SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CELSENTRI 20 mg/mL oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains 20 mg maraviroc.

Excipient with known effect: Each mL of oral solution contains 1 mg sodium benzoate (E211).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear, colourless, oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adults, adolescents and children of 2 years of age, and older and weighing at least 10 kg infected with only CCR5-tropic HIV-1 detectable (see sections 4.2 and 5.1).

4.2 Posology and method of administration

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

Posology

Before taking CELSENTRI it has to be confirmed that only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus not detected) using an adequately validated and sensitive detection method on a newly drawn blood sample. The Monogram Trofile assay was used in the clinical studies of CELSENTRI (see sections 4.4 and 5.1). The viral tropism cannot be safely predicted by treatment history and assessment of stored samples.

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

Adults
The recommended dose of CELSENTRI is 150 mg (with potent CYP3A inhibitor with or without a potent CYP3A inducer), 300 mg (without potent CYP3A inhibitors or inducers) or 600 mg twice daily (with potent CYP3A inducer without a potent CYP3A inhibitor) depending on interactions with concomitant antiretroviral therapy and other medicinal products (see section 4.5).

Children from 2 years of age and weighing at least 10kg
The recommended dose of CELSENTRI should be based on body weight (kg) and should not exceed the recommended adult dose. CELSENTRI oral solution (20 mg per mL) formulation should be prescribed if a child is unable to reliably swallow CELSENTRI tablets.

The recommended dose of CELSENTRI differs depending on interactions with concomitant antiretroviral therapy and other medicinal products. Refer to section 4.5 for corresponding adult dosage.

Many medicines have profound effects on maraviroc exposure due to drug-drug interactions. Prior to deciding the dose of CELSENTRI by weight, please refer to Table 2 in section 4.5 to carefully determine the corresponding adult dose. The corresponding paediatric dose can then be obtained from Table 1 below. If uncertainty still exists, contact a pharmacist for advice.

Table 1 Recommended dosing regimen in children aged 2 years and above and weighing at least 10 kg

Adult dosage*	**Concomitant Medications**	**Dose of CELSENTRI in children based on weight**			
		10 to less than 20 kg	**20 to less than 30 kg**	**30 to less than 40 kg**	**at least 40 kg**
150 mg twice daily	CELSENTRI with products that are potent CYP3A inhibitors (with or without a CYP3A inducer)	50 mg twice daily	75 mg twice daily	100 mg twice daily	150 mg twice daily
300 mg twice daily	CELSENTRI with products that are not potent CYP3A inhibitors or potent CYP3A inducers	Data to support these doses are lacking.		300 mg twice daily	300 mg twice daily
600 mg twice daily	CELSENTRI with products that are CYP3A inducers (without a potent CYP3A inhibitor)	Data to support these doses are lacking and CELSENTRI is not recommended in children taking concomitant interacting medicinal products that in adults would require a 600 mg twice daily dose.			

* Based on drug-drug Interactions (refer to section 4.5)

Special populations

Elderly
There is limited experience in patients >65 years of age (see section 5.2), therefore CELSENTRI should be used with caution in this population.

Renal impairment
In adult patients with a creatinine clearance of <80 mL/min, who are also receiving potent CYP3A4 inhibitors, the dose interval of maraviroc should be adjusted to 150 mg once daily (see sections 4.4 and 4.5).

Examples of agents/regimens with such potent CYP3A4-inhibiting activity are:

- ritonavir-boosted protease inhibitors (with the exception of tipranavir/ritonavir),
- cobicistat,
- itraconazole, voriconazole, clarithromycin and telithromycin,
- telaprevir and boceprevir.

CELSENTRI should be used with caution in adult patients with severe renal impairment

(CLcr <30 mL/min) who are receiving potent CYP3A4 inhibitors (see sections 4.4 and 5.2).

There are no data available to recommend a specific dose in paediatric patients with renal impairment. Therefore, CELSENTRI should be used with caution in this population.

