TRADENAMES
The tradename for this product is CELSENTRI.

FORMULATION AND STRENGTHS

Each tablet contains either 150 mg or 300 mg of maraviroc:

150 mg Tablets: blue, biconvex, oval film-coated tablets debossed with "MVC 150" on one side.

300 mg Tablets: blue, biconvex, oval film-coated tablets debossed with "MVC 300" on one side.

CLINICAL INFORMATION

Indications

Maraviroc, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients (*see Clinical Studies*).

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

- Treatment history should guide the use of CELSENTRI. Tropism testing is required for the appropriate use of maraviroc (*see Warnings and Precautions*).
- Use of maraviroc is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group.
- The safety and efficacy of maraviroc have not been established in treatment-naïve adult patients or pediatric patients.

Dosage and Administration

Pharmaceutical form: Film-coated tablets

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

Before taking maraviroc it has to be confirmed that only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus not detected) using an adequately validated and sensitive detection method on a newly drawn blood sample. The Monogram Trofile assay was used in the clinical studies of maraviroc. Other phenotypic and genotypic assays are currently being evaluated. The viral tropism cannot be safely predicted by treatment history and assessment of stored samples.

There are currently no data regarding the reuse of maraviroc in patients that currently have only CCR5-tropic HIV-1 detectable, but have a history of failure on maraviroc (or other CCR5 antagonists) with a CXCR4 or dual/mixed tropic virus. There are no data regarding the switch from a medicinal product of a different antiretroviral class to maraviroc in virologically suppressed patients. Alternative treatment options should be considered.

Adults: the recommended dose of maraviroc is 150 mg, 300 mg or 600 mg twice daily depending on interactions with concomitant antiretroviral therapy and other medicinal products (*see Table 1 and Interactions*). Maraviroc can be taken with or without food.

Table 1 Recommended Dosing Regimen

Concomitant Medications	**Recommended Maraviroc Dose**
Potent CYP3A inhibitors (with or without a CYP3A inducer) including, but not limited to: • delavirdine, boosted elvitegravir • ketoconazole, itraconazole, clarithromycin • other potent CYP3A inhibitors (e.g., nefazodone, telithromycin) • protease inhibitors (except tipranavir/ritonavir) • boceprevir, telaprevir	150 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including, but not limited to: • carbamazepine, phenobarbital, and phenytoin • efavirenz • etravirine • rifampicin	600 mg twice daily
Other concomitant medicinal products that are not potent CYP3A inhibitors or potent CYP3A inducers, including: • all NRTIs • enfuvirtide • nevirapine • raltegravir • tipranavir/ritonavir	300 mg twice daily

Children: the safety and efficacy for the use of maraviroc in children younger than 18 years of age have not been established, therefore use in children is not recommended (*see Pharmacokinetics*).

Elderly: there is limited experience in patients above 65 years of age. Therefore caution should be exercised when administering maraviroc in elderly patients (*see Pharmacokinetics*).

Renal impairment: dosage adjustment is only recommended in patients with renal impairment who are receiving potent CYP3A inhibitors such as:

- protease inhibitors (except tipranavir/ritonavir and fosamprenavir/ritonavir) (*see Table 2*).
- boceprevir, telaprevir
- delavirdine, boosted elvitegravir
- ketoconazole, itraconazole, clarithromycin, nefazodone, telithromycin.

Maraviroc should be used with caution in patients with severe renal impairment (creatinine clearance < 30 mL/min) who are receiving potent CYP3A inhibitors (*see Warnings and Precautions and Pharmacokinetics*).

Maraviroc should be dosed every 24 hours in renally impaired patients (creatinine clearance < 80 mL/min), including patients with end stage renal disease (ESRD) requiring dialysis, who are receiving maraviroc in combination with potent CYP3A inhibitors (*see Warnings and Precautions, Interactions and Pharmacokinetics*). These dosing recommendations are based on data from a renal impairment study (*see Pharmacokinetics*) in addition to modelling of pharmacokinetic data in subjects with varying degrees of renal impairment.

No dose adjustment is necessary for renally impaired patients, including patients with ESRD, requiring dialysis, not receiving a potent CYP3A inhibitor in combination with maraviroc. Table 2 below provides dosing interval adjustment guidelines.

Table 2 Dose and interval adjustments for patients with renal impairment

Recommended maraviroc dose interval	**Creatinine clearance < 80 mL/min***
If administered without potent CYP3A inhibitors or if co-administered with tipranavir/ritonavir	No dose interval adjustment required (maraviroc 300 mg every 12 hours)
If co-administered with fosamprenavir/ritonavir	maraviroc 150 mg every 12 hours
If co-administered with potent CYP3A inhibitors, e.g. saquinavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, atazanavir/ritonavir, ketoconazole, delavirdine, boceprevir, telaprevir	maraviroc 150 mg every 24 hours

*including subjects with ESRD requiring dialysis

Hepatic impairment: limited data in patients with mild and moderate hepatic impairment demonstrated a small increase in the mean C_{max} of maraviroc, suggesting no dose adjustment is required. However, maraviroc should be used with caution in patients with hepatic impairment (*see Warnings and Precautions and Pharmacokinetics*).

Contraindications

Hypersensitivity to the active substance or to any of the excipients (*see Excipients*).

Warnings and Precautions

Tropism: maraviroc 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 Pharmacodynamics*). The Monogram Trofile assay was used in the clinical studies of maraviroc.

Other phenotypic and genotypic assays are currently being evaluated. The viral tropism cannot be predicted by treatment history or assessment of stored samples; only a current sample from the patient may be used to assess viral tropism.

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.

Background resistance to other classes of antiretrovirals have been shown to be similar in previously undetected CXCR4-tropic virus of the minor viral population, as that found in CCR5-tropic virus.

Dose adjustment: physicians should ensure that appropriate dose adjustment of maraviroc is made when maraviroc is co-administered with potent CYP3A inhibitors and/or inducers since maraviroc concentrations and its therapeutic effects may be affected (*see Dosage and Administration and Interactions*). Refer to the respective product information of other medicinal products used in combination with maraviroc.

Postural hypotension: when maraviroc 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. Caution should be used when administering maraviroc in patients with severe renal insufficiency, have a history of or risk factors for postural hypotension or patients on concomitant medicinal products known to lower blood pressure.

