AUSTRALIAN PRODUCT INFORMATION

CELSENTRI (maraviroc) tablets

1 NAME OF THE MEDICINE

Maraviroc

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains either 150 or 300 mg of maraviroc.

Tablets contain no excipients with a known effect. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

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

CELSENTRI is supplied for oral administration in two strengths: 150 and 300 mg blue, biconvex, oval film-coated tablets debossed with “MVC” followed by the tablet strength on one tablet side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

The use of other active agents with CELSENTRI is associated with a greater likelihood of treatment response.

4.2 DOSE AND METHOD OF 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 using an assay with appropriate validation and sensitivity, resistance testing and treatment history should guide the use of CELSENTRI.
- Adult patients infected with only CCR5-tropic HIV-1 should use CELSENTRI.
- CCR5 tropism should be confirmed using a highly sensitive, appropriately validated tropism assay prior to initiation of CELSENTRI therapy. Outgrowth of pre-existing low-level CXCR4 or dual/mixed-tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure on CELSENTRI.
- CELSENTRI is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1.
- In treatment-naïve subjects, more subjects treated with CELSENTRI experienced virologic failure and developed lamivudine resistance compared to efavirenz.

- The safety and efficacy of CELSENTRI have not been established in children younger than 18 years of age.

Adults
The recommended dose of CELSENTRI 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

CELSENTRI can be taken with or without food.

Table 1: Recommended Dosing Regimen

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

Children
The safety and efficacy for the use of CELSENTRI in children younger than 18 years of age has not been established. Therefore, use in children is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Elderly
There is limited experience in patients above 65 years of age; therefore, caution should be exercised when administering CELSENTRI in elderly patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment
Table 2 provides dosing recommendations for patients based on renal function and

concomitant medications.

Table 2: Recommended dosing regimens based on renal function

Concomitant Medications*	CELSENTRI dose based on Renal Function				
	Normal	Mild	Moderate	Severe	End Stage Renal Disease (ESRD)
	CrCl >80 mL/min	CrCl >50 mL/min and ≤ 80-mL/min	CrCl >30 mL/min and ≤ 50-mL/min	CrCl ≤ 30-mL/min	On Regular Haemodialysis
Potent CYP3A inhibitors (with or without CYP3A inducer)*	150 mg twice daily	150 mg twice daily	150 mg twice daily	NR	NR
Other concomitant medications*	300 mg twice daily	300 mg twice daily	300 mg twice daily	300 mg twice daily#	300 mg twice daily#
Potent CYP3A inducers (without CYP3A inhibitor)*	600 mg twice daily	600 mg twice daily	600 mg twice daily	NR	NR

NR = not recommended
*See Table 3 for list of concomitant medications
The CELSENTRI dose should be reduced to 150 mg twice daily if there are any symptoms of postural hypotension (see Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties)

Hepatic impairment
Limited data in mild and moderate hepatic impairment patients demonstrated small increase in the mean C_{max} of maraviroc, suggesting no dose adjustment is required. However, CELSENTRI should be used with caution in patients with hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Initiating therapy
The following points should be considered when initiating therapy with CELSENTRI (see Section 4.1 THERAPEUTIC INDICATIONS, Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic effects):

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

- The viral tropism cannot be predicted by treatment history or assessment of stored samples.

- Adult patients infected with only CCR5-tropic HIV-1 should use CELSENTRI.

- CCR5 tropism should be confirmed using a highly sensitive tropism assay prior to initiation of CELSENTRI therapy. Outgrowth of pre-existing low-level CXCR4- or dual/mixed-tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure on CELSENTRI.

- CELSENTRI is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1.

- In treatment-naïve subjects, more subjects treated with CELSENTRI experienced virologic failure and developed lamivudine resistance compared to efavirenz. The main reason for discontinuations in the efavirenz group was treatment-related adverse events (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Table 14).

The safety and efficacy of CELSENTRI have not been established in children younger than 18 years of age.

Severe skin and hypersensitivity reactions
Hypersensitivity reactions including severe and potentially life-threatening events have been reported in patients taking CELSENTRI, 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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.

Cardiovascular safety
Use with caution in patients at increased risk for cardiovascular events. Eleven patients (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 in treatment-experienced studies [total exposure of 609 patient-years (309 patient-years for BD + 300 patient-years for OD)], while no patients who received placebo had such events (total exposure 111 patient-years). These patients generally had cardiac disease or cardiac risk factors prior to CELSENTRI use, and the relative contribution of CELSENTRI to these events is not known.

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

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

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

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.

Tropism
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 susceptible (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic Effects).

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 potent CYP3A4 inhibitors and/or inducers since maraviroc concentrations and its therapeutic effects may be affected (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Refer to the respective prescribing information of the other medicinal products used in combination with CELSENTRI.

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.

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 patients 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.

Use in hepatic impairment
An increase in hepatic adverse reactions with CELSENTRI was observed during studies of treatment-experienced patients with HIV infection, although there was no overall increase in ACTG Grade 3/4 liver function test abnormalities (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Hepatotoxicity accompanied by severe rash or systemic allergic reaction including potentially life-threatening events has been reported. Hepatic laboratory parameters including ALT, AST, and bilirubin should be obtained prior to starting CELSENTRI and at other time points during treatment as clinically indicated. If rash or symptoms or signs of hepatitis or allergic reaction develop, hepatic laboratory parameters should be monitored. Discontinuation of CELSENTRI 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 Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). 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 prescribing 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 CELSENTRI have not been specifically studied in patients with significant underlying liver disorders. Since there is limited experience in patients with reduced hepatic function, therefore, CELSENTRI should be used with caution in this population (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in 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.

Study A4001075 evaluated the pharmacokinetics and safety of CELSENTRI in combination with saquinavir/ritonavir in participants with mild and moderate renal impairment compared to healthy adult volunteers (see Section 5.2 PHARMACOKINETIC PROPERTIES, Renal impairment).

All 18 participants received saquinavir/ritonavir 1000/100 mg in addition to 150 mg maraviroc at different dose frequencies: healthy volunteers - every 12 hours (n = 6); mild renal impairment - every 24 hours (n = 6); moderate renal impairment - every 48 hours (n = 6). Treatment duration was 7 days.

The most frequently reported treatment-related adverse event by preferred term was blood creatinine increased, reported in eight (8) of the twelve (12) participants with mild and moderate renal impairment. Nocturia, considered study drug related, was reported by 6 of the 12 participants with mild and moderate renal impairment. Patients in the study with normal renal function demonstrated a decrease in mean creatinine clearance over the course of the study, though no patient with normal function had decreased creatinine clearance reported as an adverse event.

On the basis of these results it is recommended that renal function is monitored if patients on maraviroc are co-administered saquinavir/ritonavir. The effect of this drug interaction on renal function in patients with severe renal failure has not been studied. The effect of multiple dose treatment with maraviroc without concomitant CYP3A4 has not been studied.

Table 2 provides dose and/or interval adjustment guidelines for patients with renal impairment with and without co-administered potent CYP3A4 inhibitors (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly
There were insufficient numbers of patients aged 65 and over in the clinical studies to determine whether they respond differently from younger patients. 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use
The safety and efficacy of CELSENTRI in paediatric patients have not been established, therefore use in children is not recommended (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETICS PROPERTIES).