Hepatic impairment
Limited data are available in adult patients with hepatic impairment and no data are available to recommend a specific dose for paediatric patients. Therefore, CELSENTRI should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric patients (children younger than 2 years of age or weighing less than 10 kg)
The safety and efficacy of CELSENTRI in children younger than 2 years of age or weighing less than 10 kg has not been established (see section 5.2). No data are available.

Method of administration

Oral use.
CELSENTRI can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic disease

The safety and efficacy of maraviroc have not been specifically studied in patients with significant underlying liver disorders.

Cases of hepatotoxicity and hepatic failure with allergic features have been reported in association with maraviroc. In addition, an increase in hepatic adverse reactions with maraviroc was observed during studies of treatment-experienced subjects with HIV infection, although there was no overall increase in ACTG Grade 3/4 liver function test abnormalities (see section 4.8). Hepatobiliary disorders reported in treatment-naïve patients were uncommon and balanced between treatment groups (see section 4.8). Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency

of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice.

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

There are limited data in patients with hepatitis B and/or C virus co-infection (see section 5.1). Caution should be exercised when treating these patients. In case of concomitant antiviral therapy for hepatitis B and/or C, please refer to the relevant product information for these medicinal products.

There is limited experience in patients with reduced hepatic function, therefore maraviroc should be used with caution in this population (see sections 4.2 and 5.2).

Severe skin and hypersensitivity reactions

Hypersensitivity reactions including severe and potentially life threatening events have been reported in patients taking maraviroc, in most cases concomitantly with other medicinal products associated with these reactions. These reactions included rash, fever, and sometimes organ dysfunction and hepatic failure. Discontinue maraviroc and other suspect agents immediately if signs or symptoms of severe skin or hypersensitivity reactions develop. Clinical status and relevant blood chemistry should be monitored and appropriate symptomatic therapy initiated.

Cardiovascular safety

Limited data exist with the use of maraviroc in patients with severe cardiovascular disease, therefore special caution should be exercised when treating these patients with maraviroc. In the pivotal studies of treatment-experienced patients coronary heart disease events were more common in patients treated with maraviroc than with placebo (11 during 609 PY vs 0 during 111 PY of follow-up). In treatment-naïve patients such events occurred at a similarly low rate with maraviroc and control (efavirenz).

Postural hypotension

When maraviroc was administered in studies with healthy volunteers at doses higher than the recommended dose, cases of symptomatic postural hypotension were seen at a greater frequency than with placebo. Caution should be used when administering maraviroc in patients on concomitant medicinal products known to lower blood pressure. Maraviroc should also be used with caution in patients with severe renal insufficiency and in patients who have risk factors for, or have a history of postural hypotension. Patients with cardiovascular co-morbidities could be at increased risk of cardiovascular adverse reactions triggered by postural hypotension.

Renal impairment

An increased risk of postural hypotension may occur in patients with severe renal insufficiency who are treated with potent CYP3A inhibitors or boosted protease inhibitors (PIs) and maraviroc. This risk is due to potential increases in maraviroc maximum concentrations when maraviroc is co-administered with potent CYP3A inhibitors or boosted PIs in these patients.

Immune reconstitution syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), 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 CART. 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 and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Tropism

Maraviroc should only be used when only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus not detected) as determined by an adequately validated and sensitive detection method (see sections 4.1, 4.2 and 5.1). The Monogram Trofile assay was used in the clinical studies of maraviroc. The viral tropism cannot be predicted by treatment history or assessment of stored samples.

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

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

Maraviroc is not recommended to be used in treatment-naïve patients based on the results of a clinical study in this population (see section 5.1).

Dose adjustment

Physicians should ensure that appropriate dose adjustment of maraviroc is made when maraviroc is co-administered with potent CYP3A4 inhibitors and/or inducers since maraviroc concentrations and its therapeutic effects may be affected (see sections 4.2 and 4.5). Please also refer to the respective Summary of Product Characteristics of the other antiretroviral medicinal products used in the combination.

Osteonecrosis

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

Potential effect on immunity

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

Excipients

CELSENTRI contains 1 mg sodium benzoate (E211) in each mL.