Patients with severe renal insufficiency who are treated with potent CYP3A inhibitors or boosted protease inhibitors (PIs) have an increased risk of experiencing postural hypotension due to an increase in maraviroc concentrations (*see Dosage and Administration, Interactions and Pharmacokinetics).*

Patients with cardiovascular co-morbidities could be at increased risk of cardiovascular adverse events triggered by postural hypotension.

Potential effect on immunity: CCR5 antagonists could potentially impair the immune response to certain infections. This should be taken into consideration when treating infections such as active tuberculosis and invasive fungal infections. The incidence of AIDS-defining infections was similar between maraviroc and placebo arms in the pivotal studies.

Cardiovascular safety: use with caution in patients at increased risk for cardiovascular events. Limited data exist with the use of maraviroc in patients with severe cardiovascular disease, therefore special caution should be exercised when treating these patients with maraviroc.

Immune reconstitution syndrome: in HIV-infected patients with severe immune deficiency at the time of starting of highly active antiretroviral therapy (HAART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of HAART.

Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment initiated when necessary.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Osteonecrosis: although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Hepatic safety: a case of possible maraviroc induced hepatotoxicity and hepatic failure with allergic features has been reported in a study in healthy volunteers (*see Adverse Reactions*). An increase in hepatic adverse reactions with maraviroc was observed during studies of treatment-experienced subjects with HIV infection, although there was no

overall increase in ACTG Grade 3/4 liver function test abnormalities (*see Adverse Reactions*). There were fewer cases of hepatobiliary disorders reported in treatment-naïve patients on maraviroc than with efavirenz but the overall incidence of hepatic adverse events and ACTG Grade 3/4 liver function test abnormalities in treatment-naïve patients was similar between maraviroc and efavirenz.

Discontinuation of maraviroc should be strongly 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).

There are limited data in patients with hepatitis B and/or C virus co-infection (*see Clinical Studies*). Caution should be exercised when treating these patients. In case of concomitant antiviral therapy for hepatitis B and/or C, please refer to the relevant product information for these medicinal products.

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.

The safety and efficacy of maraviroc have not been specifically studied in patients with significant underlying liver disorders. Since there is limited experience in patients with reduced hepatic function, therefore maraviroc should be used with caution in this population (*see Dosage and Administration and Pharmacokinetics*).

Renal impairment: a study evaluated the pharmacokinetics and safety of maraviroc in subjects with varying degrees of renal impairment compared to healthy volunteers. In this study, transient decreases in mean creatinine clearance were observed in subjects with mild and moderate renal impairment as well as in healthy volunteers receiving maraviroc 150 mg (dosing frequency: healthy volunteers – once every 12 hours; mild impairment – once every 24 hours; moderate impairment – once every 48 hours) and saquinavir/ritonavir 1000/100 mg twice daily which resolved with continued dosing. There was no relationship between the decreases in mean creatinine clearance, and the mean baseline serum creatinine. Generally, maraviroc was well tolerated in this study with more adverse events (mostly mild) reported in subjects with mild and moderate renal impairment receiving maraviroc and saquinavir/ritonavir.

No studies have been performed in subjects with severe renal impairment co-treated with potent CYP3A inhibitors. Dosing interval adjustments are based on pharmacokinetic modelling and simulations.

Table 2 provides dose and/or interval adjustment guidelines for patients with renal impairment with and without co-administered potent CYP3A inhibitors (*see Dosage and Administration, Interactions and Pharmacokinetics*).

Severe skin and hypersensitivity reactions: hypersensitivity reactions including severe and potentially life threatening events have been reported in patients taking maraviroc, in most cases concomitantly with other drugs associated with these reactions. These reactions were characterised by features including rash, constitutional findings, and sometimes organ dysfunction and hepatic failure. Cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported (*see Adverse Reactions*). Discontinue maraviroc and other suspect agents immediately if signs or symptoms of severe skin or hypersensitivity reactions develop. Delay in stopping maraviroc treatment or other suspect drugs after the onset of rash may result in a life-threatening reaction. Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated.

Soya lecithin: CELSENTRI contains soya lecithin. If a patient is hypersensitive to peanut or soya, CELSENTRI should not be used.

Interactions

Maraviroc is metabolized by cytochrome P450 CYP3A. Maraviroc is also a substrate for P-glycoprotein, OATP1B1 and MRP2 in vitro. Co-administration of maraviroc with medicinal products that induce those enzymes and transporters may decrease maraviroc concentrations and reduce its therapeutic effects. Co-administration of maraviroc with medicinal products that inhibit those enzymes and transporters may increase maraviroc plasma concentrations. Dose adjustment of maraviroc is recommended when maraviroc is co-administered with potent CYP3A inhibitors and/or inducers. Further details for concomitantly administered medicinal products are provided below (*see Table 3, 4, Warnings and Precautions and Dosage and Administration and Table 1*).

In vitro studies have shown that maraviroc does not inhibit OATP1B1, MRP2 or 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 6β-hydroxycortisol/cortisol ratio, suggesting no inhibition or induction of CYP3A4 *in vivo*. Despite lack of *in vitro* inhibition of CYP2D6, maraviroc caused an increase in debrisoquine metabolic ratio at 600 mg once daily although not at 300 mg twice daily. Therefore, 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 CYP3A inhibitors. As both passive and active processes are involved, there is the potential for competition for elimination with other renally eliminated active substances. However, in vitro studies have shown that maraviroc is not a substrate for and does not inhibit any of the major renal uptake inhibitors (OAT1, OAT3, OCT2, OCTN1, and OCTN2) at clinically relevant concentrations. Additionally, co-administration of maraviroc 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 maraviroc 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 *in vitro* (IC_{50} is 183 μM). However, maraviroc does not significantly affect the pharmacokinetics of digoxin *in vivo*, suggesting that maraviroc neither inhibits nor induces the activity of P-glycoprotein.

Table 3. Interactions and dose recommendations with other medical products

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Anti-infectives		
Antiretrovirals		
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Lamivudine 150 mg BID (maraviroc 300 mg BID)	Lamivudine AUC_{12}: ↔ 1.13 (0.98, 1.32) Lamivudine C_{max}: ↔ 1.16 (0.88, 1.54) Maraviroc concentrations not measured, no effect is expected.	**CELSENTRI 300 mg twice daily[1]** No clinically significant interaction observed or expected with NRTIs.

