroviral agents in vitro, the combination of maraviroc produced additive/synergistic antiviral effects with protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) and was generally additive with the NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine and zidovudine) and the NNRTIs (delavirdine, efavirenz and nevirapine). Maraviroc was additive/synergistic with the HIV fusion inhibitor enfuvirtide. Protein binding studies have shown that the antiviral activity of maraviroc decreases on average 2-fold in conditions where plasma proteins are present.

Maraviroc has no activity against viruses that use CXCR4 as their co-receptor (CXCR4-tropic or dual-tropic, collectively termed 'CXCR4-using' virus below). The antiviral activity of maraviroc against HIV-2 has not been evaluated.

Resistance:

Viral escape from maraviroc can occur via 2 routes: the selection of virus which can use CXCR4 as its entry co-receptor (CXCR4-using virus) or the selection of virus that continues to use exclusively CCR5 (CCR5-tropic virus).

Resistance in vitro:

HIV-1 variants with reduced susceptibility to maraviroc have been selected in vitro, following serial passage of two CCR5-tropic clinical viral isolates. The maraviroc-resistant viruses remained CCR5-tropic and there was no conversion from a CCR5-tropic virus to a CXCR4-using virus.

Phenotypic resistance: concentration response curves for the maraviroc-resistant viruses were characterized by curves that did not reach 100% inhibition in assays using serial dilutions of maraviroc, consistent with the resistant viruses being able to use CCR5 as a co-receptor for cell entry even when maraviroc is bound. Traditional EC₅₀ fold-change was not a useful parameter to measure phenotypic resistance, as those values were sometimes unchanged despite significantly reduced sensitivity.

Genotypic resistance: mutations were found to accumulate in the gp120 envelope glycoprotein (the viral protein that binds to the CCR5 co-receptor). The position of these mutations was not consistent between different isolates. Hence, the relevance of these mutations to maraviroc susceptibility in other viruses is not known.

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Tropism switching from CCR5- to CXCR4-tropic variants occurred spontaneously in vitro in maraviroc-treated and control cultures, and represents a theoretical mechanism for maraviroc resistance in vivo.

Cross-resistance:

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and enfuvirtide were all susceptible to maraviroc in cell culture. Maraviroc-resistant viruses that emerged in vitro remained sensitive to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.

Resistance in patients:

Treatment-experienced patients: In the pivotal studies (MOTIVATE 1 and MOTIVATE 2), 7.6% of patients had a change in tropism result from CCR5-tropic to CXCR4-tropic or dual/mixed-tropic between screening and baseline (a period of 4-6 weeks).

Failure with CXCR4-using virus:

CXCR4-using virus was detected at failure in approximately 60% of subjects who failed treatment on maraviroc, as compared to 6% of subjects who experienced treatment failure in the OBT alone 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 OBT alone arm) in whom CXCR4-using virus was detected. This analysis indicated that CXCR4-using virus emerged from a pre-existing CXCR4-using reservoir not detected at baseline, rather than from mutation of CCR5-tropic virus present at baseline. An analysis of tropism following failure of maraviroc therapy with CXCR4-using virus, demonstrated that the virus population reverted back to CCR5 tropism in the majority of patients during follow up after discontinuation of maraviroc. Out of 44 patients studied, the virus population in 30 reverted back to exclusively CCR5-tropism during a median follow-up of 203 days; 14 patients continued to have detectable CXCR4-using virus. However, the follow-up period in these patients was shorter (median 16 days). At time of failure with CXCR4-using virus, the resistance pattern to other antiretrovirals appears similar to that of the CCR5-tropic population at baseline, based on available data. Hence, in the selection of a treatment regimen, it should be assumed that viruses forming part of the previously undetected CXCR4-using population (i.e. minor viral population) harbours the same resistance pattern as the CCR5-tropic population.

Failure with CCR5-tropic virus:

Phenotypic resistance: in patients with CCR5-tropic virus at time of treatment failure with maraviroc, 15 out of 36 patients had virus with reduced sensitivity to maraviroc. In the remaining 21 patients, there was no evidence of virus with reduced sensitivity. A clinically-validated cut-off value for reduced virological response has not yet been established. Therefore, continued use of maraviroc after treatment failure cannot be generally recommended regardless of the viral tropism seen.

Genotypic resistance: the resistance profile of virus from treatment-experienced subjects has not yet been fully characterised. Specific mutations associated with reduced susceptibility to

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maraviroc have been identified in viruses from 5 patients but for each patient there was a unique pattern of mutations.

Pharmacokinetics

Absorption

Peak maraviroc plasma concentrations are attained 0.5-4 hours following single oral doses of 1-1200 mg administered to healthy 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

Co-administration of a 300 mg 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 TRIALS). Therefore, maraviroc can be taken with or without food at the recommended dose (see DOSAGE AND ADMINISTRATION).

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.

Preclinical data indicate low cerebrospinal fluid exposure with concentrations of maraviroc in the CSF of rats approximately 10% of free plasma concentrations.