CELSENTRI contains less than 1 mmol sodium (23 mg) in each mL, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Maraviroc is metabolised by cytochrome P450 CYP3A4 and CYP3A5. Co-administration of maraviroc with medicinal products that induce CYP3A4 may decrease maraviroc concentrations and reduce its therapeutic effects. Co-administration of maraviroc with medicinal products that inhibit CYP3A4 may increase maraviroc plasma concentrations. Dose adjustment of maraviroc is recommended when maraviroc is co-administered with potent CYP3A4 inhibitors and/or inducers. Further details for concomitantly administered medicinal products are provided below (see Table 2).

Maraviroc is a substrate for the transporters P-glycoprotein and OATP1B1, but the effect of these transporters on the exposure to maraviroc is not known.

Based on the *in vitro* and clinical data, the potential for maraviroc to affect the pharmacokinetics of co-administered medicinal products is low. *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.

Renal clearance accounts for approximately 23% of total clearance of maraviroc when maraviroc is administered without CYP3A4 inhibitors. *In vitro* studies have shown that maraviroc does not inhibit any of the major renal uptake transporters at clinically relevant concentrations (OAT1, OAT3, OCT2, OCTN1, and OCTN2). Additionally, co-administration of maraviroc with tenofovir (substrate for renal elimination) and cotrimoxazole (contains trimethoprim, a renal cation transport inhibitor), showed no effect on the pharmacokinetics of maraviroc. In addition, co-administration of maraviroc with lamivudine/zidovudine showed no effect of maraviroc on lamivudine (primarily renally cleared) or zidovudine (non-P450 metabolism and renal clearance) pharmacokinetics. Maraviroc inhibits P-glycoprotein *in vitro* (IC_{50} is 183 μM). However, maraviroc does not significantly affect the pharmacokinetics of digoxin *in vivo*. It may not be excluded that maraviroc can increase the exposure to the P-glycoprotein substrate dabigatran etexilate.

Table 2: Interactions and adult[a] dose recommendations with other medicinal products