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Tenofovir 300 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↔ 1.03 (0.98, 1.09) Maraviroc C_{max}: ↔ 1.03 (0.90, 1.19) Tenofovir concentrations not measured, no effect is expected.	
Zidovudine 300 mg BID (maraviroc 300 mg BID)	Zidovudine AUC_{12}: ↔ 0.98 (0.79, 1.22) Zidovudine C_{max}: ↔ 0.92 (0.68, 1.24) Maraviroc concentrations not measured, no effect is expected.	
Integrase Inhibitors		
Elvitegravir/ritonavir 150/100mg QD (maraviroc 150 mg BID)	Maraviroc AUC_{12}: ↑ 2.86 (2.33, 3.51) Maraviroc C_{max}: ↑ 2.15 (1.71, 2.69) Maraviroc C_{12}: ↑ 4.23 (3.47, 5.16) Elvitegravir AUC_{24}: ↔ 1.07 (0.96, 1.18) Elvitegravir C_{max}: ↔ 1.01 (0.89, 1.15) Elvitegravir C_{24}: ↔ 1.09 (0.95, 1.26)	**CELSENTRI 150 mg twice daily** when co-administered with boosted elvitegravir.
Raltegravir 400 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↓ 0.86 (0.80, 0.92) Maraviroc C_{max}: ↓ 0.79 (0.67, 0.94) Raltegravir AUC_{12}: ↓ 0.63 (0.44, 0.90) Raltegravir C_{max}: ↔ 0.67 (0.41, 1.08) Raltegravir C_{12}: ↓ 0.72 (0.58, 0.90)	**CELSENTRI 300 mg twice daily**[1] No clinically significant interaction observed.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz 600 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↓ 0.55 (0.49, 0.62) Maraviroc C_{max}: ↓ 0.49 (0.38, 0.63) Efavirenz concentrations not measured, no effect is expected.	**CELSENTRI 600 mg twice daily** when co-administered with efavirenz in the absence of a potent CYP3A inhibitor. For combination of efavirenz and PI, see below.
Etravirine 200 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↓ 0.47 (0.38, 0.58) Maraviroc C_{max}: ↓ 0.40 (0.28, 0.57) Etravirine AUC_{12}: ↔ 1.06 (0.99, 1.14) Etravirine C_{max}: ↔ 1.05 (0.95, 1.17) Etravirine C_{12}: ↔ 1.08 (0.98, 1.19)	**CELSENTRI 600 mg twice daily** when co-administered with etravirine in the absence of a potent CYP3A inhibitor. For combination of etravirine and PI, see below.
Nevirapine 200 mg BID (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.	**CELSENTRI 300 mg twice daily**[1]
Delavirdine	Limited data are available for co-administration with delavirdine. Delavirdine is a potent CYP3A inhibitor. Population PK analysis in phase 3 studies suggests dose reduction of maraviroc when co-administered with delavirdine gives appropriate maraviroc exposure.	**CELSENTRI 150 mg twice daily**
Protease Inhibitors (PIs)		

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Atazanavir 400 mg QD (maraviroc 300 mg BID)	Maraviroc $AUC_{12:}$ ↑ 3.57 (3.30, 3.87) Maraviroc C_{max}: ↑ 2.09 (1.31, 4.19) Atazanavir concentrations not measured, no effect is expected.	**CELSENTRI 150 mg twice daily** when co-administered with either a boosted or an unboosted Protease Inhibitor, except for tipranavir/ritonavir (see below for separate recommendation for tipranavir/ritonavir). Maraviroc 150 mg twice daily has not been shown to have a clinically significant effect on PI exposure levels.
Nelfinavir	Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A inhibitor and would be expected to increase maraviroc concentrations.	
Indinavir	Limited data are available for co-administration with indinavir. Indinavir is a potent CYP3A inhibitor. Population PK analysis in phase 3 studies suggests dose reduction of maraviroc when co-administered with indinavir gives appropriate maraviroc exposure.	
Atazanavir/ritonavir 300 mg/100 mg QD (maraviroc 300 mg BID)	Maraviroc $AUC_{12:}$ ↑ 4.88 (3.28, 6.49) Maraviroc C_{max}: ↑ 2.67 (1.72, 2.55) Atazanavir/ritonavir concentrations not measured, no effect is expected.	
Lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc $AUC_{12:}$ ↑ 3.95 (3.43, 4.56) Maraviroc C_{max}: ↑ 1.97 (1.66, 2.34) Lopinavir/ritonavir concentrations not measured, no effect is expected.	
Saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)	Maraviroc $AUC_{12:}$ ↑ 9.77 (7.87, 12.1) Maraviroc C_{max}: ↑ 4.78 (3.41, 6.71) Saquinavir/ritonavir concentrations not measured, no effect is expected.	
Darunavir/ritonavir 600 mg/100 mg BID (maraviroc 150 mg BID)	Maraviroc $AUC_{12:}$ ↑ 4.05 (2.94, 5.59) Maraviroc C_{max}: ↑ 2.29 (1.46, 3.59) Darunavir/ritonavir concentrations were consistent with historical data.	

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Fosamprenavir/ritonavir 700 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↑ 2.49 (2.19, 2.82) Maraviroc C_{max}: ↑ 1.52 (1.27, 1.82) Maraviroc C_{12}: ↑ 4.74 (4.03, 5.57) Amprenavir AUC_{12}: ↓ 0.65 (0.59, 0.71) Amprenavir C_{max}: ↓ 0.66 (0.59, 0.75) Amprenavir C_{12}: ↓ 0.64 (0.57, 0.73) Ritonavir AUC_{12}: ↓ 0.66 (0.58, 0.76) Ritonavir C_{max}: ↓ 0.61 (0.50, 0.73) Ritonavir C_{12}: ↔ 0.86 (0.14, 5.28)	
Fosamprenavir/ritonavir 1400 mg/100 mg QD (maraviroc 300 mg QD)	Maraviroc $AUC_{24:}$ ↑ 2.26 (1.99, 2.58) Maraviroc C_{max}: ↑ 1.45 (1.20, 1.74) Maraviroc C_{24}: ↑ 1.80 (1.53, 2.13) Amprenavir AUC_{24}: ↓ 0.70 (0.64, 0.77) Amprenavir C_{max}: ↓ 0.71 (0.62, 0.80) Amprenavir C_{24}: ↓ 0.85 (0.75, 0.97) Ritonavir AUC_{24}: ↓ 0.70 (0.61, 0.80) Ritonavir C_{max}: ↓ 0.69 (0.57, 0.84) Ritonavir C_{24}: ↔ 2.66 (0.41, 17.23)	
Tipranavir/ritonavir 500 mg/200 mg BID (maraviroc 150 mg BID)	Maraviroc $AUC_{12:}$ ↔ 1.02 (0.85, 1.23) Maraviroc C_{max}: ↔ 0.86 (0.61, 1.21) Tipranavir/ritonavir concentrations were consistent with historical data.	**CELSENTRI 300 mg twice daily**[1]
NNRTI + PI		
Efavirenz 600 mg QD + lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↑ 2.53 (2.24, 2.87) Maraviroc C_{max}: ↑ 1.25 (1.01, 1.55) Efavirenz, lopinavir/ritonavir concentrations not measured, no effect expected.	**CELSENTRI 150 mg twice daily** when co-administered with either efavirenz or etravirine and a Protease Inhibitor (except fosamprenavir/ritonavir where the dose should be 300 mg twice daily or tipranavir/ritonavir where the dose should be 600 mg twice daily).
Efavirenz 600 mg QD + saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↑ 5.00 (4.26, 5.87) Maraviroc C_{max}: ↑ 2.26 (1.64, 3.11) 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.	