Metabolism

Studies in humans and in vitro studies using human liver microsomes and expressed enzymes have demonstrated that maraviroc is principally metabolised by the cytochrome P450 system, with CYP3A4 being the major metabolising enzyme. In vitro studies indicate that polymorphic enzymes CYP2C9, CYP2D6 and CYP2C19 do not contribute significantly to the metabolism of maraviroc.

Maraviroc is the major circulating component (accounting for approximately 42% of 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 (approximately 22% of plasma 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.

Elimination

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 faeces over 168 hours. Maraviroc was the major component present in urine

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(mean of 8% dose) and faeces (mean of 26% dose). The remainder was excreted as metabolites.

Paediatric

The pharmacokinetics of maraviroc in paediatric patients have not been established (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Elderly

The pharmacokinetics of maraviroc have not been formally studied in elderly patients over 65 years of age (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Renal impairment

The pharmacokinetics of maraviroc have not been studied in patients with renal impairment. However, renal clearance contributes approximately 23% of maraviroc total clearance in the absence of CYP3A4 inhibitors, therefore the impact of renal impairment on maraviroc elimination should be minimal. In the presence of metabolic inhibitors, renal clearance may account for up to 70% of total clearance of maraviroc and hence renal impairment may result in increased maraviroc exposures in this case (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Hepatic impairment

The pharmacokinetics of maraviroc have not been sufficiently studied in patients with hepatic impairment. Since maraviroc is metabolised by the liver, concentrations are likely to be increased in these patients (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Race

No dosage adjustment is necessary on the basis of race.

Gender

No dosage adjustment is necessary on the basis of gender.

CLINICAL TRIALS

Studies in CCR5-tropic Treatment-Experienced Patients:

The clinical efficacy of CELSENTRI (in combination with other antiretroviral medicinal products) on plasma HIV RNA levels and CD4 counts have been investigated in two ongoing, randomised, double blind, multicentre studies (A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2) in patients infected with CCR5 tropic HIV-1 virus. These studies are supported by one study (A4001029) in patients infected with dual/mixed tropic HIV-1 virus.

Patients 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 medicinal product from three of the four antiretroviral medicinal product 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 patients received an Optimised Background Therapy (OBT) consisting of 3 to 6 antiretroviral medicinal products (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 OBT, patients were then randomised in a 2:2:1 ratio to CELSENTRI 300 mg once daily, CELSENTRI 300 mg twice daily, or placebo. Doses were adjusted based on background therapy as described in DOSAGE AND ADMINISTRATION section.

In the pooled analysis for studies A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2, the demographics and baseline characteristics of the treatment groups were comparable (Table 1 and 2). Table 1 compares the demographic characteristics of the patients in the CELSENTRI 300 mg twice daily + OBT and OBT alone arms. Table 2 compares the baseline characteristics of the patients on CELSENTRI 300 mg twice daily + OBT with those on OBT alone.

Table 1: Demographic Characteristics of Patients in Studies A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2 (Pooled Analysis)

Demographic Characteristics	CELSENTRI 300 mg twice daily + OBT N = 426	OBT alone N = 209
Age (years) (Range, years)	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%)	26 (12.4%)
Other	12 (2.8%)	5 (2.4%)
Mean Baseline Plasma HIV-1 RNA (log ₁₀ copies/mL)	4.85	4.86
Median Baseline CD4+ Cell Count (cells/mm ³) (range, cells/mm ³)	166.8 (2.0-820.0)	171.3 (1.0-675.0)
Patients with Screening Viral Load ≥100,000 copies/mL	179 (42.0%)	84 (40.2%)
Patients with Baseline CD4+ Cell Count ≤200 cells/mm ³	250 (58.7%)	118 (56.5%)

Table 2: Baseline Characteristics of Patients in Studies A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2 (Pooled Analysis)

Demographic Characteristics	CELSENTRI 300 mg Twice daily + OBT N =426	OBT alone N = 209
Number (Percentage) of patients with GSS score:		
0	102 (23.9%)	51 (24.4%)
1	138 (32.4%)	53 (25.4%)
2	80 (18.8%)	41 (19.6%)

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≥3	104 (24.4%)	59 (28.2%)
Number (Percentage) of patients with enfuvirtide resistance mutations	90/424 (21%)	45/209 (22%)
Median Number of Resistance-Associated [†] :	10	10
PI mutations	1	1
NNRTI mutations	6	6
NRTI mutations		

[†] Based on the IAS-USA list of mutations (March 2005): D30N, L33F/I, M46I/L, G48V, I50L/V, V82A/F/L/S/T, I84A/C/V, L90M

After 24 weeks of therapy, the mean change in plasma HIV-1 RNA from baseline to week 24 was -1.96 log₁₀ copies/mL for patients receiving CELSENTRI 300 mg twice daily + OBT compared to -0.99 log₁₀ copies/mL for patients receiving OBT alone. The mean increase in CD4+ counts was higher on CELSENTRI 300 mg twice daily + OBT (106.34 cells/mm³) than on OBT alone (57.37 cells/mm³). The proportion of subjects with HIV-1 RNA <400/<50 copies/mL was 60.8%/45.3% for patients receiving CELSENTRI 300 mg twice daily + OBT, compared to 27.8%/23% for patients receiving OBT alone (see Table 3).