Medicinal product by therapeutic areas (dose of CELSENTRI used in study)	**Effects on active substance levels Geometric mean change if not stated otherwise**	**Recommendations concerning co-administration in adults**
ANTI-INFECTIVES		
Antiretrovirals		
Pharmacokinetic Enhancers		
Cobicistat	Interaction not studied. Cobicistat is a potent CYP3A inhibitor.	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with cobicistat containing regimen.
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Lamivudine 150 mg BID (maraviroc 300 mg BID)	Lamivudine AUC_{12}: ↔ 1.13 Lamivudine C_{max}: ↔ 1.16 Maraviroc concentrations not measured, no effect is expected.	No significant interaction seen/expected. CELSENTRI 300 mg twice daily and NRTIs can be co-administered without dose adjustment.
Tenofovir 300 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↔ 1.03 Maraviroc C_{max}: ↔ 1.03 Tenofovir concentrations not measured, no effect is expected.	
Zidovudine 300 mg BID (maraviroc 300 mg BID)	Zidovudine AUC_{12}: ↔ 0.98 Zidovudine C_{max}: ↔ 0.92 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)	Elvitegravir as a single agent is indicated only in combination with certain ritonavir boosted PIs. Elvitegravir per se is not expected to affect maraviroc exposure to a clinically relevant degree and the observed effect is attributed to ritonavir. Thus, CELSENTRI dose should be modified in line with the recommendation for co-administration with respective PI/ritonavir combination (see 'Protease Inhibitors').
Raltegravir 400 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↓ 0.86 Maraviroc C_{max}: ↓ 0.79 Raltegravir AUC_{12}: ↓ 0.63 Raltegravir C_{max}: ↓ 0.67 Raltegravir C_{12}: ↓ 0.72	No clinically significant interaction seen. CELSENTRI 300 mg twice daily and raltegravir can be co-administered without dose adjustment.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz 600 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↓ 0.55 Maraviroc C_{max}: ↓ 0.49 Efavirenz concentrations not measured, no effect is expected.	CELSENTRI dose should be increased to 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 BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↓ 0.47 Maraviroc C_{max}: ↓ 0.40 Etravirine AUC_{12}: ↔ 1.06 Etravirine C_{max}: ↔ 1.05 Etravirine C_{12}: ↔ 1.08	Etravirine is only approved for use with boosted protease inhibitors. For combination with etravirine + PI, see below.
Nevirapine 200 mg BID (maraviroc 300 mg Single Dose)	Maraviroc AUC_{12}: ↔ compared to historical controls Maraviroc C_{max}: ↑ compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Comparison to exposure in historical controls suggests that CELSENTRI 300 mg twice daily and nevirapine can be co-administered without dose adjustment.
Protease Inhibitors (PIs)		
Atazanavir 400 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12} ↑ 3.57 Maraviroc C_{max}: ↑ 2.09 Atazanavir concentrations not measured, no effect is expected.	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with a PI; except in combination with tipranavir/ritonavir where the CELSENTRI dose should be 300 mg BID.
Atazanavir/ritonavir 300 mg/100 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12} ↑ 4.88 Maraviroc C_{max}: ↑ 2.67 Atazanavir/ritonavir concentrations not measured, no effect is expected.	
Lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12} ↑ 3.95 Maraviroc C_{max}: ↑ 1.97 Lopinavir/ritonavir concentrations not measured, no effect is expected.	
Saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)	Maraviroc AUC_{12} ↑ 9.77 Maraviroc C_{max}: ↑ 4.78 Saquinavir/ritonavir concentrations not measured, no effect is expected.	
Darunavir/ritonavir 600 mg/100 mg BID (maraviroc 150 mg BID)	Maraviroc AUC_{12} ↑ 4.05 Maraviroc C_{max}: ↑ 2.29 Darunavir/ritonavir concentrations were consistent with historical data.	
Nelfinavir	Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A4 inhibitor and would be expected to increase maraviroc concentrations.	

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.	
Tipranavir/ritonavir 500 mg/200 mg BID (maraviroc 150 mg BID)	Maraviroc AUC_{12} ↔ 1.02 Maraviroc C_{max}: ↔ 0.86 Tipranavir/ritonavir concentrations were consistent with historical data.	
Fosamprenavir/ritonavir 700 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc $AUC_{12:}$ ↑ 2.49 Maraviroc C_{max}: ↑ 1.52 Maraviroc C_{12}: ↑ 4.74 Amprenavir AUC_{12}: ↓ 0.65 Amprenavir C_{max}: ↓ 0.66 Amprenavir C_{12}: ↓ 0.64 Ritonavir AUC_{12}: ↓ 0.66 Ritonavir C_{max}: ↓ 0.61 Ritonavir C_{12}: ↔ 0.86	Concomitant use is not recommended. Significant reductions in amprenavir C_{min} observed may result in virological failure in patients
NNRTI + PI		
Efavirenz 600 mg QD + lopinavir/ritonavir 400mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc $AUC_{12:}$ ↑ 2.53 Maraviroc C_{max}: ↑ 1.25 Efavirenz, lopinavir/ritonavir concentrations not measured, no effect expected.	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with efavirenz and a PI (except tipranavir/ritonavir where the dose should be 600 mg twice daily).
Efavirenz 600 mg QD + saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)	Maraviroc $AUC_{12:}$ ↑ 5.00 Maraviroc C_{max}: ↑ 2.26 Efavirenz, saquinavir/ritonavir concentrations not measured, no effect expected.	