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Etravirine and darunavir/ritonavir (maraviroc 150 mg BID)	Maraviroc AUC_{12}: ↑ 3.10 (2.57, 3.74) Maraviroc C_{max}: ↑ 1.77 (1.20, 2.60) Etravirine AUC_{12}: ↔ 1.00 (0.86, 1.15) Etravirine C_{max}: ↔ 1.08 (0.98, 1.20) Etravirine C_{12}: ↓ 0.81 (0.65, 1.01) Darunavir AUC_{12}: ↓ 0.86 (0.76, 0.96) Darunavir C_{max}: ↔ 0.96 (0.84, 1.10) Darunavir C_{12}: ↓ 0.77 (0.69, 0.85) Ritonavir AUC_{12}: ↔ 0.93 (0.75, 1.16) Ritonavir C_{max}: ↔ 1.02 (0.80, 1.30) Ritonavir C_{12}: ↓ 0.74 (0.63, 0.86)	
Etravirine and lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir	Not studied. Based on the extent of inhibition by lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir in the absence of etravirine, an increased exposure is expected.	
Antibiotics		
Sulphamethoxazole/ Trimethoprim 800 mg/160 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↔ 1.11 (1.01, 1.21) Maraviroc C_{max}: ↔ 1.19 (1.04, 1.37) Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected.	**CELSENTRI 300 mg twice daily**[1]
Rifampicin 600 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↓ 0.37 (0.33, 0.41) Maraviroc C_{max}: ↓ 0.34 (0.26, 0.43) Rifampicin concentrations not measured, no effect expected.	**CELSENTRI 600 mg twice daily** when co-administered with rifampicin in the absence of a potent CYP3A inhibitor. This dose adjustment has not been studied in HIV patients.
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 CYP3A a net inhibitory effect on maraviroc is expected.	**CELSENTRI 150 mg twice daily** when co-administered with rifabutin and a PI (except tipranavir/ritonavir where the dose should be 300 mg twice daily).
Clarithromycin, Telithromycin	Not studied, but both are potent CYP3A inhibitors and would be expected to increase maraviroc concentrations.	**CELSENTRI 150 mg twice daily**

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Antifungals		
Ketoconazole 400 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↑ 5.00 (3.98, 6.29) Maraviroc C_{max}: ↑ 3.38 (2.38, 4.78) Ketoconazole concentrations not measured, no effect is expected.	**CELSENTRI 150 mg twice daily**
Itraconazole	Not studied. Itraconazole is a potent CYP3A inhibitor and would be expected to increase the exposure of maraviroc.	**CELSENTRI 150 mg twice daily**
Fluconazole	Fluconazole is considered to be a moderate CYP3A inhibitor. Population PK studies suggest that a dose adjustment of maraviroc is not required.	**CELSENTRI 300 mg twice daily**[1] No clinically significant interaction expected with fluconazole
Antivirals		
HCV agents		
Boceprevir 800 mg TID (maraviroc 150 mg BID)	Maraviroc AUC_{12}: ↑ 3.02 (2.53, 3.59) Maraviroc C_{max}: ↑ 3.33 (2.54, 4.36) Maraviroc C_{12}: ↑ 2.78 (2.40, 3.23) Boceprevir concentrations were consistent with historical data.	**CELSENTRI 150 mg twice daily** when co-administered with boceprevir.
Pegylated interferon and ribavirin	Pegylated interferon and ribavirin have not been studied, no interaction is expected.	**CELSENTRI 300 mg twice daily**[1]
Telaprevir 750 mg TID (maraviroc 150 mg BID)	Maraviroc AUC_{12}: ↑ 9.49 (7.94, 11.34) Maraviroc C_{max}: ↑ 7.81 (5.92, 10.32) Maraviroc C_{12}: ↑ 10.17 (8.73, 11.85) Telaprevir concentrations were consistent with historical data.	**CELSENTRI 150 mg twice daily** when co-administered with telaprevir.
Anticonvulsants		
Carbamazepine Phenobarbital Phenytoin	Not studied, but these are potent CYP3A inducers and would be expected to decrease maraviroc concentrations.	**CELSENTRI 600 mg twice daily** when co-administered with carbamazepine, phenobarbital or phenytoin in the absence of a potent CYP3A inhibitor.
Drug Abuse		
Methadone	Not studied, no interaction expected.	**CELSENTRI 300 mg twice daily**[1]
Buprenorphine	Not studied, no interaction expected.	**CELSENTRI 300 mg twice daily**[1]
Lipid Lowering Medicinal Products		
Statins	Not studied, no interaction expected.	**CELSENTRI 300 mg twice daily**[1]
Antiarrhythmics		

Medicinal product by therapeutic areas (dose of maraviroc used in study)	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Digoxin 0.25 mg single dose (maraviroc 300 mg BID)	Digoxin AUC_t: ↔ 1.00 Digoxin C_{max}: ↔ 1.04 Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily[1]**
Oral contraceptives		
Ethinylestradiol 30 mcg QD (maraviroc 100 mg BID)	Ethinylestradiol AUC_{12}: ↔ 1.00 (0.95, 1.05) Ethinylestradiol C_{max}: ↔ 0.99 (0.91, 1.06) Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily[1]**
Levonorgestrel 150 mcg QD (maraviroc 100 mg BID)	Levonorgestrel. AUC_{12}: ↔ 0.98 (0.92, 1.04) Levonorgestrel. C_{max}: ↔ 1.01 (0.93, 1.08) Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily[1]**
Benzodiazepines		
Midazolam 7.5 mg single dose (maraviroc 300 mg BID)	Midazolam AUC: ↔ 1.18 (1.04, 1.34) Midazolam C_{max}: ↔ 1.21 (0.92, 1.60) Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily[1]**
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.