Effects on laboratory tests
See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Tables 5 and 8.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Maraviroc is metabolised by cytochrome P450 CYP3A. Maraviroc is also a substrate for P-glycoprotein, OATP1B1 and MRP2 *in vitro*. Co-administration of CELSENTRI with medicinal products that induce those enzymes and transporters may decrease maraviroc concentrations and reduce its therapeutic effects. Co-administration of CELSENTRI with medicinal products that inhibit those enzymes and transporters may increase maraviroc plasma concentrations. Dose adjustment of CELSENTRI is recommended when

CELSENTRI is co-administered with potent CYP3A4 inhibitors and/or inducers. Further details for concomitantly administered medicinal products are provided below (see Table 3 and Section 4.2 DOSE AND METHOD OF ADMINISTRATION, 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.* 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, *in vitro* studies have shown that maraviroc is not a substrate for and does not inhibit any of the major renal uptake inhibitors at clinically relevant concentrations (OAT1, OAT3, OCT2 OCTN1, and OCTN2). Additionally, 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* (IC_{50} is 183 microM). Systemic effects on P-gp are unlikely to be of relevance. Maraviroc could inhibit P-gp in the gut and may thus affect the bioavailability of certain drugs. 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 medicinal 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		
NRTIs		
Lamivudine 150 mg twice daily (maraviroc 300 mg twice daily)	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.	**Maraviroc 300 mg twice daily**[1] No clinically significant interaction observed or expected with NRTIs.
Tenofovir 300 mg once daily (maraviroc 300 mg twice daily)	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.	

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**
Zidovudine 300 mg twice daily (maraviroc 300 mg twice daily)	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)	**Maraviroc 150 mg twice daily when co-administered with boosted elvitegravir**
Raltegravir 400 mg twice daily (maraviroc 300 mg twice daily)	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)	**Maraviroc 300 mg twice daily**[1] No clinically significant interaction observed
NNRTIs		
Efavirenz 600 mg once daily (maraviroc 100 mg twice daily)	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.	**Maraviroc 600 mg twice daily** when co-administered with efavirenz in the absence of a potent CYP3A4 inhibitor. For combination with efavirenz + PI, see separate recommendations below.
Etravirine 200 mg twice daily (maraviroc 300 mg twice daily)	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)	**Maraviroc 600 mg twice** daily when co-administered with etravirine in the absence of a PI (except tipranavir/ritonavir or fosamprenavir/ritonavir) or other potent CYP3A4 inhibitor. For combination with etravirine + PI, see below.
Nevirapine 200 mg twice daily (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**[1] **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 150 mg twice daily.**
Protease Inhibitors (PIs)		
Atazanavir 400 mg once daily (maraviroc 300 mg twice daily)	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.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.
Atazanavir/ritonavir 300 mg/100 mg once daily (maraviroc 300 mg twice daily)	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.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.
Lopinavir/ritonavir 400 mg/100 mg twice daily (maraviroc 300 mg twice daily)	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.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.

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**
Saquinavir/ritonavir 1000 mg/100 mg twice daily (maraviroc 100 mg twice daily)	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.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.
Darunavir/ritonavir 600 mg/100 mg twice daily (maraviroc 150 mg twice daily	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.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.
Nelfinavir	Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A4 inhibitor and would be expected to increase maraviroc concentrations.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.
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 co-administered with indinavir gives appropriate maraviroc exposure.	**Maraviroc 150 mg twice daily.** Maraviroc does not significantly affect PI drug levels.
Fosamprenavir/ritonavir 700 mg/100 mg BID (maraviroc 300 mg BID) Fosamprenavir/ritonavir 1400 mg/100 mg QD (maraviroc 300 mg QD***)***	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) 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)	**Maraviroc 150 mg twice daily.** Maraviroc significantly reduces PI exposure by approximately 30 – 35 %.
Tipranavir/ritonavir 500 mg/200 mg twice daily (maraviroc 150 mg twice daily)	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.	**Maraviroc 300 mg twice daily.**
NNRTI + PI		
Efavirenz 600 mg once daily + lopinavir/ritonavir 400 mg/100 mg twice daily (maraviroc 300 mg twice daily)	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.	**Maraviroc 150 mg twice daily** when co-administered with efavirenz and lopinavir/ritonavir
Efavirenz 600 mg once daily + saquinavir/ritonavir 1000 mg/100 mg twice daily (maraviroc 100 mg twice daily)	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.	**Maraviroc 150 mg twice daily** when co-administered with efavirenz and saquinavir/ritonavir
Efavirenz and atazanavir/ritonavir or darunavir/ritonavir.	Not studied. Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir of efavirenz, an increased exposure is expected.	**Maraviroc 150 mg twice daily** when co-administered with efavirenz and atazanavir, atazanavir/ritonavir, darunavir/ritonavir.

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**
Efavirenz and fosamprenavir/ritonavir	Not studied. Based on the extent of inhibition by fosamprenavir/ritonavir, in the absence of efavirenz, no clinically significant change in exposure is expected.	**Maraviroc 300 mg twice daily** when co-administered with efavirenz and fosamprenavir/ritonavir can be co-administered without dose adjustment.
Efavirenz and tipranavir/ritonavir	Not studied. Based on the absence of an effect with tipranavir/ritonavir in the absence of efavirenz and the extent of induction by efavirenz alone.	**Maraviroc 600 mg twice daily** when co-administered with efavirenz and tipranavir/ritonavir.
Etravirine and darunavir/ritonavir (maraviroc 150 mg twice daily)	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)	**Maraviroc 150 mg twice daily** when co-administered with etravirine and darunavir/ritonavir
Etravirine and atazanavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir	Not studied. Based on the extent of inhibition by atazanavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir in the absence of etravirine, an increased exposure is expected.	**Maraviroc 150 mg twice daily** when co-administered with etravirine and atazanavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir
Etravirine and fosamprenavir/ritonavir	Not studied. Based on the extent of inhibition by fosamprenavir/ritonavir, in the absence of etravirine, no clinically significant change in exposure is expected.	**Maraviroc 300 mg twice daily** when co-administered with etravirine and fosamprenavir/ritonavir can be co-administered without dose adjustment.
Antibiotics		
Sulphamethoxazole/ Trimethoprim 800 mg/160 mg twice daily (maraviroc 300 mg twice daily)	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.	**Maraviroc 300 mg twice daily**
Rifampicin 600 mg once daily (maraviroc 100 mg twice daily)	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.	**Maraviroc 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.
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 is expected.	**Maraviroc 150 mg twice daily** when co-administered with rifabutin and a PI **(except tipranavir/ritonavir where the dose should be 300 mg twice daily).** See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.
Clarithromycin, Telithromycin	Not studied, but both are potent CYP3A4 inhibitors and would be expected to increase maraviroc concentrations.	**Maraviroc 150 mg twice daily.**
Antifungals		
Ketoconazole 400 mg once daily (maraviroc 100 mg twice daily)	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.	**Maraviroc 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**
Itraconazole	Not studied. Itraconazole is a potent CYP3A4 inhibitor and would be expected to increase the exposure of maraviroc.	**Maraviroc 150 mg twice daily.**
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[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.	**Maraviroc 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.	**Maraviroc 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.	**Maraviroc 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.	**Maraviroc 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.	**Maraviroc 300 mg twice daily[1].**
Buprenorphine	Not studied, no interaction expected.	**Maraviroc 300 mg twice daily[1].**
LIPID LOWERING MEDICINAL PRODUCTS		
Statins	Not studied, no interaction expected.	**Maraviroc 300 mg twice daily[1].**
ANTIARRHYTHMICS		
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.	**Maraviroc 300 mg twice daily[1].**
ORAL ONTRACEPTIVES		
Ethinylestradiol 30 mcg once daily (maraviroc 100 mg twice daily)	Ethinylestradiol. AUC_{24}: ↔ 1.00 (0.95, 1.05) Ethinylestradiol. C_{max}: ↔ 0.99 (0.91, 1.06) Maraviroc concentrations not measured, no interaction expected.	**Maraviroc 300 mg twice daily[1].**
Levonorgestrel 150 mcg once daily (maraviroc 100 mg twice daily)	Levonorgestrel. AUC_{24}: ↔ 0.98 (0.92, 1.04) Levonorgestrel. C_{max}: ↔ 1.01 (0.93, 1.08) Maraviroc concentrations not measured, no interaction expected.	**Maraviroc 300 mg twice daily[1].**
BENZODIAZEPINES		
Midazolam 7.5 mg single dose (maraviroc 300 mg twice daily)	Midazolam. AUC: ↔ 1.18 (1.04, 1.34) Midazolam. C_{max}: ↔ 1.21 (0.92, 1.60) Maraviroc concentrations not measured, no interaction expected.	**Maraviroc 300 mg twice daily[1].**
HERBAL PRODUCTS		
St John's Wort	Co-administration 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 TID = three times daily C = concentration
BID = twice daily AUC = area under the curve
[1] If co-administered with a potent CYP3A inhibitor and/or inducer, dose maraviroc according to Table 1.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 $AUC_{0\text{-}24h}$ for a 300 mg twice daily dose.