Efavirenz and atazanavir/ritonavir or darunavir/ritonavir	Not studied. Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir in the absence of efavirenz, an increased exposure is expected.	Concomitant use of CELSENTRI and fosamprenavir/ritonavir is not recommended.
Etravirine and darunavir/ritonavir (maraviroc 150 mg BID)	Maraviroc $AUC_{12:}$ ↑ 3.10 Maraviroc C_{max}: ↑ 1.77 Etravirine AUC_{12}: ↔ 1.00 Etravirine C_{max}: ↔ 1.08 Etravirine C_{12}: ↓ 0.81 Darunavir AUC_{12}: ↓ 0.86 Darunavir C_{max}: ↔ 0.96 Darunavir C_{12}: ↓ 0.77 Ritonavir AUC_{12}: ↔ 0.93 Ritonavir C_{max}: ↔ 1.02 Ritonavir C_{12}: ↓ 0.74	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with etravirine and a PI. Concomitant use of CELSENTRI and fosamprenavir/ritonavir is not recommended.
Etravirine and lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir	Not studied. Based on the extent of inhibition by lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir in the absence of etravirine, an increased exposure is expected.	
ANTIBIOTICS		
Sulphamethoxazole/ Trimethoprim 800 mg/160 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↔ 1.11 Maraviroc C_{max}: ↔ 1.19 Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected.	CELSENTRI 300 mg twice daily and sulphamethoxazole/ trimethoprim can be co-administered without dose adjustment.
Rifampicin 600 mg QD (maraviroc 100 mg BID)	Maraviroc $AUC_{:}$ ↓ 0.37 Maraviroc C_{max}: ↓ 0.34 Rifampicin concentrations not measured, no effect expected.	CELSENTRI dose should be increased to 600 mg twice daily when co-administered with rifampicin in the absence of a potent CYP3A4 inhibitor. This dose adjustment has not been studied in HIV patients. See also section 4.4.

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 CELSENTRI 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.	CELSENTRI dose should be decreased to 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 also section 4.4. Concomitant use of CELSENTRI and fosamprenavir/ritonavir is not recommended.
Clarithromycin, Telithromycin	Not studied, but both are potent CYP3A4 inhibitors and would be expected to increase maraviroc concentrations.	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with clarithromycin and telithromycin.
ANTICONVULSANTS		
Carbamezepine, Phenobarbital, Phenytoin	Not studied, but these are potent CYP3A4 inducers and would be expected to decrease maraviroc concentrations.	CELSENTRI dose should be increased to 600 mg twice daily when co-administered with carbamazepine, phenobarbital or phenytoin in the absence of a potent CYP3A4 inhibitor.
ANTIFUNGALS		
Ketoconazole 400 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{tau}: ↑ 5.00 Maraviroc C_{max}: ↑ 3.38 Ketoconazole concentrations not measured, no effect is expected.	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with ketoconazole.
Itraconazole	Not studied. Itraconazole, is a potent CYP3A4 inhibitor and would be expected to increase the exposure of maraviroc.	CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with itraconazole.

Fluconazole	Fluconazole is considered to be a moderate CYP3A4 inhibitor. Population PK studies suggest that a dose adjustment of maraviroc is not required.	CELSENTRI 300 mg twice daily should be administered with caution when co-administered with fluconazole.
ANTIVIRALS		
Anti-HBV		
Pegylated interferon	Pegylated interferon has not been studied, no interaction is expected.	CELSENTRI 300 mg twice daily and pegylated interferon can be co-administered without dose adjustment.
Anti-HCV		
Ribavirin	Ribavirin has not been studied, no interaction is expected.	CELSENTRI 300 mg twice daily and ribavirin can be co-administered without dose adjustment.
DRUG ABUSE		
Methadone	Not studied, no interaction expected.	CELSENTRI 300 mg twice daily and methadone can be co-administered without dose adjustment.
Buprenorphine	Not studied, no interaction expected.	CELSENTRI 300 mg twice daily and buprenorphine can be co-administered without dose adjustment.
LIPID LOWERING MEDICINAL PRODUCTS		
Statins	Not studied, no interaction expected.	CELSENTRI 300 mg twice daily and statins can be co-administered without dose adjustment.
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.	CELSENTRI 300 mg twice daily and digoxin can be co-administered without dose adjustment. The effect of maraviroc on digoxin at the dose of 600 mg BID has not been studied.
ORAL CONTRACEPTIVES		
Ethinylestradiol 30 mcg QD (maraviroc 100 mg BID)	Ethinylestradiol. $AUC_{t:}$ ↔ 1.00 Ethinylestradiol. C_{max}: ↔ 0.99 Maraviroc concentrations not measured, no interaction expected.	CELSENTRI 300 mg twice daily. and ethinylestradiol can be co-administered without dose adjustment.
Levonorgestrel 150 mcg QD (maraviroc 100 mg BID)	Levonorgestrel. $AUC_{12:}$ ↔ 0.98 Levonorgestrel. C_{max}: ↔ 1.01 Maraviroc concentrations not measured, no interaction expected.	CELSENTRI 300 mg twice daily and levonorgestrel can be co-administered without dose adjustment.
SEDATIVES		
Benzodiazepines		
Midazolam 7.5 mg Single Dose (maraviroc 300 mg BID)	Midazolam. AUC: ↔ 1.18 Midazolam. C_{max}: ↔ 1.21 Maraviroc concentrations not measured, no interaction expected.	CELSENTRI 300 mg twice daily and midazolam can be co-administered without dose adjustment.
HERBAL PRODUCTS		
St. John's Wort (Hypericum Perforatum)	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 or products containing St. John's Wort is not recommended.