QD = once daily

BID = twice daily, TID = three times daily, C = concentration, AUC = Area Under the Curve

[1] If co-administered with a potent CYP3A inhibitor and/or inducer, dose maraviroc according to Table 1.

Pregnancy and lactation

Fertility

There are no data on the effects of maraviroc on human fertility. In rats, there were no adverse effects on male or female fertility (*see Non-Clinical Information*).

Pregnancy

No meaningful clinical data on exposure during pregnancy are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (*see Non-Clinical Information*). Maraviroc should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Studies in lactating rats indicate that maraviroc is extensively excreted into rat milk. Primary pharmacological activity (CCR5 receptor affinity) was limited in these species. It is unknown whether maraviroc is excreted into human milk. Mothers should be instructed not to breast-feed if they are receiving maraviroc because of the potential for HIV transmission as well as any possible undesirable effects in breast-fed infants.

Ability to perform tasks that require Judgement, Motor or Cognitive Skills

There have been no studies to investigate the effects of maraviroc on the ability to perform tasks that require judgement, motor or cognitive skills.

However, patients should be informed about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking maraviroc. If affected, patients should avoid potentially hazardous tasks such as driving, cycling, or operating machinery.

Adverse Reactions

Clinical trial data

Maraviroc has been studied in 1374 HIV-1 infected patients who received at least one dose of maraviroc during three Phase 3 clinical studies. This includes 426 patients who received the recommended dose 300 mg (dose equivalent) twice daily and a further 414 patients who received 300 mg once daily for at least 24 weeks. The safety profile of maraviroc is based on 786 HIV-1 infected patients who received maraviroc 300mg (dose equivalent) twice daily. Assessment of treatment related adverse reactions is based on pooled data at the recommended dose from two Phase 3 studies (MOTIVATE-1 and MOTIVATE-2) in CCR5-tropic HIV-1 infected patients.

The rates of permanent discontinuation due to any adverse reactions were similar in treatment-experienced patients receiving maraviroc twice daily + optimised background therapy (OBT) (3.5%) and those receiving OBT alone (3.3%).

The adverse reactions are listed by system organ class (SOC) and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥1/1000 to <1/100). The adverse reactions and laboratory abnormalities presented below are not exposure adjusted.

Table 4 and **Table 5** summarise all double-blind treatment data (twice daily=551, placebo=160 Patient years of exposure) pooled across the Phase 3 MOTIVATE 1 and 2 studies.

Table 4 Adverse reactions of all intensities occurring among treatment-experienced patients receiving maraviroc 300 mg (dose equivalent) twice daily + OBT with an incidence of ≥1% and a higher rate

incidence than patients receiving placebo + OBT alone (pooled studies MOTIVATE-1 and MOTIVATE-2)

System Organ Class	Adverse Reaction	Highest frequency
Metabolism and nutrition disorders	Weight decreased	Common
Psychiatric disorders	Insomnia	Common
Nervous system disorders	Neuropathy peripheral, dizziness, paraesthesia, dysgeusia, somnolence	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Abdominal pain, abdominal distention, constipation, dyspepsia	Common
Hepatobiliary disorders	Alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, gamma-glutamyltransferase (GGT) increased	Common
Skin and subcutaneous tissue disorders	Rash, alopecia	Common
Musculoskeletal and connective tissue disorders	Muscle spasms, back pain, pain in extremity, blood creatine phosphokinase increased	Common
General disorders and administration site conditions	Asthenia, fatigue	Common

Laboratory abnormalities in treatment-experienced

Table 5: Incidence ≥1% of grade 3-4 abnormalities (ACTG criteria) based on maximum shift in laboratory test values without regard to baseline studies MOTIVATE-1 and MOTIVATE-2 (pooled analysis, up to 48 weeks)

Laboratory parameter	Limit	CELSENTRI 300 mg Twice daily + OBT N = 421* (%)	OBT alone N = 207* (%)
Hepatobiliary disorders			
Aspartate aminotransferase	>5.0x ULN	4.8	2.9
Alanine aminotransferase	>5.0x ULN	2.6	3.4
Total bilirubin	>5.0x ULN	5.5	5.3
Gastrointestinal disorders			
Amylase	>2.0x ULN	5.7	5.8
Lipase	>2.0x ULN	4.9	6.3
Blood and lymphatic system disorders			
Absolute neutrophil count	$<750/mm^3$	4.3	1.9

ULN: Upper Limit of Normal
OBT: Optimised Background Therapy
*Percentages based on total patients evaluated for each laboratory parameter.

MOTIVATE-1 and MOTIVATE-2 were unblinded after the Week 48 visit of the last enrolled patient, and eligible patients could then switch to an open-label MVC BID phase extending to Week 96. A subsequent observational phase extending to 5 years was completed to assess the incidence of Long Term Safety/Selected Endpoints (LTS/SE) including death, AIDS-defining events, hepatic failure, MI/cardiac ischemia, malignancies, rhabdomyolysis and other serious infectious events with MVC treatment. The incidence of these selected endpoints was consistent with the 96 week data.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (*see Warnings and Precautions*).

Other clinically important adverse reactions of moderate intensity or greater occurring in less than 1% of adult patients receiving maraviroc in Phase 2b/3 studies included Stevens-Johnson Syndrome.

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 Warnings and Precautions*).

Post-marketing data

Very rarely, severe hypersensitivity reactions have been reported. These included drug rash with eosinophilia and systemic symptoms (DRESS), severe cutaneous reactions (SJS and TEN) as well as hepatotoxicity and hepatic failure with allergic features.

In rare cases, postural hypotension which can result in syncope has been reported.

Overdosage

Symptoms and signs

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 plasma concentrations 6 and 12 times, respectively, to those expected in humans at the maximum recommended 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 maraviroc to prolong the QT interval.

Treatment

There is no specific antidote for overdose with maraviroc. Treatment of overdose should consist of general supportive measures including keeping the patient in a supine position, careful assessment of patient vital signs, blood pressure and ECG.

If indicated, elimination of unabsorbed active maraviroc should be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since maraviroc is moderately protein bound, dialysis may be beneficial in removal of this medicine. Further management should be as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

ATC code

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.