Use in pregnancy
Pregnancy Category: B1

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 $AUC_{0\text{-}24h}$ 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
Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breastfeeding during antiretroviral therapy.

It is expected that maraviroc will be secreted into human milk based on animal data, although this has not been confirmed in humans.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of CELSENTRI 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 CELSENTRI. If affected, patients should avoid potentially hazardous tasks such as driving, cycling or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse effects are discussed in other sections of the Product Information:

- Hepatotoxicity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Cardiovascular effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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

Assessment of treatment-emergent adverse events is based on the pooled data from two studies in patients with CCR5-tropic HIV-1 (MOTIVATE-1 and MOTIVATE-2). The median duration of maraviroc therapy for patients in these studies was 48 weeks, with the total exposure on CELSENTRI twice daily at 309 patient-years versus 111 patient-years on placebo + OBT. The population was 89% male and 84% white, with mean age of 46 years (range 17-75 years). Patients 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 upper respiratory tract infections, cough, pyrexia, rash and dizziness. Additional adverse events that occurred with once daily dosing at a higher rate than both placebo and twice daily dosing were diarrhoea, oedema, influenza, oesophageal candidiasis, sleep disorders, rhinitis, parasomnias and urinary abnormalities. In these two studies, the rate of discontinuation due to adverse events was 5% for patients who received CELSENTRI twice daily + optimised background therapy (OBT) as well as those who received 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 patients reporting infections were 233 (55%) and 84 (40%) 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 133 for both CELSENTRI twice daily and placebo.

Dizziness or postural dizziness occurred in 8% of patients on either CELSENTRI or placebo, with 2 patients (0.5%) on CELSENTRI permanently discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) permanently discontinuing therapy due to dizziness.

Treatment-emergent adverse events, regardless of causality, from Studies MOTIVATE-1 and MOTIVATE-2 are summarised in Table 4. Selected events occurring at ≥ 2% of patients and at a numerically higher rate in patients treated with CELSENTRI + OBT are included; events that occurred at the same or higher rate on OBT alone are not displayed.

Table 4: Percentage of Patients with Selected Treatment-Emergent Adverse Events (All Causality) (≥2% on CELSENTRI + OBT and at a higher rate compared to OBT alone) Studies MOTIVATE-1 and MOTIVATE-2 (Pooled analysis, 48 Weeks)

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

	CELSENTRI Twice Daily* + OBT	Exposure-adjusted rate (per 100 pt-yrs) PYE=309**	**OBT alone**	Exposure-adjusted rate (per 100 pt-yrs) PYE=111**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Coughing and associated symptoms	14	21	5	10
Upper respiratory tract signs and symptoms	6	9	3	6
Nasal congestion and inflammations	4	6	3	5
Breathing abnormalities	4	5	2	5
Paranasal sinus disorders	3	4	0.5	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	11	16	5	11
Apocrine and eccrine gland disorders	5	7	4	7.5
Pruritus	4	5	2	4
Lipodystrophies	3	5	0.5	1
Erythemas	2	3	1	2
VASCULAR DISORDERS				
Vascular hypertensive disorders	3	4	2	4

***** 300 mg dose equivalent

** PYE = patient years of exposure

Laboratory abnormalities

Table 5 shows the treatment-emergent Grade 3-4 laboratory abnormalities that occurred in ≥ 2% of patients receiving CELSENTRI.

Table 5: Maximum Shift in Laboratory Test Values (Without Regard to Baseline) Incidence ≥2% of Grade 3-4 Abnormalities (ACTG Criteria) Studies A4001027 and A4001028 (Pooled analysis, 48 Weeks)

Laboratory Parameter Preferred Term,	**Abnormality Grade**	**Abnormality Range**	**Celsentri 300 mg twice daily + OBT N =421* (%)**	**OBT alone N =207* (%)**
Aspartate aminotransferase	Grade 3	>5.0x ULN	4.3 (18/421)	2.9 (6/207)
	Grade 4	>10.0x ULN	1.4 (6/421)	0
Alanine aminotransferase	Grade 3	>5.0x ULN	2.4 (10/421)	3.4 (7/207)
	Grade 4	>10.0x ULN	1.0 (4/421)	0.5 (1/207)
Total bilirubin	Grade 3	>2.5x to 5.0x ULN	5.0 (21/421)	3.9 (8/207)
	Grade 4	>5.0x ULN	5.5 (23/421)	1.5 (3/207)
Amylase	Grade 3	>2.0x to 5.0x ULN	5.7 (24/419)	5.8 (12/207)
	Grade 4	>5.0x ULN	0.2 (1/419)	0
Lipase	Grade 3	>2.0x to 5.0x ULN	5.0 (8/159)	7.7 (7/91)
	Grade 4	>5.0x ULN	1.3 (2/159)	0
Absolute neutrophil count	Grade 3	0.5 to 0.749	3.1 (13/420)	2.4 (5/207)
	Grade 4	<0.5	1.2 (5/420)	0

ULN: Upper Limit of Normal

* 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 switch to an open-label phase of CELSENTRI twice daily extending to week 96. A subsequent observational phase extending to 5 years on treatment

was conducted to assess the incidence of the following long-term safety selected endpoints; death, AIDS defining events, hepatic failure, MI/cardiac ischemia, malignancies, rhabdomyolysis, and other serious infectious events. The incidence of these selected endpoints was consistent with those seen at earlier time points in the studies and listed in Table 6.