[a] Refer to Table 1 for maraviroc paediatric dosing recommendations when co-administered with antiretroviral therapy and other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of maraviroc in pregnant women. The effect of maraviroc on human pregnancy is unknown. Studies in animals showed reproductive toxicity at high exposures. Primary pharmacological activity (CCR5 receptor affinity) was limited in the species studied (see section 5.3). Maraviroc should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether maraviroc is excreted in human milk. Available toxicological data in animals has shown extensive excretion of maraviroc in milk. Primary pharmacological activity (CCR5 receptor affinity) was limited in the species studied (see section 5.3). A risk to the newborn/infants cannot be excluded.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

There is no data on the effects of maraviroc on human fertility. In rats, there were no adverse effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Maraviroc may have a minor influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with maraviroc. The clinical status of the patient and the adverse reaction profile of maraviroc should be borne in mind when considering the patient's ability to drive, cycle or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

Adults
Assessment of treatment related adverse reactions is based on pooled data from two Phase 2b/3 studies in treatment-experienced adult patients (MOTIVATE 1 and MOTIVATE 2) and one study in treatment-naïve adult patients (MERIT) infected with CCR5-tropic HIV-1 (see sections 4.4 and 5.1).

The most frequently reported adverse reactions occurring in the Phase 2b/3 studies were nausea, diarrhoea, fatigue and headache. These adverse reactions were common ($\geq$ 1/100 to < 1/10).

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class (SOC) and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) , or not known (cannot be estimated from the available data). The adverse reactions and laboratory abnormalities presented below are not exposure adjusted.

Table 3: Adverse reactions observed in clinical trials or post-marketing

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Pneumonia, oesophageal candidiasis	uncommon
Neoplasm benign, malignant and unspecified (including cysts and polyps)	Bile duct cancer, diffuse large B-cell lymphoma, Hodgkin's disease, metastases to bone, metastases to liver, metastases to peritoneum, nasopharyngeal cancer, oesophageal carcinoma	rare
Blood and lymphatic system disorders	Anaemia	common
	Pancytopenia, granulocytopenia	rare
Metabolism and nutrition disorders	Anorexia	common
Psychiatric disorders	Depression, insomnia	common
Nervous system disorders	Seizures and seizure disorders	uncommon
Cardiac disorders	Angina pectoris	rare
Vascular disorders	Postural hypotension (see section 4.4)	uncommon
Gastrointestinal disorders	Abdominal pain, flatulence, nausea	common
Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased	common
	Hyperbilirubinaemia, gamma-glutamyltransferase increased	uncommon
	Hepatitis toxic, hepatic failure, hepatic cirrhosis, blood alkaline phosphatase increased	rare
	Hepatic failure with allergic features	very rare
Skin and subcutaneous tissue disorders	Rash	common
	Stevens-Johnson syndrome / Toxic epidermal necrolysis	rare / not known
Musculoskeletal and connective tissue disorders	Myositis, blood creatine phosphokinase increased	uncommon
	Muscle atrophy	rare
Renal and urinary disorders	Renal failure, proteinuria	uncommon
General disorders and administration site conditions	Asthenia	common