Pharmacodynamic effects

Antiviral activity in cell culture:

The EC_{90} value in 43 primary CCR5-tropic HIV-1 clinical isolates was 0.57 (0.06 – 10.7) nanogram/mL (unbound fraction), without significant changes between different subtypes tested.

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

When used with other antiretroviral medicinal products in cell culture, the combination of maraviroc was not antagonistic with a range of NRTIs, NNRTIs, PIs or the HIV fusion inhibitor enfuvirtide.

Virologic Escape:

Virologic escape from maraviroc can occur via two routes: the emergence of pre-existing virus which can use CXCR4 as its entry co-receptor (CXCR4-using virus) or the selection of virus that continues to use exclusively drug-bound CCR5 (CCR5-tropic virus).

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 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 characterised by curves that did not reach 100% inhibition in assays using serial dilutions of maraviroc (<100% maximal percentage inhibition (MPI)). Traditional EC_{50} 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.

Cross-resistance: HIV-1 clinical isolates resistant to NRTIs, NNRTIs, PIs and enfuvirtide were all susceptible to maraviroc in cell culture. Maraviroc-resistant viruses that emerged in cell culture remained sensitive to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.

In vivo:

Both routes to virologic escape have been observed in clinical studies of both treatment-naïve and treatment-experienced patients.

The presence of CXCR4-using virus at virological failure appears to originate from a pre-existing viral population. Pre-therapy testing for the presence of this viral form can reduce the incidence of failure through this mechanism.

In patients failing therapy with CCR5-tropic virus only, the virus may still be considered susceptible to maraviroc if the MPI value is ≥95% (PhenoSense Entry assay). Residual activity *in vivo* for viruses with MPI-values <95% has not been determined. Resistance of CCR5-tropic virus through the increase of EC_{50} fold-change does not appear to be an important mechanism of failure.

Genotypic resistance: A relatively small number of individuals receiving maraviroc-containing therapy have failed with phenotypic resistance (i.e. the ability to use drug-bound CCR5 with MPI <95%). To date, no signature mutation(s) have been identified. The gp120 amino acid substitutions identified so far are context dependent and inherently unpredictable with regards to maraviroc susceptibility.

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 four-six 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 CELSENTRI arms and 4 subjects from the OBT alone arm) in whom CXCR4-using virus was detected at treatment failure. This analysis indicated that CXCR4-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 CELSENTRI therapy with CXCR4-using virus, demonstrated that the virus population reverted back to CCR5 tropism in 33 of 36 patients with more than 35 days of follow-up. At the 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, 22 out of 58 patients had virus with reduced sensitivity to maraviroc. 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, but the significance of this is unclear. In the remaining patients, there was no evidence of virus with reduced sensitivity as identified by exploratory virology analyses on a representative group. The latter group had markers of low drug exposure, in some cases associated with poor compliance.

Pharmacokinetics

Absorption
The absorption of maraviroc is variable with multiple peaks. Median peak maraviroc plasma concentrations is attained at two hours (range 0.5-4 hours) following single oral doses of 300 mg commercial tablet administered to healthy volunteers. The pharmacokinetics of oral maraviroc are not dose proportional over the dose range of 1-1200 mg. 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.

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 Pharmacodynamics*). Therefore, maraviroc can be taken with or without food at the recommended doses (*see Dosage and Administration*).

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

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 (approximately 42% radioactivity) following a single oral dose of 300 mg. The most significant circulating metabolite in humans is a secondary amine (approximately 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 radioactivity.

Elimination
A mass balance/excretion study was conducted using a single 300 mg 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 (mean of 8% dose) and faeces (mean of 25% dose). The remainder was excreted as metabolites. After intravenous administration (30 mg), the half-life of maraviroc was 13.2 hours, 22% of the dose was excreted unchanged in the urine and the values of total clearance and renal clearance were 44.0 L/hour and 10.17 L/hour respectively.

Special patient populations

Children
The pharmacokinetics of maraviroc in children below 18 years of age has not been established (*see Dosage and Administration*).

Elderly
Population analysis of the Phase 1/2a and Phase 3 studies (16-65 years of age) has been conducted and no effect of age has been observed. The pharmacokinetics of maraviroc in patients above 65 years of age has not been established (*see Dosage and Administration*).

Renal impairment

A study compared the pharmacokinetics of a single 300 mg dose of maraviroc in subjects with severe renal impairment (creatinine clearance < 30mL/min, n=6) and end stage renal disease (ESRD) to healthy volunteers (n=6). The geometric mean AUC_{inf} (CV%) for maraviroc was as follows: healthy volunteers (normal renal function) 1348.4 nanogram·h/mL (61%); severe renal function 4367.7 nanogram·h/mL (52%); ESRD (dosing after dialysis) 2677.4 nanogram·h/mL (40%); and ESRD (dosing before dialysis) 2805.5 nanogram·h/mL (45%). The C_{max} (CV%) was 335.6 nanogram/mL (87%) in healthy volunteers (normal renal function); 801.2 nanogram/mL (56%) in severe renal function; 576.7 nanogram/mL (51%) in ESRD (dosing after dialysis) and 478.5 nanogram/mL (38%) in ESRD (dosing before dialysis). Dialysis had a minimal effect on exposure in subjects with ESRD. Exposures observed in subjects with severe renal impairment and ESRD were within the range observed in single maraviroc 300 mg dose studies in healthy volunteers with normal renal function. Therefore, no dose adjustment is necessary in patients with renal impairment receiving maraviroc without a potent CYP3A inhibitor (*see Dosage and Administration, Warnings and Precautions and Interactions*).

In addition, the study compared the pharmacokinetics of multiple dose maraviroc in combination with saquinavir/ritonavir 1000/100 mg twice daily (a potent CYP3A inhibitor combination) for seven days in subjects with mild renal impairment (creatinine clearance >50 and ≤80 mL/min, n=6) and moderate renal impairment (creatinine clearance ≥30 and ≤50 mL/min, n=6) to healthy volunteers (n=6). Subjects received 150 mg of maraviroc at different dose frequencies (healthy volunteers – every 12 hours; mild renal impairment – every 24 hours; moderate renal impairment – every 48 hours). The average concentration (C_{avg}) of maraviroc over 24 hours was 445.1 nanogram/mL, 338.3 nanogram/mL, and 223.7 nanogram/mL for subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively. The C_{avg} of maraviroc from 24-48 hours for subjects with moderate renal impairment was low (C_{avg}: 32.8 nanogram/mL). Therefore, in subjects with moderate renal impairment (and by extrapolation in severe renal impairment) dosing frequencies of longer than 24 hours may result in inadequate exposure between 24-48 hours. In patients with renal impairment receiving maraviroc with potent CYP3A inhibitors a dose of 150 mg every 24 hours is recommended (*see Dosage and Administration, Warnings and Precautions and Interactions*).