Table 6: Exposure Adjusted Rates of Long-Term Safety Selected Endpoints (LTS/SE) – Trials A4001027 and A4001028 (Motivate 1 and 2)
All 5-Year CELSENTRI data (including Double-Blind, Open Label and Observational On-treatment Phases)

LTS/SE, n (%) [events/100 Patient Years][a]	All CELSENTRI Data N=938 Patient Years=2639.2
Hepatic failure	5 (0.5%) [0.2/100 PY]
Myocardial Infarction / Ischaemia	26 (3%) [1.1/100 PY]
Malignancies	61 (7%) [3.0/100 PY]
AIDS-related events	78 (8%) [3.7/100 PY]
Serious infections	114 (12%) [6.2/100 PY]
Rhabdomyolysis	5 (0.5%) [0.2/100 PY]

[a] (Total number of events per total patient years of exposure) x 100

Study in treatment-naïve patients

Treatment-emergent adverse events

Treatment-emergent adverse events, regardless of causality, from the MERIT study, a double-blind comparative controlled study in which 721 treatment-naïve patients received CELSENTRI 300 mg BID (N = 360) or efavirenz (N = 361) in combination with zidovudine/lamivudine for 96 weeks, are summarized in Table 7. Selected events occurring at ≥ 2% of patients and at a numerically higher rate in patients treated with CELSENTRI are included; events that occurred at the same or higher rate on efavirenz are not displayed.

Table 7: Percentage of Patients with Selected Treatment-Emergent Adverse Events (All Causality) (≥2% on CELSENTRI and at a higher rate compared to efavirenz) MERIT study (96 Weeks)

	CELSENTRI + zidovudine/lamivudine 300 mg BID N = 360 (%)	EFAVIRENZ + zidovudine/lamivudine 600 mg QD N = 361 (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemias NEC	8	5
Neutropenias	4	3
EAR AND LABYRINTH DISORDERS		
Ear disorders NEC	3	2
GASTROINTESTINAL DISORDERS		
Flatulence, bloating and distension	10	7

	CELSENTRI + zidovudine/lamivudine 300 mg BID N = 360 (%)	EFAVIRENZ + zidovudine/lamivudine 600 mg QD N = 361 (%)
Gastrointestinal atonic and hypomotility disorders NEC	9	5
Gastrointestinal signs and symptoms NEC	3	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Body temperature perception	3	1
INFECTIONS AND INFESTATIONS		
Bronchitis	13	9
Herpes Infection	7	6
Upper respiratory tract infection	32	30
Bacterial infections NEC	6	3
Herpes zoster/varicella	5	4
Lower respiratory tract and lung infections	3	2
Neisseria infections	3	0
Tinea infections	4	3
Viral infections NEC	3	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Joint related signs and symptoms	6	5
NERVOUS SYSTEM DISORDERS		
Memory loss (excluding dementia)	3	1
Paresthesias and dysesthesias	4	3
RENAL AND URINARY DISORDERS		
Bladder and urethral symptoms	4	3
REPRODUCTIVE, SYSTEM AND BREAST DISORDERS		
Erection and ejaculation conditions and disorders	3	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Upper respiratory tract signs and symptoms	9	5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Acnes	3	2
Alopecias	2	1
Lipodystrophies	4	3
Nail and nail bed conditions (excluding infections and infestations	6	2

Laboratory abnormalities: See Table 8.

Table 8: Maximum Shift in Laboratory Test Values (Without Regard to Baseline) Incidence ≥2% of Grade 3-4 Abnormalities (ACTG Criteria) MERIT study (96 Weeks)

Laboratory Parameter Preferred Term	Abnormality Grade	Abnormality Range	CELSENTRI 300 mg twice daily + zidovudine/ lamivudine N =353* (%)	EFAVIRENZ 600 mg QD + zidovudine/ lamivudine N =350* (%)
Aspartate aminotransferase	Grade 3	>5.0x ULN	2.3 (8/353)	3.4 (12/350)
	Grade 4	>10.0x ULN	1.7 (6/353)	0.6 (2/350)
Alanine aminotransferase	Grade 3	>5.0x ULN	3.1 (11/353)	3.4 (12/350)
	Grade 4	>10.0x ULN	0.8 (3/353)	0.6 (2/350)
Creatine kinase	Grade 3	>10.0x to 20.0x ULN	2.8 (10/353)	3.1 (11/350)
	Grade 4	>20.0x ULN	1.1 (4/353)	1.7 (6/350)
Amylase	Grade 3	>2.0x to 5.0x ULN	4.0 (14/352)	5.7 (20/350)
	Grade 4	>5.0x ULN	0.3 (1/352)	0.3 (1/350)
Absolute neutrophil count	Grade 3	0.5 to 0.749	4.3 (15/352)	4.0 (14/349)
	Grade 4	<0.5	1.4 (5/352)	0.9 (3/349)
Haemoglobin	Grade 3	6.5 to 6.9	0.6 (2/352)	0.6 (2/350)
	Grade 4	<6.5	2.3 (8/352)	1.7 (6/350)

*N = total number of patients evaluable for laboratory abnormalities.
Percentages based on total patients evaluated for each laboratory parameter. If the same subject in a given treatment group had >1 occurrence of the same abnormality, only the most severe is counted.

Less common adverse events in clinical trials

The following adverse events occurred in < 2% of CELSENTRI-treated patients. These events have been included because of their seriousness and either increased frequency on CELSENTRI or are potential risks due to the mechanism of action. Events attributed to the patient's underlying HIV infection are not listed.

Blood and lymphatic system: Marrow depression and hypoplastic anaemia.

Cardiac disorders: Unstable angina, acute cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, myocardial ischemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatobiliary disorders: Hepatic cirrhosis, hepatic failure, cholestatic jaundice, portal vein thrombosis, hypertransaminaseamia, jaundice.

Infections and infestations: Endocarditis, infective myositis, viral meningitis, pneumonia, treponema infections, septic shock, *Clostridium difficile* colitis, meningitis.

Musculoskeletal and connective tissue disorders: Myositis, osteonecrosis, rhabdomyolysis, blood CK increased.

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Abdominal neoplasia, anal cancer, basal cell carcinoma, Bowen's disease, cholangiocarcinoma, diffuse large B-cell lymphoma, metastases to liver, oesophageal

carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, tongue neoplasia (malignant stage unspecified), anaplastic large cell lymphomas T- and null-cell types, bile duct neoplasms malignant, endocrine neoplasms malignant and unspecified.

Nervous system disorders: Cerebrovascular accident, convulsions and epilepsy, tremor (excluding congenital).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatotoxicity and hepatic failure with allergic features have been reported in association with CELSENTRI in clinical trials and post marketing (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

After unblinding of the study following the last subject's week 96 visit, subjects could be eligible for continued treatment during the open-label extension phase of the study with the same study drug to which they had been randomised. Safety results at week 240 on treatment were consistent with those seen at week 96.