Table 3: Outcomes of Randomised Treatment at Week 24 (Pooled Studies A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2)

Outcomes	CELSENTRI 300 mg twice daily + OBT N=426	OBT alone N=209	Treatment Difference	Confidence Interval*	p-value
HIV-1 RNA Change from baseline (log ₁₀ copies/mL)	-1.96	-0.99	-0.97	(-1.24, -0.71)	< 0.0001
CD4 cell count Change from baseline (cells/mm ³)	106.34	57.37	48.97	(31.08, 66.85)	< 0.0001
Percentage of patients with HIV RNA <400 copies/ml or at least ≥1.0 log ₁₀ decrease	69.2%	35.9%	Odds ratio: 4.25	(2.98, 6.07)	< 0.0001
Number (%) of patients with HIV RNA <400 copies/ml	259 (60.8%)	58 (27.8%)	Odds ratio: 4.49	(3.10, 6.51)	< 0.0001
Number (%) of patients with HIV RNA <50 copies/ml	193 (45.3%)	48 (23.0%)	Odds ratio: 3.02	(2.05, 4.44)	< 0.0001

*For all efficacy endpoints the confidence intervals were 95%, except for HIV-1 RNA Change from baseline which was 97.5%

CELSENTRI 300 mg twice daily + OBT was associated with a higher proportion of patients reaching <400 copies/ml or <50 copies/ml across all subgroups based on baseline HIV-1

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RNA and the number of active antiretrovirals (ARVs) in the OBT. However, subjects with baseline HIV-1 RNA <5.0 log₁₀ copies/ml and/or other active ARVs in their OBT were more likely to achieve a HIV-1 RNA of <400 copies/ml or <50 copies/ml on either of the treatment regimens (see Table 4).

Table 4: Proportion of Patients achieving <400 copies/ml and <50 copies/ml at Week 24 by subgroup (pooled Studies A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2, ITT)

Subgroups	HIV-1 RNA <400 copies/ml		HIV-1 RNA <50 copies/ml	
	CELSENTRI 300 mg twice daily + OBT N=426	OBT alone N=209	CELSENTRI 300 mg twice daily + OBT N=426	OBT alone N=209
Baseline HIV-1 RNA <5.0 log ₁₀ copies/ml	182/243 (74.90%)	50/123 (40.65%)	140/243 (57.61%)	42/123 (34.15%)
Baseline HIV-1 RNA ≥5.0 log ₁₀ copies/ml	91/176 (51.70%)	13/84 (15.48%)	61/176 (34.66%)	9/84 (10.71%)
0 Active ARVs in background ^{1,2}	50/101 (49.50%)	3/51 (5.88%)	33/101 (32.67%)	1/51 (1.96%)
1 Active ARV in background ^{1,2}	83/137 (60.58%)	7/53 (13.21%)	64/137 (46.72%)	6/53 (11.32%)
2 Active ARVs in background ^{1,2}	60/79 (75.95%)	18/41 (43.90%)	44/79 (55.70%)	15/41 (36.59%)
≥3 Active ARVs in background ^{1,2}	79/100 (79%)	34/57 (59.65%)	59/100 (59%)	29/57 (50.88%)

¹Discontinuations or virological failures considered as failures.

²Based on GSS score.

Studies in Non-CCR5-tropic Treatment-Experienced Patients:

Study A4001029 was an exploratory, randomised, double blind, multicentre trial to determine the safety and efficacy of CELSENTRI in patients infected with dual/mixed co-receptor tropic HIV-1. The inclusion/exclusion criteria were similar to those for studies A4001027 MOTIVATE-1 and A4001028 MOTIVATE -2 above and the patients were randomised in a 1:1:1 ratio to CELSENTRI 300 mg once daily, CELSENTRI 300 mg twice daily or OBT alone. The mean changes in viral load and CD4+ counts are shown in Table 5.

Table 5: Outcomes of Randomised Treatment at Week 24 in Dual/Mixed-tropic Patients (Study A4001029)

Outcome	CELSENTRI 300 mg twice daily + OBT N = 52	OBT alone N= 58
Baseline characteristics: - Mean HIV-1 RNA (log ₁₀ copies/mL) - Median CD4 cell count (cells/μL)	5.10 43.1	5.0 41.4
Mean change from baseline HIV-1 RNA to week 24	-1.2	-0.96
Percentage of patients <400 copies/mL at week 24	30.8	24.1
Percentage of patients <50 copies/mL at week 24	26.9	15.5
Change from baseline absolute CD4 counts	+62	+36

INDICATIONS

CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable.

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced patients.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

CELSENTRI should be taken as part of an antiretroviral combination regimen. CELSENTRI should optimally be combined with other antiretrovirals to which the patient's virus is sensitive (see PHARMACOLOGY, Pharmacological actions).

CELSENTRI should only be used when only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus not detected) as determined by an adequately validated and sensitive detection method (see INDICATIONS, DOSAGE AND ADMINISTRATION, and PHARMACOLOGY, Pharmacological actions). The viral tropism cannot be predicted by treatment history or assessment of stored samples.