Description of selected adverse reactions

Delayed type hypersensitivity reactions, typically occurring within 2-6 weeks after start of therapy and including rash, fever, eosinophilia and liver reactions have been reported (see also section 4.4). Skin and liver reactions can occur as single events, or in combination.

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. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Cases of syncope caused by postural hypotension have been reported.

Laboratory abnormalities

Table 4 shows the incidence ≥1% of Grade 3-4 Abnormalities (ACTG Criteria) based on the maximum shift in laboratory test values without regard to baseline values.

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

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

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

The MOTIVATE studies were extended beyond 96 weeks, with an observational phase extended to 5 years in order to assess the long term safety of maraviroc. The Long Term Safety/Selected Endpoints (LTS/SE) included death, AIDS-defining events, hepatic failure, Myocardial infarction/cardiac ischaemia, malignancies, rhabdomyolysis and other serious infectious events with maraviroc treatment. The incidence of these selected endpoints for subjects on maraviroc in this observational phase was consistent with the incidence seen at earlier timepoints in the studies.

In treatment-naïve patients, the incidence of grade 3 and 4 laboratory abnormalities using ACTG criteria was similar among the maraviroc and efavirenz treatment groups.

Paediatric population

The adverse reaction profile in paediatric patients is based on 48 Week safety data from study A4001031 in which 103 HIV-1 infected, treatment-experienced patients aged 2 to <18 years received maraviroc twice-daily with optimised background therapy (OBT). Overall, the safety profile in paediatric patients was similar to that observed in adult clinical studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via Yellow Card Scheme
Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google
Play or Apple App Store.

4.9 Overdose

Symptoms

The highest dose administered in clinical studies was 1,200 mg. The dose limiting adverse reaction was postural hypotension.

Prolongation of the QT interval was seen in dogs and monkeys at plasma concentrations 6 and 12 times, respectively, those expected in humans at the maximum recommended dose of 300 mg twice daily. However, no clinically significant QT prolongation compared to placebo + OBT was seen in the Phase 3 clinical studies using the recommended dose of maraviroc or in a specific pharmacokinetic study to evaluate the potential of maraviroc to prolong the QT interval.

Management

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX09

Mechanism of action

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

Antiviral activity *in vitro*

Maraviroc has no antiviral activity *in vitro* against viruses which can use CXCR4 as their entry co-receptor (dual-tropic or CXCR4-tropic viruses, collectively termed 'CXCR4-using' virus below). The serum adjusted EC90 value in 43 primary HIV-1 clinical isolates was 0.57 (0.06 – 10.7) ng/mL without significant changes between different subtypes tested. The antiviral activity of maraviroc against HIV-2 has not been evaluated. For details please refer to the pharmacology section of the CELSENTRI European Public Assessment Report (EPAR) on the European Medicines Agency (EMA) website.

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

Virologic Escape

Virologic escape from maraviroc can occur via 2 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).

In vitro

HIV-1 variants with reduced susceptibility to maraviroc have been selected *in vitro,* following serial passage of two CCR5-tropic viruses (0 laboratory strains, 2 clinical isolates). The maraviroc-resistant viruses remained CCR5-tropic and there was no conversion from a CCR5-tropic virus to a CXCR4-using virus.

Phenotypic resistance

Concentration response curves for the maraviroc-resistant viruses were characterized phenotypically by curves that did not reach 100% inhibition in assays using serial dilutions of maraviroc (<100% maximal percentage inhibition (MPI)). Traditional IC_{50}/IC_{90} fold-change was not a useful parameter to measure phenotypic resistance, as those values were sometimes unchanged despite significantly reduced sensitivity.