Hepatic impairment

Maraviroc is primarily metabolized and eliminated by the liver. A study compared the pharmacokinetics of a single 300 mg dose of maraviroc in patients with mild (Child-Pugh Class A, n=8), and moderate (Child-Pugh Class B, n=8) hepatic impairment compared to healthy subjects (n=8). Geometric mean ratios for C_{max} and AUC_{last} 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. The effects of moderate hepatic impairment may be underestimated due to limited data in patients with decreased metabolic capacity and higher renal clearance in these subjects. The results should therefore be interpreted with caution. The pharmacokinetics of maraviroc have not been studied in subjects with severe hepatic impairment (*see Dosage and Administration and Warnings and Precautions*).

Other patient characteristics

Race: Population pharmacokinetic analysis of pooled Phase 1/2a data indicated exposure was 26.5% higher in Asians (n=95) as compared to non-Asians (n=318). However, a study designed to evaluate pharmacokinetic differences between Caucasians (n=12) and Asians (n=12) showed no difference between these two populations. Population pharmacokinetic analysis of data from all subjects who received maraviroc in MERIT showed a statistically significant higher exposure (17.5%) in Blacks (n=143) and others (n=35) combined when compared with Whites (n=327) and Asians (n=10) combined. *In a Phase 1 study in healthy subjects, Blacks were shown to have higher maraviroc exposures (17%) as compared to Caucasians with the same CYP3A5 genotype (No CYP3A5*1 alleles).* No dose adjustment based on race is needed (see Pharmacogenomics).

Gender: Population pharmacokinetic analysis of pooled Phase 1/2a data indicated gender (female: n=96, 23.2% of the total population) does not affect maraviroc concentrations. No dosage adjustment is necessary on the basis of gender.

Pharmacogenomics

In a Phase 1 study conducted in healthy subjects, Blacks with a CYP3A5 genotype conferring extensive maraviroc metabolism (2 CYP3A5*1 alleles; n=12) had a 37% and 26% lower AUC when dosed with maraviroc 300 mg twice daily compared with Black (n=11) and Caucasian (n=12) subjects with genotypes associated with poor maraviroc metabolism via CYP3A5 (No CYP3A5*1 alleles), respectively. Blacks with a CYP3A5 genotype conferring extensive maraviroc metabolism (n=12) and poor metabolism (n=11) had a 17% lower maraviroc AUC with maraviroc 150 mg once daily in the presence of a potent CYP3A inhibitor (darunavir/cobicistat). All subjects in this study achieved the C_{avg} concentration shown to be associated with near maximal virologic efficacy with maraviroc (75 ng/mL) in the Phase 3 MERIT study. In a retrospective analysis of the MERIT study (A4001026), where maraviroc was dosed at 300 mg twice daily in the absence of a potent CYP3A inhibitor with or without food, CYP3A5 genotype was not shown to impact maraviroc efficacy (n=303). Therefore, despite differences in CYP3A5 genotype prevalence by race, the effect of CYP3A5 genotype on maraviroc exposure is not considered clinically significant and no maraviroc dose adjustment according to CYP3A5 genotype, race or ethnicity is needed.

Clinical Studies

Studies in CCR5-tropic Treatment-Experienced Patients:

The clinical efficacy of maraviroc (in combination with other antiretroviral medicinal products) on plasma HIV RNA levels and CD4+ cell counts have been investigated in two pivotal, randomised, double-blind, multicentre studies (MOTIVATE 1 and MOTIVATE 2, n= 1049) in patients infected with CCR5 tropic HIV-1 (as determined by the Trofile Assay).

The primary timepoint for efficacy was Week 48. Patients who were eligible for these studies had prior exposure to at least three antiretroviral medicinal product classes [≥1 nucleoside reverse transcriptase inhibitors (NRTI), ≥1 non-nucleoside reverse transcriptase inhibitors (NNRTI), ≥2 protease inhibitors (PI), and/or enfurvirtide] or documented resistance to at least one member of each class. Patients were randomised in a 2:2:1 ratio to maraviroc 300 mg (dose equivalent) once daily, twice daily or placebo in combination with an Optimized Background Therapy (OBT) consisting of three to six antiretroviral medicinal products (excluding low-dose ritonavir). The OBT was selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements.

Table 8 Demographic and baseline characteristics of patients (pooled studies MOTIVATE-1 and MOTIVATE-2)

Demographic and Baseline Characteristics	CELSENTRI 300 mg BID + OBT N = 426	OBT alone N = 209
Age (years) (Range, years)	46.3 21-73	45.7 29-72
Male Sex	89.7%	88.5%
Race -White -Black -Other	85.2% 12% 2.8%	85.2% 12.4% 2.4%
Subjects with Previous Enfuvirtide Use	143 (33.6%)	60 (28.7%)
Subjects with Enfuvirtide as Part of OBT	182 (42.7%)	90 (43.1%)
Mean Baseline HIV-1 RNA (log_{10} copies/mL)	4.9	4.9
Median Baseline CD4+ Cell Count(cells/mm^3) (range, cells/mm^3)	166.8 (2.0 – 820.0)	170.8 (1.0 – 675.0)
Screening Viral Load ≥100,000 copies/mL	179 (42.0%)	84 (40.2%)
Baseline CD4+ Cell Count ≤200 cells/mm^3	250 (58.7%)	118 (56.5%)
Subjects with Overall Susceptibility Score (OSS):[1] 0 1 2 ≥3	 57 (13.4%) 136 (31.9%) 103 (24.2%) 126 (29.6%)	 35 (16.7%) 43 (20.6%) 59 (28.2%) 67 (32.1%)
Subjects with enfuvirtide resistance mutations	90 (21.2%)	44 (21.2%)
Median Number of Resistance-Associated[2]: PI mutations NNRTI mutations NRTI mutations	 10 1 6	 10 1 6

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

Table 9 Efficacy Outcomes at Week 48 (pooled studies MOTIVATE-1 and MOTIVATE-2)

Outcomes	CELSENTRI BID + OBT N=426	OBT alone N=209	Difference[1] (CI)
HIV-1 RNA Change from baseline (log copies/mL)	-1.837	-0.785	-1.055 (-1.327, -0.783)[1]

Percentage of patients with HIV-1 RNA <400 copies/mL	56.1%	22.5%	34.1 (27.1, 41.2)[2]
Percentage of patients with HIV-1 RNA <50 copies/mL	45.5%	16.7%	28.8 (21.4, 36.3)[1]
CD4+ cell count (cells/µL) Mean change from baseline	122.78	59.17	63.13 (44.28, 81.99)[2]

[1] Treatment difference and 97.5% Confidence interval adjusted for randomization strata.