Changes in viral tropism occur over time in HIV-1 infected patients. Therefore there is a need to start therapy shortly after a tropism test.

Dose Adjustment: physicians should ensure that appropriate dose adjustment of CELSENTRI is made when CELSENTRI is co-administered with CYP3A4 inhibitors and/or inducers since maraviroc concentrations and its therapeutic effects may be affected (see DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES). Please also refer to the respective prescribing information of the other antiretroviral medicinal products used in the combination.

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Information for Patients: patients should be advised that antiretroviral therapies including CELSENTRI have not been shown to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. They should continue to use appropriate precautions. Patients should also be informed that CELSENTRI is not a cure for HIV-1 infection.

Cardiovascular Safety: Use with caution in patients at increased risk for cardiovascular events. Eleven subjects (1.3%) who received CELSENTRI had cardiovascular events that may be linked to coronary heart diseases including myocardial ischemia and/or infarction during the Phase 3 studies in CCR5 tropic patients [total exposure of 526 patient-years (267 patient-years for BD + 259 patient-years for OD)], while no subjects who received placebo had such events (total exposure 99 patient-years). These subjects generally had cardiac disease or cardiac risk factors prior to CELSENTRI use, and the relative contribution of CELSENTRI to these events is not known.

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

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.

Potential Risk of Infections: CELSENTRI antagonises 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 infections, as well as AIDS-defining category C infections, was comparable in the treatment groups during the Phase 3 studies of CELSENTRI. Patients should be monitored closely for evidence of infections while receiving CELSENTRI.

Potential Risk of Malignancy: While no increase in malignancy has been observed in subjects receiving CELSENTRI in Phase 3 studies, 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 required to more fully assess whether CELSENTRI increases the risk of malignancy.

Hepatic safety: the safety and efficacy of CELSENTRI have not been specifically studied in patients with significant underlying liver disorders.

A case of possible CELSENTRI-induced hepatotoxicity with allergic features has been reported in a study in healthy volunteers. In addition, an increase in hepatic adverse reactions with CELSENTRI 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

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abnormalities (see ADVERSE EFFECTS). Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice.

Discontinuation of CELSENTRI should be considered in any patient with signs or symptoms of acute hepatitis, in particular if drug-related hypersensitivity is suspected or with increased liver transaminases combined with rash or other systemic symptoms of potential hypersensitivity (e.g. pruritic rash, eosinophilia or elevated IgE).

Since there are very limited data in patients with hepatitis B/C co-infection, special caution should be exercised when treating these patients with CELSENTRI. In case of concomitant antiviral therapy for hepatitis B and/or C, please refer also to the relevant prescribing information for these medicinal products.

There is limited experience in patients with reduced hepatic function, therefore CELSENTRI should be used with caution in this population (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics).

Renal impairment: the safety and efficacy of CELSENTRI have not been specifically studied in patients with renal impairment, therefore CELSENTRI 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 and hence renal impairment is not expected to significantly alter maraviroc exposures.

In the presence of metabolic inhibitors, renal clearance may account for up to 70% of total clearance of maraviroc, hence renal impairment may result in increased maraviroc exposures in this case. Therefore, CELSENTRI should be used with caution in patients with renal impairment ($CL_{cr} < 80\text{ml/min}$) who are also taking potent CYP3A4 inhibitors (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. CELSENTRI may cause dizziness. Patients should be instructed that if they experience dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

Effects on fertility

Maraviroc did not impair mating or fertility of male or female rats, and did not affect sperm of male rats at oral doses up to 1000 mg/kg/day. Systemic exposure to free maraviroc at this dose level was 39-fold higher than the estimated free clinical $AUC_{0-24\text{ h}}$ for a 300 mg twice daily dose.

Use in pregnancy

Pregnancy Category: B1

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Embryofetal development studies were conducted in rats and rabbits at oral doses up to 1000 and 200 mg/kg/day, respectively. Systemic exposure to free maraviroc at these doses was 40- (rats) and 35-times (rabbits) the free clinical $AUC_{0-24\text{ h}}$ for a 300 mg twice daily dose. The animal studies revealed no evidence of harm to the embryo or fetus except for an increase in pre-implantation loss in rats dosed with maraviroc at a maternotoxic dose of 1000 mg/kg/day from 2 weeks prior to mating to gestation day 7.

Pre- and postnatal development studies were performed in rats at oral doses up to 1000 mg/kg/day (relative exposure to free maraviroc, 28). The only effect in the offspring was a slight increase in motor activity in high-dose male rats at both weaning and as adults, while no effects were seen in females. Other developmental parameters of these offspring, including fertility and reproductive performance, were not affected by the maternal administration of maraviroc.

No meaningful clinical data on exposure during pregnancy are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or postnatal development. CELSENTRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation

Studies in lactating rats indicate that maraviroc and its metabolites are extensively excreted into rat milk. It is not known whether maraviroc is excreted into human milk. Mothers must be instructed not to breast-feed if they are receiving CELSENTRI because of the potential for HIV transmission and possible adverse effects in breast-fed infants.