Post marketing experience
Very rarely, severe hypersensitivity reactions have been reported. These included drug rash with eosinophilia and systemic symptoms (DRESS), severe cutaneous reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) as well as hepatotoxicity and hepatic failure with allergic features.

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

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 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 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.

If indicated, elimination of unabsorbed active CELSENTRI should be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since CELSENTRI is moderately protein bound, dialysis may be beneficial in removal of this medicine.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Pharmacodynamic Effects
Antiviral activity in cell culture
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* IC_{50} (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 nanoM (0.05 to 2.3 nanogram/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 antiviral activity in cell culture 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.

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)), consistent with the resistant viruses being able to use CCR5 as a co-receptor for cell entry even when maraviroc is bound. 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.

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 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.

Resistance *in vivo*
The two mechanisms of virologic escape observed *in vivo* include the unmasking of CXCR4-using virus and the selection of virus that continues to use CCR5 but with reduced susceptibility to maraviroc, as indicated by a maximal plateau of inhibition of < 95%. Both routes to virologic escape have been observed in clinical studies of both treatment-naïve and treatment-experienced patients.

CXCR4-using virus presence at virological failure appears to originate from a pre-existing viral population. Resistance of CCR5-tropic virus through the increase of EC_{50} fold-change does not appear to be an important mechanism of failure.

Sequencing of the V3 loop of virus with reduced susceptibility to maraviroc has identified changes in the amino acid sequence for the majority; however, no signature mutation has

been identified. Mutations within Gp160 but outside of the V3 loop, contributing to the maraviroc resistance phenotype have been reported but appear uncommon.

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 in approximately 55% of patients who failed treatment on maraviroc, as compared to 6% of patients who experienced treatment failure in the Optimised Background Therapy (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 patients (16 patients from the maraviroc arms and 4 patients 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 in patients with CCR5 virus at baseline, 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 patients 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 exposure, in some cases associated with poor compliance. 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.

Treatment-naïve patients
In the pivotal study of treatment-naïve patients (MERIT week 96), 13/343 (3.8%) had a change in tropism result from CCR5-tropic to CXCR4-tropic or dual/mixed-tropic in the four-six week interval between screening and baseline during which time no treatment was administered.

Failure with CXCR4-using virus
In the analysis of week 96 data, using a time to loss of virologic response (HIV-1 RNA<50 copies/mL) endpoint, CXCR4-using virus was detected at failure in approximately 24/86 (28%) of the patients with CCR5-tropic virus at baseline and who failed treatment on

maraviroc, as compared to none of patients who experienced treatment failure in the efavirenz arm. A retrospective analysis of tropism at Screening was performed using a modified tropism assay with enhanced sensitivity (100% X4 virus detection at 0.3% prevalence compared with 10% with the original assay). Data from enrolled patients who originally screened with the R5 virus, but who screened retrospectively with CXCR4-using virus, were censored. Of the remaining subjects with CCR5-tropic virus at Baseline and who experienced virologic failure, CXCR4-using virus was detected in 17% (11/65) as compared to none in the efavirenz arm.

A detailed clonal analysis was conducted for two previously antiretroviral treatment-naïve patients enrolled in a Phase 2a monotherapy study and who had CXCR4-using virus observed after 10 day treatment with maraviroc. Consistent with the detailed clonal analysis conducted in treatment-experienced patients, the CXCR4-using variant was found to be pre-existing prior to starting therapy.

All but one (11/12; 92%) of the maraviroc failures failing with CXCR4 or dual/mixed-tropic virus also had genotypic and phenotypic resistance to the background drug lamivudine at failure and 33% (4/12) developed zidovudine-associated resistance substitutions.

Failure with CCR5-tropic virus
Phenotypic resistance: in patients with CCR5-tropic virus at time of treatment failure with maraviroc, 6 out of 38 patients had virus with reduced sensitivity to maraviroc. In the remaining 32 patients, there was no evidence of virus with reduced sensitivity as identified by exploratory virology analyses on a representative group. One additional subject had a ≥ 3-fold shift in EC_{50} value for maraviroc at the time of failure.

Clinical trials
The clinical efficacy and safety of CELSENTRI is derived from analyses of data from three ongoing studies in adult patients infected with CCR5-tropic HIV-1: MOTIVATE-1 A4001027 and MOTIVATE-2 A4001028, in antiretroviral treatment-experienced adult patients and MERIT A4001026 in treatment-naïve patients. These studies are supported by a 48-week study in antiretroviral treatment-experienced adult patients infected with dual/mixed-tropic HIV-1, A4001029.

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+ cell counts have been investigated in two pivotal ongoing, randomised, double-blind, multicentre studies (MOTIVATE-1 and MOTIVATE-2, n = 1076) in patients infected with CCR5-tropic HIV-1. The primary objective of these studies was to assess whether CELSENTRI added to OBT provided an additional reduction in plasma HIV-1 RNA level compared with OBT alone, based on the mean changes from baseline in plasma HIV-1 RNA level at Week 48. Efficacy analyses were performed on the full analysis set and per protocol populations. Patients were analysed as both *As Treated* and *As Randomised* to assess the effect on the results of subjects receiving treatments other than those to which they were randomised.

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 enfuvirtide] 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, maraviroc 300 mg twice daily or placebo in combination with an OBT consisting of three to six antiretroviral medicinal products (excluding low-dose ritonavir). The OBT was selected on the basis of the patient's prior treatment history and baseline genotypic and phenotypic viral resistance measurements.

Table 9 illustrates the demographic and baseline characteristics of patients from the pooled analysis from the MOTIVATE-1 and MOTIVATE-2 studies.

Table 9: Demographic and baseline characteristics of patients in studies MOTIVATE-1 and MOTIVATE -2 (Week 48 pooled analysis)

Demographic and Baseline 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
Male Sex	382 (89.7%)	185 (88.5%)
Race (White/Black/Other)	85.2% / 12% / 2.8%	85.2% / 12.4% / 2.4%
Patients with Previous Enfuvirtide Use	143 (33.6)	(28.7%)
Patients 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)	171.3 (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%)
Patients with Overall Susceptibility Score (OSS):[a] 0 1 2 ≥3	 57 (13.4%) 136 (31.9%) 104 (24.4%) 125 (29.3%)	 35 (16.7%) 44 (21.1%) 59 (28.2%) 66 (31.6%)
Patients with enfuvirtide resistance mutations	90 (21.2%)	44 (21.2%)
Median Number of Resistance-Associated:[b] PI mutations NNRTI mutations NRTI mutations	 10 1 6	 10 1 6

[a] OSS – Sum of active drugs in OBT based on combined information from genotypic and phenotypic testing.
[b] Resistance mutations based on International Aids Society guidelines

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

After 24 weeks of therapy, the mean change in plasma HIV-1 RNA from baseline to week 24 was -1.96 log_{10} copies/mL for patients receiving CELSENTRI 300 mg twice daily + OBT compared to -0.99 log_{10} 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/mm^3) than

on OBT alone (57.37 cells/mm^3). 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 10).