[2] Treatment difference and 95% Confidence interval adjusted for randomization strata.

Table 10. Proportion of patients achieving <50 copies/ml at Week 48 by subgroup (pooled Studies MOTIVATE-1 and MOTIVATE-2)

Subgroups	**HIV-1 RNA <50 copies/ mL**	
	Maraviroc 300 mg BID + OBT (n=426)	**OBT alone (n=209)**
Screening HIV-1 RNA (copies/mL):		
<100,000	58.4%	26.0%
≥100,000	34.7%	9.5%
Baseline CD4+ (cells/µL):		
<50	16.5%	2.6%
50-100	36.4%	12.0%
101-200	56.7%	21.8%
201-350	57.8%	21.0%
≥ 350	72.9%	38.5%
Number of active ARVs in OBT[1]:		
0	32.7%	2.0%
1	44.5%	7.4%
2	58.2%	31.7%
≥3	62%	38.6%

[1] Based on GSS.

Limited numbers of patients from ethnicities other than Caucasian were included in the pivotal clinical studies, therefore very limited data are available in these patient populations.

The mean increase in CD4+ cell count from baseline in patients who failed with a change in tropism result to dual/mixed tropic or CXCR4, in the CELSENTRI 300 mg twice daily + OBT (+56 cells/mm^3) group was greater than that seen in patients failing OBT alone (+13.8 cells/mm^3) regardless of tropism.

In a retrospective analysis of the MOTIVATE studies with a more sensitive assay for screening of tropism (Trofile ES), the response rates (<50 copies/mL at Week 48) in patients with only CCR5-tropic virus detected at baseline was 48.2% in those treated with maraviroc + OBT (n=328), and 16.3% in those treated with placebo + OBT (n=178).

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

Study A4001029 was an exploratory study in patients infected with dual/mixed or CXCR4 tropic HIV-1 with a similar design as the studies MOTIVATE 1 and MOTIVATE 2. In this study, neither superiority nor non-inferiority to OBT alone were demonstrated although there was no adverse outcome on viral load or CD4+ cell count.

Studies on Patients co-infected with hepatitis B and/or hepatitis C virus:

The hepatic safety of maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects with HIV RNA <50 copies/mL, co-infected with Hepatitis C and/or Hepatitis B Virus was evaluated in a multi-center, randomized, double-blinded, placebo-controlled study. 70 subjects (Child-Pugh Class A, n=64; Child-Pugh Class B, n=6) were randomized to the maraviroc group and 67 subjects (Child-Pugh Class A, n=59; Child-Pugh Class B, n=8) were randomized to the placebo group.

The primary objective assessed the incidence of Grade 3 and 4 ALT abnormalities (>5x upper limit of normal (ULN) if baseline ALT ≤ ULN; or >3.5x baseline if baseline ALT > ULN) at Week 48. One subject in each treatment arm met the primary endpoint by Week 48 (at Week 8 for placebo and Week 36 for the maraviroc arm).

NON-CLINICAL INFORMATION

Carcinogenesis/mutagenesis

Primary pharmacological activity (CCR5 receptor affinity) was present in the monkey (100% receptor occupancy) and limited in the mouse, rat, rabbit and dog. In mice and human beings that lack CCR5 receptors through genetic deletion, no significant adverse consequences have been reported.

In vitro and *in vivo* studies showed that maraviroc has a potential to increase QTc interval at supratherapeutic doses with no evidence of arrhythmia.

Repeated dose toxicity studies in rats identified the liver as the primary target organ for toxicity (increases in transaminases, bile duct hyperplasia, necrosis).

Maraviroc was evaluated for carcinogenic potential by a 6 month transgenic mouse study and a 24 month study in rats. In mice, no statistically significant increase in the incidence of any tumour was reported at systemic exposures from 7 to 39 times the human exposure (unbound AUC 0-24h measurement) at a dose of 300 mg twice daily. In rats, administration of maraviroc at a systemic exposure 21 times the expected human exposure produced thyroid adenomas associated with adaptive liver changes. These findings are considered of low human relevance. In addition, cholangiocarcinomas (2/60 males at 900 mg/kg) and cholangioma (1/60 females at 500 mg/kg) were reported in the rat study at a systemic exposure at least 15 times the expected free human exposure.

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

Reproductive Toxicology

Fertility

Maraviroc did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats up to 1000 mg/kg. The exposure at this dose level corresponded to 39-fold the estimated free clinical AUC for a 300 mg twice daily dose.

Pregnancy

Embryofoetal development studies were conducted in rats and rabbits at doses up to 39- and 34-fold the estimated free clinical AUC for a 300 mg twice daily dose. In rabbit, 7 foetuses had external anomalies at maternally toxic doses and 1 foetus at the mid dose of 75 mg/kg.

Pre- and post-natal developmental studies were performed in rats at doses up to 27-fold the estimated free clinical AUC for a 300 mg twice daily dose. A slight increase in motor activity in high-dose male rats at both weaning and as adults was noted, 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.

PHARMACEUTICAL INFORMATION

Excipients

Tablet core:
Cellulose, microcrystalline
Calcium hydrogen phosphate, anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat:
Poly (vinyl alcohol)
Titanium dioxide
Macrogol 3350
Talc
Soya Lecithin
Indigo carmine aluminium lake (E132)

Shelf life

Refer to EXP date on outer carton.

Storage

The storage conditions are detailed on the packaging.

Nature and contents of container

Polyvinyl chloride (PVC) blisters with aluminium lidding foil or PVC blisters with child-resistant aluminium/ polyethylene terephthalate (PET) lidding foil in a carton containing 30, 60, 90 film-coated tablets.

Not all presentations are available in every country.

Incompatibilities

Not applicable.

Special precautions for disposal

No special requirements.

MANUFACTURER

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