Paediatric use

The safety and efficacy of CELSENTRI in paediatric patients have not been established, therefore use in children is not recommended (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics)

Use in the elderly

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 CELSENTRI in elderly patients, also reflecting the greater frequency of decreased hepatic and renal function, of concomitant disease and other drug therapy (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics).

Carcinogenicity

Maraviroc was evaluated for carcinogenic potential in a 6 month transgenic mouse study and a 24 month study in rats. In mice, maraviroc did not cause a statistically significant increase in the incidence of any tumour type at oral doses up to 1500 mg/kg/day, producing systemic exposure to unbound maraviroc 39-(males) or 72-times (females) higher than that obtained in humans at the standard clinical dose of 300 mg twice daily. In rats, administration of maraviroc produced thyroid adenomas, associated with adaptive liver changes, at 900 mg/kg/day PO (relative exposure based on $AUC_{0-24\text{ h}}$ for free maraviroc, 18-25). The thyroid tumours in rats are unlikely to be of human relevance.

Genotoxicity

Maraviroc was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including bacterial reverse mutation, chromosome aberrations in human lymphocytes and mouse bone marrow micronucleus.

INTERACTIONS WITH OTHER MEDICINES

Maraviroc is a substrate of cytochrome P450 CYP3A4. Co-administration of CELSENTRI with medicinal products that induce CYP3A4 may decrease maraviroc concentrations and reduce its therapeutic effects. Co-administration of CELSENTRI with medicinal products that inhibit CYP3A4 may increase maraviroc plasma concentrations. Dose adjustment of CELSENTRI is recommended when CELSENTRI is co-administered with CYP3A4 inhibitors and/or inducers. Further details for concomitantly administered medicinal products are provided below (see Table 6 and DOSAGE AND ADMINISTRATION, Table 9).

Studies in human liver microsomes and recombinant enzyme systems have shown that maraviroc does not inhibit any of the major P450 enzymes at clinically relevant concentrations (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinylestradiol and levonorgestrel, or urinary 6 β -hydroxycortisol/cortisol ratio, suggesting no inhibition or induction of CYP3A4 in vivo. At higher exposure of maraviroc a potential inhibition of CYP2D6 cannot be excluded. Based on the in vitro and clinical data, the potential for maraviroc to affect the pharmacokinetics of co-administered medicinal products is low.

Renal clearance accounts for approximately 23% of total clearance of maraviroc when maraviroc is administered without CYP3A4 inhibitors. As both passive and active processes are involved, there is the potential for competition for elimination with other renally eliminated active substances. However, co-administration of CELSENTRI with tenofovir (substrate for renal elimination) and Cotrimoxazole (contains trimethoprim, a renal cation transport inhibitor), showed no effect on the pharmacokinetics of maraviroc. In addition, co-administration of CELSENTRI with lamivudine/zidovudine showed no effect of maraviroc on lamivudine (primarily renally cleared) or zidovudine (non-P450 metabolism and renal clearance) pharmacokinetics. Maraviroc inhibits P-glycoprotein (P-gp) in vitro (IC₅₀ 183 μ M). Systemic effects on P-gp is unlikely to be of relevance. Maraviroc could inhibit P-gp in the gut and may thus affect the bioavailability of certain drugs.

Table 6. Interactions and dose recommendations with other medicinal products

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio (range) if not stated otherwise	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Lamivudine 150 mg BD (maraviroc 300 mg BD)	Lamivudine AUC ₁₂ : \leftrightarrow 1.13 (0.82, 2.09) Lamivudine C _{max} : \leftrightarrow 1.16 (0.46, 2.55) Maraviroc concentrations not measured, no effect is expected.	No significant interaction seen/expected. Maraviroc 300 mg twice daily and NRTIs can be co-