Table 10: Outcomes of randomised treatment at Week 48 (pooled studies MOTIVATE-1 and MOTIVATE-2)

Outcomes	CELSENTRI 300 mg twice daily + OBT N=426	OBT alone N=209	Treatment Difference[1] (Confidence Interval[2])
HIV-1 RNA Change from baseline (log_{10} copies/mL)	-1.84	-0.78	-1.06 (-1.33, -0.78)
Proportion of patients with HIV RNA <400 copies/mL	56.1%	22.5%	Odds ratio: 4.76 (3.24, 7.00)
Proportion of patients with HIV RNA <50 copies/mL	45.5%	16.7%	Odds ratio: 4.49 (2.96, 6.83)
CD4+ cell count Change from baseline (cells/mm^3)	124.07	60.93	63.13 (44.28, 81.99)

[1] p-values<0.0001
[2] For all efficacy endpoints the confidence intervals were 95%, except for HIV-1 RNA Change from baseline which was 97.5%

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 or CXCR4-tropic HIV-1. The inclusion/exclusion criteria were similar to those for MOTIVATE-1 and MOTIVATE-2 above and the patients were randomised in a 1:1:1 ratio to CELSENTRI once daily, CELSENTRI twice daily or OBT alone. The mean changes in viral load and CD4+ counts are shown in Table 11.

Table 11: 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

Study in treatment-naïve patients

Study A4001026 is a randomised, double-blind, multicenter study in patients infected with CCR5-tropic HIV-1 classified by the original Trofile™ tropism assay. The primary objective was to assess whether antiviral activity (plasma viral load < 400/50 copies/mL at week 48) of CELSENTRI in combination zidovudine/lamivudine was non-inferior to a reference regimen of efavirenz plus zidovudine/lamivudine. Patients were required to have plasma HIV-1 RNA ≥ 2000 copies/mL and could not have: 1) previously received any antiretroviral therapy for > 14 days, 2) an active or recent opportunistic infection or a suspected primary HIV-1 infection, or 3) phenotypic or genotypic resistance to zidovudine, lamivudine, or efavirenz. Patients were randomized in a 1:1:1 ratio to CELSENTRI 300 mg once daily, CELSENTRI 300 mg twice daily, or efavirenz 600 mg once daily, each in combination with zidovudine/lamivudine. The efficacy and safety of CELSENTRI are based on the comparison of CELSENTRI twice daily versus efavirenz. A one-sided 97.5% confidence interval (CI) was constructed based on the normal approximation to the binomial distribution for the treatment difference in percentages stratified by the randomisation strata (screening viral load and geographic region). A step down procedure was used to control for multiple comparisons (i.e. < 400 and < 50). Non-inferiority was to be concluded if the lower bound of the one-sided 97.5% CI was > -10%. In a pre-planned interim analysis at 16 weeks, the CELSENTRI 300 mg once per day treatment arm failed to meet the pre-specified criteria for demonstrating non-inferiority and was discontinued.

The demographic and baseline characteristics of the CELSENTRI and efavirenz treatment groups were comparable (Table 12). Patients were stratified by screening HIV-1 RNA levels and by geographic region. The median CD4 cell counts and mean HIV-1 RNA at baseline were similar for both treatment groups.

Table 12: Demographic and Baseline Characteristics of Patients in the Treatment-Naïve Study* (MERIT)

	CELSENTRI 300 mg BID + ZDV/3TC (N=360)	**Efavirenz 600 mg QD + ZDV/3TC (N=361)**
Age (years)		
Mean (SD)	36.7 (9.4)	37.4 (9.8)
Range	20-69	18-77
Gender n (%)		
Male	256 (71.1)	259 (71.7)
Female	104 (28.9)	102 (28.3)
Race, n (%)		
White	204 (56.7)	198 (54.8)
Black	123 (34.2)	133 (36.8)
Asian	6 (1.7)	5 (1.4)
Other	27 (7.5)	25 (6.9)
Median (Min, Max) CD4 cell count (cells/µL)	241 (5-1422)	254 (8-1053)
Median (Min, Max) HIV-1 RNA (log 10 copies/mL)	4.9 (3.1-6.8)	4.9 (2.9 – 6.7)

* Data from Full Analysis Set. Similar results were observed for the Per Protocol population.

The treatment outcomes through week 48 for the treatment-naïve study (MERIT) are shown in Table 13. Treatment outcomes (responders) include reanalysis of the screening samples using a more sensitive tropism assay, enhanced sensitivity Trofile HIV tropism assay, which became available after the Week 48 analysis.

Table 13: Outcomes* of Randomised Treatment at Week 48 in Treatment-Naïve Patients (MERIT)**

Outcome at Week 48	CELSENTRI 300 mg BID + ZDV/3TC N=360	Efavirenz 600 mg QD + ZDV/3TC N=361	Difference in Proportions [1] Maraviroc vs Efavirenz (%)	
			Difference	Lower Bound of 1-sided 97.5% CI
Responder (Original Trofile) < 400 copies/mL < 50 copies/mL	 70.6% 65.3%	 73.1% 69.3%	 -3.0 -4.2	 -9.5 -10.9
Responder (Enhanced Trofile) < 400 copies/mL < 50 copies/mL	 73.3% 68.5%	 72.3% 68.3%	 0.6 -0.2	 -6.4 -7.4
Virologic Failure (TLOVR)[2] < 400 copies/mL < 50 copies/mL	 27.7% 32.0%	 5.3% 8.8%		
Rebound[2] < 400 copies/mL < 50 copies/mL	 20.8% 19.7%	 16.0% 14.7%		
Never suppressed[2] < 400 copies/mL < 50 copies/mL	 0 5.7%	 0 2.0%		
Death[3]	1 (0.3)	2(0.6)		
Discontinuations - Adverse events - (all causality) - Insufficient response - Other reasons	 15 (4.1) 43 (11.9) 38 (10.5)	 49 (13.6) 15 (4.2) 27 (7.5)		

* Non-inferiority: Criterion: lower bound of 97.5% CI > -10%

** Data obtained with Original Tropism Assay (unless otherwise indicated).

[1] Adjusted for randomisation strata

[2] Based on Time to Loss of Virologic Response (TLOVR) algorithm, Full Analysis Set.

[3] Death during study or within 28 days of the last dose at week 48.

The primary efficacy endpoints were defined as the percentage of patients with HIV-1 RNA undetectable by the standard method (< 400 copies/mL and < 50 copies/mL). After 48 weeks of combination therapy with zidovudine/lamivudine, maraviroc 300 mg BID demonstrated non-inferiority to efavirenz 600 mg QD in the proportion of patients with undetectable viral load measured at < 400 copies/mL but not at < 50 copies/mL (lower bound of 97.5% CI > -10% for non-inferiority). However, reanalysis of the data following rescreening of the samples using the enhanced sensitivity tropism assay demonstrated non-inferiority for maraviroc 300 mg BID compared to efavirenz 600 mg QD in the proportion of patients with viral loads of < 400 copies/mL and < 50 copies/mL.

The median increase from baseline in CD4+ cell counts at Week 48 was 157 cells/mm3 for the CELSENTRI arm compared to 127 cells/mm3 for the efavirenz arm.