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Tenofovir 300 mg OD (maraviroc 300 mgBD)	Maraviroc AUC ₁₂ : ↔ 1.03 (0.83, 1.19) Maraviroc C _{max} : ↔ 1.03 (0.68, 1.45) Tenofovir concentrations not measured, no effect is expected.	administered without dose adjustment.
Zidovudine 300 mg BD (maraviroc 300 mg BD)	Zidovudine AUC ₁₂ : ↔ 0.98 (0.45, 1.88) Zidovudine C _{max} : ↔ 0.93 (0.38, 2.70) Maraviroc concentrations not measured, no effect is expected.	
NNRTIs		
Efavirenz 600 mg OD (maraviroc 100 mg BD)	Maraviroc AUC ₁₂ : ↓ 0.55 (90% CI: 0.49, 0.62) Maraviroc C _{max} : ↓ 0.49 (90% CI : 0.38, 0.63) Efavirenz concentrations not measured, no effect is expected.	Maraviroc dose should be increased to 600 mg twice daily when co-administered with efavirenz in the <u>absence</u> of a PI or other potent CYP3A4 inhibitor. For combination with efavirenz + PI, see below.
Nevirapine 200 mg BD (maraviroc 300 mg Single Dose)	Maraviroc AUC ₁₂ : ↔ compared to historical controls Maraviroc C _{max} : ↑ compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Comparison to exposure in historical controls suggests that maraviroc 300 mg twice daily and nevirapine can be co-administered without dose adjustment.
Delavirdine	Limited data are available for co-administration with delavirdine. Delavirdine is a potent CYP3A4 inhibitor. Population PK analysis in phase 3 studies suggests dose reduction of maraviroc when co-administered with delavirdine gives appropriate maraviroc exposure	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with delavirdine.
PIs		
Atazanavir 400 mg OD (maraviroc 300 mg BD)	Maraviroc AUC ₁₂ ↑ 3.57 (2.55, 4.45) Maraviroc C _{max} : ↑ 2.09 (1.31, 4.19) Atazanavir concentrations not measured, no effect is expected.	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with a PI; <u>except in combination with tipranavir/ritonavir or fosamprenavir/ritonavir where the dose should be 300 mg BD.</u> Maraviroc does not significantly affect PI drug levels.
Atazanavir/ritonavir 300 mg/100 mg OD (maraviroc 300 mg BD)	Maraviroc AUC ₁₂ ↑ 4.88 (3.28, 6.49) Maraviroc C _{max} : ↑ 2.67 (1.52, 3.90) Atazanavir/ritonavir concentrations not measured, no effect is expected.	
Lopinavir/ritonavir 400 mg/100 mg BD (maraviroc 300 mg BD)	Maraviroc AUC ₁₂ ↑ 3.95 (2.32, 5.52) Maraviroc C _{max} : ↑ 1.97 (1.26, 2.70) Lopinavir/ritonavir concentrations not measured, no effect is expected.	
Saquinavir/ritonavir 1000 mg/100 mg BD (maraviroc 100 mg BD)	Maraviroc AUC ₁₂ ↑ 9.77 (5.42, 20.5) Maraviroc C _{max} : ↑ 4.78 (2.11, 9.88) Saquinavir/ritonavir concentrations not measured, no effect is expected.	
Nelfinavir	Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A4 inhibitor and would be expected to increase maraviroc concentrations.	

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Indinavir	Limited data are available for co-administration with indinavir. Indinavir is a potent CYP3A4 inhibitor. Population PK analysis in phase 3 studies suggests dose reduction of maraviroc when coadministered with indinavir gives appropriate maraviroc exposure.	
Fosamprenavir/ritonavir	Fosamprenavir is considered to be a moderate CYP3A4 inhibitor. Population PK studies suggest that a dose adjustment of maraviroc is not required.	
Tipranavir/ritonavir 500 mg/200 mg BD (maraviroc 150 mg BD)	Maraviroc AUC ₁₂ ↔ 1.02 (0.65, 1.87) Maraviroc C _{max} : ↔ 0.86 (0.37, 3.20) Tipranavir/ritonavir concentrations were consistent with historical data.	Maraviroc 300 mg twice daily and tipranavir/ritonavir can be co-administered without dose adjustment.
NNRTI + PI		
Efavirenz 600 mg OD + lopinavir/ritonavir 400 mg/100 mg BD (maraviroc 300 mg BD)	Maraviroc AUC ₁₂ : ↑ 2.53 (1.71, 3.15) Maraviroc C _{max} : ↑ 1.25 (0.87, 2.82) Efavirenz, lopinavir/ritonavir concentrations not measured, no effect expected.	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with efavirenz in the presence of a PI.
Efavirenz 600 mg OD + saquinavir/ritonavir 1000 mg/100 mg BD (maraviroc 100 mg BD)	Maraviroc AUC ₁₂ : ↑ 5.00 (3.04, 6.31) Maraviroc C _{max} : ↑ 2.26 (0.68, 4.09) Efavirenz, saquinavir/ritonavir concentrations not measured, no effect expected.	
Efavirenz and-atazanavir/ritonavir or darunavir/ritonavir	Not studied. Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir in the absence of efavirenz, an increased exposure is expected.	
Antibiotics		
Sulphamethoxazole/ Trimethoprim 800 mg/160 mg BD (maraviroc 300 mg BD)	Maraviroc AUC ₁₂ : ↔ 1.11 (0.84, 1.53) Maraviroc C _{max} : ↔ 1.19 (0.69, 1.73) Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected.	Maraviroc 300 mg twice daily and sulphamethoxazole/trimethoprim can be co-administered without dose adjustment.
Rifampicin 600 mg OD (maraviroc 100 mg BD)	Maraviroc AUC: ↓ 0.37 (90% CI: 0.33, 0.41) Maraviroc C _{max} : ↓ 0.34 (90% CI: 0.26, 0.43) Rifampicin concentrations not measured, no effect expected.	Maraviroc dose should be increased to 600 mg twice daily when co-administered with rifampicin in the absence of a potent CYP3A4 inhibitor. This dose adjustment has not been studied in HIV patients. See PRECAUTIONS.
Rifampicin + efavirenz	Combination with two inducers has not been studied. There may be a risk of suboptimal levels with risk of loss of virologic response and resistance development.	Concomitant use of maraviroc and rifampicin + efavirenz is not recommended.
Rifabutin + PI	Not studied. Rifabutin is considered to be a weaker inducer than rifampicin. When combining rifabutin with protease inhibitors that are potent inhibitors of CYP3A4 a net inhibitory effect on	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with rifabutin in the presence of

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	maraviroc is expected.	a PI (except tipranavir/ritonavir where the dose should be 300 mg twice daily). See PRECAUTIONS.
Clarithromycin, Telithromycin	Not studied, but both are potent CYP3A4 inhibitors and would be expected to increase maraviroc concentrations.	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with clarithromycin and telithromycin.
Antifungals		
Ketoconazole 400 mg OD (maraviroc 100 mg BD)	Maraviroc AUC _{tau} : ↑ 5.00 (2.40, 9.62) Maraviroc C _{max} : ↑ 3.38 (1.11, 7.68) Ketoconazole concentrations not measured, no effect is expected.	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with ketoconazole.
Itraconazole	Not studied. Itraconazole is a potent CYP3A4 inhibitor and would be expected to increase the exposure of maraviroc.	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with itraconazole.
Fluconazole	Fluconazole is considered to be a moderate CYP3A4 inhibitor. Population PK studies suggest that a dose adjustment of maraviroc is not required.	Maraviroc 300 mg twice daily should be administered with caution when coadministered with fluconazole.
Antivirals		
HCV agents		
	Pegylated interferon and ribavirin have not been studied, no interaction is expected.	Maraviroc 300 mg twice daily and pegylated interferon or ribavirin can be coadministered without dose adjustment.
DRUG ABUSE		
Methadone	Not studied, no interaction expected.	Maraviroc 300 mg twice daily and methadone can be coadministered without dose adjustment.
Buprenorphine	Not studied, no interaction expected.	Maraviroc 300 mg twice daily and buprenorphine can be coadministered without dose adjustment.
LIPID LOWERING MEDICINAL PRODUCTS		
Statins		
	Not studied, no interaction expected.	Maraviroc 300 mg twice daily and statins can be coadministered without dose adjustment.
ORAL CONTRACEPTIVES		
Ethinylestradiol 30 mcg OD (maraviroc 100 mg BD)	Ethinylestradiol. AUC _t : ↔ 1.00 (0.79, 1.20) Ethinylestradiol. C _{max} : ↔ 0.99 (0.61, 1.32) Maraviroc concentrations not measured, no interaction expected.	Maraviroc 300 mg twice daily and ethinylestradiol can be co-administered without dose adjustment.
Levonorgestrel 150 mcg OD (maraviroc 100 mg BD)	Levonorgestrel. AUC ₁₂ : ↔ 0.99 (0.70, 1.31) Levonorgestrel. C _{max} : ↔ 1.01 (0.66, 1.51)	Maraviroc 300 mg twice daily and levonorgestrel can be co-administered without dose adjustment.

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	Maraviroc concentrations not measured, no interaction expected.	
SEDATIVES		
Benzodiazepines		
Midazolam 7.5 mg Single Dose (maraviroc 300 mg BD)	Midazolam. AUC: ↔ 1.18 (0.68, 1.77) Midazolam. C _{max} : ↔ 1.21 (0.51, 2.97) Maraviroc concentrations not measured, no interaction expected.	Maraviroc 300 mg twice daily and midazolam can be co-administered without dose adjustment.
HERBAL PRODUCTS		
St John's Wort	Coadministration of maraviroc with St. John's Wort is expected to substantially decrease maraviroc concentrations and may result in suboptimal levels and lead to loss of virologic response and possible resistance to maraviroc.	Concomitant use of maraviroc and St. John's Wort (Hypericum Perforatum) or products containing St. John's wort is not recommended.

ADVERSE EFFECTS

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

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

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

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

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

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Treatment-emergent adverse events, regardless of causality, from Studies A4001027 and A4001028 are summarised in Table 7. Selected events occurring at $\geq 2\%$ of subjects and at a numerically higher rate in subjects treated with CELSENTRI + OBT are included; events that occurred at a higher rate on OBT alone are not displayed.

Table 7:
Percentage of Subjects with Selected Treatment-Emergent Adverse Events (All Causality)
($\geq 2\%$ on CELSENTRI + OBT and at a higher rate compared to OBT alone)

Pooled Studies A4001027 and A4001028

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

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

* 300 mg dose equivalent

** PYE = patient years of exposure

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

Bronchitis: bronchitis, acute bronchitis, bacterial bronchitis

Herpes simplex infection: Herpes simplex, Herpes virus, Herpes ophthalmic, proctitis Herpes,

Influenza: Influenza, influenza-like illness

Pneumonia: Pneumonia, lobar pneumonia, pneumonia bacterial, bronchopneumonia

Sinusitis: sinusitis, acute sinusitis, chronic sinusitis, sinobronchitis

Upper Respiratory Infection: upper respiratory tract infection, laryngitis, laryngopharyngitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, viral respiratory tract infection

Clinically important adverse reactions occurring in less than 2% of adult patients in Phase 3 studies are listed below by system organ class designated with the frequency estimation “uncommon” ($\geq 1/1000$ to $< 1/100$).