The treatment outcomes at 96 weeks for the treatment-naïve patients study (MERIT) are shown in Table 14. Treatment outcomes are based on reanalysis of the screening samples using the enhanced sensitivity tropism assay. Approximately 15% of the patients identified as CCR5-tropic virus in the original analysis had CXCR4-using virus. Screening with the enhanced sensitivity version of the Trofile tropism assay reduced the number of maraviroc virologic failures with CXCR4-using virus at failure to 12 compared to 24 when screening with the original Trofile HIV tropism assay. The main reason for discontinuation in the maraviroc BID treatment group was treatment failure while the main reason for discontinuation in the efavirenz group was treatment-related adverse events (Section 4.4 Special Warnings and Precautions for Use) (Table 14). Note, the nucleoside backbone used in study A4001026 was zidovudine/lamivudine.

Table 14: Study Outcome at Week 96 Using Enhanced Sensitivity Assay†

Outcome at week 96	CELSENTRI 300 mg BID **+** ZDV/3TC N = 311 n (%)	Efavirenz 600 mg QD + ZDV3/TC N = 303 n (%)
Virologic Responders: (HIV-1 RNA < 400 copies/mL)	199 (64)	195 (64)
Virologic Failure:		
Non-sustained HIV-1 RNA Suppression	39 (13)	22 (7)
HIV-1 RNA Never Suppressed	9 (3)	1 (<1)
Virologic Responders: (HIV-1 RNA < 50 copies/mL)	183 (59)	190 (63)
Virologic Failure:		
Non-sustained HIV-1 RNA Suppression	43 (14)	25 (8)
HIV-1 RNA Never Suppressed	21 (7)	3 (1)
Discontinuations due to:		
Adverse Events	19 (6)	47 (16)
Death	2 (1)	2 (1)
Other[1]	43 (14)	36 (12)

† The total number of patients (Ns) in Table 14 represents the patients who had a CCR5-tropic virus in the reanalysis of screening samples using the more sensitive tropism assay. This reanalysis reclassified approximately 15% of patients shown in Table 12 as having CXCR4-using virus. These numbers are different than those presented in Table 12 because the numbers in Table 12 reflect the patients with CCR5-tropic virus according to the original tropism assay.

[1] Other reasons for discontinuation include lost to follow-up, withdrawn, protocol violation, and other.

The median increase from baseline in CD4+ cell counts at week 96 was 184 cells/mm^3 for the CELSENTRI arm compared to 155 cells/mm^3 for the efavirenz arm.

Tropism

Treatment-experienced (MOTIVATE-1 and MOTIVATE-2). In the majority of cases, treatment failure on maraviroc was associated with detection of CXCR4-using (i.e. CXCR4- or dual/mixed-tropic) virus which was not detected by the tropism assay prior to treatment. CXCR4-using virus was detected at failure in 54.8% of patients who failed treatment on

maraviroc, as compared to 5.9% of patients who experienced treatment failure in the placebo arm. To investigate the likely origin of the on-treatment CXCR4-using virus, a detailed clonal analysis was conducted on virus from 20 representative patients (16 patients from the maraviroc arms and 4 patients from the placebo arm) in whom CXCR4-using virus was detected at treatment failure. From analysis of amino acid sequence differences and phylogenetic data, CXCR4-using virus in these patients emerged from a low level of pre-existing CXCR4-using virus not detected by the tropism assay (which is population based) prior to treatment rather than from a co-receptor switch from CCR5-tropic virus to CXCR4-using virus resulting from mutation in the virus.

At Week 48 patients failing maraviroc BID with CXCR4-using virus had a lower median increase in CD4+ cell counts from baseline (+41 cells/mm^3) than those patients failing with CCR5-tropic virus (+162 cells/mm^3). The median increase in CD4+ cell count in patients failing in the placebo arm was +6.5 cells/mm^3.

Treatment-naïve (MERIT). In a 96-week study of antiretroviral treatment-naïve patients, 14% (12/85) who had CCR5-tropic virus at screening with an enhanced sensitivity tropism assay (Trofile) and failed therapy on maraviroc had CXCR4-using virus at the time of treatment failure. A detailed clonal analysis was conducted in two previously antiretroviral treatment-naïve patients enrolled in a Phase 2a monotherapy study who had CXCR4-using virus detected after 10 days treatment with maraviroc. Consistent with the detailed clonal analysis conducted in treatment-experienced patients, the CXCR4-using variants appear to emerge from outgrowth of a pre-existing undetected CXCR4-using virus. Screening with an enhanced sensitivity tropism assay reduced the number of maraviroc virologic failures with CXCR4- or dual/mixed-tropic virus at failure to 12 compared to 24 when screening with the original tropism assay.

Patients who had CCR5-tropic virus at baseline and failed maraviroc therapy with CXCR4-using virus had a median increase in CD4+ cell counts from baseline of +113 cells/mm^3 while those patients failing with CCR5-tropic virus had an increase of +135 cells/mm^3. The median increase in CD4+ cell count in patients failing in the efavirenz arm was + 95 cells/mm^3. This data is a summary for a cohort of patients identified as virologic failures using the TLOVR algorithm based on a response cut-off of plasma HIV-1 RNA < 50 copies/mL.

Studies on patients co-infected with hepatitis B and/or hepatitis C virus. The hepatic safety of maraviroc in combination with other antiretroviral agents was assessed in patients who were stable on their current antiretroviral treatment (ART).

The participating patients were HIV-1 infected patients with baseline HIV RNA < 40 copies/mL, co-infected with Hepatitis C and/or Hepatitis B Virus on concurrent antiretroviral therapy (3 to 6 drugs excluding low-dose ritonavir) and were evaluated in a multi-centre, randomized, double-blinded, placebo-controlled study. All participants with Hepatitis B received a highly active antiretroviral therapy regimen active against HBV or HBV specific antivirals.

The primary objective assessed the incidence of Grade 3 and 4 ALT abnormalities (> 5 x upper limit of normal (ULN) if baseline ALT ≤ ULN; or > 3.5 x baseline if baseline ALT >

ULN) at Week 48.

In total, 137 participants were enrolled, randomised and treated, 70 to the maraviroc group, 67 to the placebo group. Overall 21 (15%) participants discontinued from treatment prior to Week 48: 12 (17%) in the maraviroc group and 9 (13%) in the placebo group. A total of 25 participants discontinued from the study through Week 48: 14 (20.0%) in the maraviroc group and 11 (16.4%) in the placebo group. 2 participants in each group discontinued study drug but remained on study prior to Week 48. At Week 48 the 2 participants in the maraviroc continued in the study off drug, but the 2 participants in the placebo arm (who were being followed off study drug) discontinued from the study.

The majority of participants were male (85%), White (79.6%) or Black (17.5%). The age range was 28-75 years.

In the maraviroc group baseline Child-Pugh scores were Class A, n = 64; and Class B, n = 6; 22 were positive at baseline HBV, 48 for HCV; 2 had both HBV and HCV.

In the placebo group, baseline Child-Pugh scores were Class A, n = 59; Child-Pugh Class B, n = 8; 22 were positive at baseline HBV, 47 were positive for HCV and 2 were positive for both HBV and HCV.

One participant in each treatment arm was observed to meet the primary endpoint by Week 48. Note, the study was not powered to detect treatment difference between the groups for the intended safety endpoint, the number of participants was small, at baseline the patients were stable on existing ART with preserved liver function and the number of premature discontinuations during the study was large.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
The absorption of maraviroc is variable with multiple peaks. Median peak maraviroc plasma concentrations are 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.

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 Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Therefore, maraviroc can be taken with or without food at the recommended doses (see Section 4.2 DOSE AND METHOD OF 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 194 L.

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 CYP3A 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.

Excretion
A mass balance/excretion study was conducted using a single 300 mg dose of ^{14}C-labelled 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 10.2 L/hour respectively.

Children
The pharmacokinetics of maraviroc in children below 16 years of age has not been established (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Elderly
The pharmacokinetics of maraviroc in patients above 65 years of age has not been established (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment
A study compared the pharmacokinetics of a single 300 mg dose of CELSENTRI in patients with severe renal impairment (creatinine clearance < 30 mL/min, n = 6) and endstage renal disease (ESRD) (n = 6) to healthy volunteers (n = 6). Geometric mean ratios for maraviroc C_{max} and AUC_{inf} were 2.4-fold and 3.2-fold higher respectively for patients with severe renal impairment, and 1.7-fold and 2.0-fold higher respectively for patients with ESRD as compared to patients with normal renal function in this study. Haemodialysis had a minimal effect on maraviroc clearance and exposure in patients with ESRD. Exposures observed in patients with severe renal impairment and ESRD were within the range observed in previous CELSENTRI 300 mg single-dose studies in healthy volunteers with normal renal function. However, maraviroc exposures in the patients with normal renal function in this study were 50% lower than that observed in previous studies. Based on the results of this study, no

dose adjustment is recommended for patients with renal impairment receiving CELSENTRI without a potent CYP3A inhibitor or inducer. However, if patients with severe renal impairment or ESRD experience any symptoms of postural hypotension while taking CELSENTRI 300 mg twice daily, their dose should be reduced to 150 mg twice daily (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in renal impairment and see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In addition, the study compared the pharmacokinetics of multiple dose CELSENTRI in combination with saquinavir/ritonavir 1000/100 mg twice daily (a potent CYP3A inhibitor combination) for seven days in patients 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 with normal renal function (n = 6). Patients received 150 mg of CELSENTRI at different dose frequencies (healthy volunteers - every 12 hours; mild renal impairment - every 24 hours; moderate renal impairment - every 48 hours). Compared to healthy volunteers (dosed every 12 hours), geometric mean ratios for maraviroc AUC_{tau}, C_{max} and C_{min} were 50% higher, 20% higher and 43% lower, respectively for patients with mild renal impairment (dosed every 24 hours). Geometric mean ratios for maraviroc AUC_{tau}, C_{max} and C_{min} were 16% higher, 29% lower and 85% lower, respectively for patients with moderate renal impairment (dosed every 48 hours) compared to healthy volunteers (dosed every 12 hours). Based on the data from this study, no adjustment in dose is recommended for patients with mild or moderate renal impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hepatic impairment
CELSENTRI 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 individuals (n = 8). Geometric mean ratios for C_{max} and AUC_{last} were 11% and 25% higher respectively for patients with mild hepatic impairment, and 32% and 46% higher respectively for patients with moderate hepatic impairment compared to individuals 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 patients. The results should therefore be interpreted with caution. The pharmacokinetics of maraviroc have not been studied in patients with severe hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Race
No dosage adjustment is necessary on the basis of race.

Gender
No dosage adjustment is necessary on the basis of gender.

Pharmacogenomics
The pharmacokinetics of maraviroc is dependent on CYP3A5 activity and expression level, which can be modulated by genetic variation. Subjects with a functional CYP3A5 (CYP3A5*1 allele) have been shown to have a reduced exposure to maraviroc compared to subjects with defect CYP3A5 activity (e.g., CYP3A5*3, CYP3A5*6, and CYP3A5*7). The CYP3A5 allelic frequency depends on ethnicity: the majority of Caucasians (~90%) are poor

metabolisers of CYP3A5 substrates (i.e., subjects with no copy of functional CYP3A5 alleles) while approximately 40% of African-Americans and 70% of Sub-Saharan Africans are extensive metabolisers (i.e., subjects with two copies of functional CYP3A5 alleles).

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 CYP3A5 genotypes conferring poor maraviroc metabolism (No CYP3A5*1 alleles), respectively. The difference in maraviroc exposure between CYP3A5 extensive and poor metabolisers was reduced when maraviroc was administered together with a strong CYP3A inhibitor: extensive CYP3A5 metabolisers (n=12) had a 17% lower maraviroc AUC compared with poor CYP3A5 metabolisers (n=11) when dosed with maraviroc 150 mg once daily in the presence of darunavir/cobicistat (800/150 mg).

All subjects in the Phase 1 study achieved the Cav concentrations that have been shown to be associated with near maximal virologic efficacy with maraviroc (75 ng/mL) in the Phase 3 study in treatment-naïve adult patients (MERIT). 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.

5.3 PRECLINICAL SAFETY DATA

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.

Carcinogenicity
Maraviroc was evaluated for carcinogenic potential in a six 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 $AUC_{0\text{-}24h}$ for free maraviroc, 18-25). The thyroid tumours in rats are unlikely to be of human relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:

Microcrystalline cellulose,

Calcium hydrogen phosphate,

Sodium starch glycollate,

Magnesium stearate.

Film-coat [Opadry II complete film coating system 85G20583 BLUE]:

Indigo carmine aluminium lake,

lecithin,

Macrogol 3350,

Polyvinyl alcohol,

Purified talc,

Titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Maraviroc 150 mg and 300 mg film-coated tablets are supplied in polyvinyl chloride (PVC) blisters with aluminium lidding foil or PVC blisters with child-resistant* aluminium/ polyethylene terephthalate (PET) lidding foil in a carton containing 60 film-coated tablets. *complies with European Standard *EN 14375:2003 Child-resistant Non-reclosable Packaging for Pharmaceutical Products - Requirements And Testing*.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

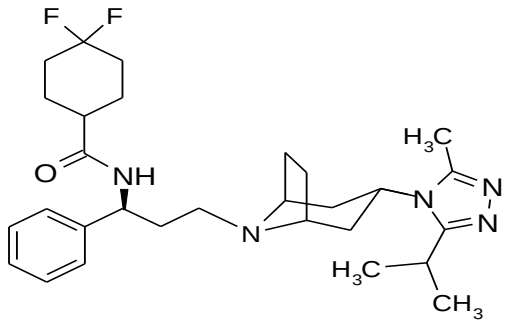
Maraviroc is a white to pale coloured powder.

CELSENTRI film-coated tablets contain maraviroc which is a member of a therapeutic class called CCR5 antagonists. 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.

Maraviroc has a molecular weight of 513.67. It is highly soluble across the physiological pH range (pH 1.0 to 7.5).

The molecular formula of maraviroc is $C_{29}H_{41}F_2N_5O$.

Chemical structure



CAS number
376348-65-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street
Abbotsford VIC 3067

9 DATE OF FIRST APPROVAL

22 January 2008

10 DATE OF REVISION

15 August 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Addition of alternative blister pack (child-resistant) and removal of bottle pack presentation
6.1	Update to the list of coating excipients in alignment with Australian Approved Name (AAN)

Version 15.0