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Blood and lymphatic system disorders

Uncommon: pancytopenia, neutropenia, lymphadenopathy

Cardiac disorders

Uncommon: myocardial infarction, myocardial ischaemia

Gastrointestinal disorders

Uncommon: pancreatitis, rectal haemorrhage

Hepatobiliary disorders

Uncommon: hepatic cirrhosis

Infections and infestations

Uncommon: pneumonia

Musculoskeletal and connective tissue disorders

Uncommon: myositis

Nervous system disorders

Uncommon: loss of consciousness, epilepsy, petit mal epilepsy, convulsion, facial palsy, polyneuropathy, areflexia

Psychiatric disorders

Uncommon: hallucination

Renal and Urinary Disorders

Uncommon: renal failure, polyuria

Respiratory, Thoracic and Mediastinal disorders

Uncommon: respiratory distress, bronchospasm

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see PRECAUTIONS).

Laboratory abnormalities

Table 8 shows the incidence $\geq 2\%$ of Grade 3-4 Abnormalities (ACTG Criteria) based on the maximum shift in laboratory test values without regard to baseline values.

Table 8: Incidence $\geq 2\%$ of Grade 3-4 Abnormalities (ACTG Criteria) based on the Maximum Shift in Laboratory Test Values Without Regard to Baseline Studies A4001027 and A4001028

Laboratory Parameter	Limit	Celsentri 300 mg twice daily + OBT N =421* (%)	OBT alone N =207* (%)
Aspartate aminotransferase	>5.0x ULN	4.5	2.9
Alanine aminotransferase	>5.0x ULN	2.4	3.4
Total bilirubin	>5.0x ULN	5.7	5.3
Amylase	>2.0x ULN	5.5	5.8
Lipase	>2.0x ULN	4.9	6.3
Absolute neutrophil count	<750/mm ³	3.8	1.9

ULN: Upper Limit of Normal

* Percentages based on total patients evaluated for each laboratory parameter

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the management of HIV infection.

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

- Tropism testing, resistance testing and treatment history should guide the use of CELSENTRI.
- Use of CELSENTRI 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.

Adults: the recommended dose of CELSENTRI is 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products (see Table 9 and INTERACTIONS WITH OTHER MEDICINES). CELSENTRI can be taken with or without food.

Table 9: Recommended Dosing Regimen

Concomitant Medications	Recommended CELSENTRI Dose
CYP3A inhibitors (with or without a CYP3A inducer) including: <ul style="list-style-type: none"> • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin • other potent CYP3A inhibitors (e.g., nefazodone, telithromycin) 	150 mg twice daily
Other concomitant medicinal products, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300mg twice daily
CYP3A inducers (without a potent CYP3A inhibitor)	600 mg twice daily

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including: <ul style="list-style-type: none">• efavirenz• rifampin• carbamezepine, phenobarbital, and phenytoin	
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Children: the safety and efficacy of CELSENTRI in paediatric patients have not been established, therefore use in children is not recommended (see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

Elderly: there is limited experience in patients >65 years of age, therefore caution should be exercised when administering CELSENTRI in elderly patients (see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

Renal impairment: no dosage adjustment is recommended in patients with renal impairment. CELSENTRI should be used with caution in patients with renal impairment (CLcr < 80ml/min) who are taking potent CYP3A4 inhibitors (see Table 9 and PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

Hepatic impairment: limited data are available in patients with hepatic impairment (see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS). CELSENTRI should be used with caution in patients with hepatic impairment (see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

Race: no dosage adjustment is necessary on the basis of race (see PHARMACOLOGY, Pharmacokinetics).

Gender: no dosage adjustment is necessary on the basis of gender (see PHARMACOLOGY, Pharmacokinetics).

OVERDOSAGE

The highest dose administered in clinical studies was 1200 mg. The dose limiting adverse reaction was postural hypotension.

Prolongation of the QT interval was seen in dogs and monkeys at free plasma concentrations of maraviroc 6 times higher than that expected in humans at the standard clinical dose of 300 mg twice daily. However, no clinically significant QT prolongation compared to OBT alone was seen in the Phase 3 clinical studies using the recommended dose of maraviroc or in a specific pharmacokinetic study to evaluate the potential of CELSENTRI to prolong the QT interval.

There is no specific antidote for overdose with CELSENTRI. 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.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. Since maraviroc is moderately protein bound, dialysis may be beneficial in removal of this medicine.

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Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

High density polyethylene (HDPE) bottles with polypropylene child resistant closures and an aluminium foil/polyethylene heat induction seal containing 180 film-coated tablets for the 150 mg and 300 mg strengths.

Polyvinyl chloride (PVC) blisters with aluminium foil backing in a carton containing 60 film-coated tablets for the 150 mg and 300 mg strengths.

Not all pack sizes may be marketed.

Store below 30°C.

MEDICINE CLASSIFICATION

Prescription medicine

NAME AND ADDRESS OF SPONSOR

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Version 3.0

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