Genotypic resistance

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

Cross-resistance in vitro

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 vitro* remained sensitive to the fusion inhibitor enfuvirtide and the PI, saquinavir.

In vivo
Treatment-Experienced Adult Patients

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

Failure with CXCR4-using virus

CXCR4-using virus was detected at failure in approximately 60% of subjects who failed treatment on maraviroc, as compared to 6% of subjects who experienced treatment failure in the placebo + OBT arm. To investigate the likely origin of the on-treatment CXCR4-using virus, a detailed clonal analysis was conducted on virus from 20 representative subjects (16 subjects from the maraviroc arms and 4 subjects from the placebo + OBT arm) in whom CXCR4-using virus was detected at treatment failure. 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. In the remaining 36 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 correlating to low compliance (low and variable drug levels and often a calculated high residual sensitivity score of the OBT). In patients failing therapy with CCR5-tropic virus only, maraviroc might be considered still active if the MPI value is ≥95% (PhenoSense Entry assay). Residual activity *in vivo* for viruses with MPI-values <95% has not been determined.

Genotypic resistance
A relatively small number of individuals receiving maraviroc-containing therapy have failed with phenotypic resistance (i.e. the ability to use drug-bound CCR5 with MPI

<95%). To date, no signature mutation(s) have been identified. The gp120 amino acid substitutions identified so far are context dependent and inherently unpredictable with regards to maraviroc susceptibility.

Treatment-Experienced Paediatric Patients

In the Week 48 analysis (N=103), non-CCR5 tropic-virus was detected in 5/23 (22%) subjects at virologic failure. One additional subject had CCR5 tropic-virus with reduced susceptibility to maraviroc at virologic failure, although this was not retained at the end of treatment. Subjects with virologic failure generally appeared to have low compliance to both maraviroc and the background antiretroviral elements of their regimens. Overall, the mechanisms of resistance to maraviroc observed in this treatment-experienced paediatric population were similar to those observed in adult populations.

Clinical results

Studies in Treatment-Experienced Adult Patients Infected with CCR5-tropic Virus

The clinical efficacy of maraviroc (in combination with other antiretroviral medicinal products) on plasma HIV RNA levels and CD4+ cell counts have been investigated in two pivotal randomized, double blind, multicentre studies (MOTIVATE 1 and MOTIVATE 2, n=1076) in patients infected with CCR5 tropic HIV-1 as determined by the Monogram Trofile Assay.

Patients who were eligible for these studies had prior exposure to at least 3 antiretroviral medicinal product classes [≥1 NRTIs, ≥1 NNRTIs, ≥2 PIs, and/or enfurvirtide] or documented resistance to at least one member of each class. Patients were randomised in a 2:2:1 ratio to maraviroc 300 mg (dose equivalence) once daily, twice daily or placebo in combination with an optimized background consisting of 3 to 6 antiretroviral medicinal products (excluding low-dose ritonavir). The OBT was selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements.

Table 5: Demographic and baseline characteristics of patients (pooled studies MOTIVATE 1 and MOTIVATE 2)

Demographic and Baseline Characteristics	Maraviroc 300 mg twice daily + OBT N = 426	Placebo + OBT N = 209
Age (years) (Range, years)	46.3 21-73	45.7 29-72
Male Sex	89.7%	88.5%
Race (White/Black/Other)	85.2% / 12% / 2.8%	85.2% / 12.4% / 2.4%
Mean Baseline HIV-1 RNA (log_{10} copies/mL)	4.85	4.86
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	166.8 (2.0-820.0)	171.3 (1.0-675.0)
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%)
Number (Percentage) of patients with GSS score[1]: 0 1 2 ≥3	 102 (23.9%) 138 (32.4%) 80 (18.8%) 104 (24.4%)	 51 (24.4%) 53 (25.4%) 41 (19.6%) 59 (28.2%)

[1]Based on GeneSeq resistance assay.

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

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

Table 6: Efficacy Outcomes at week 48 (pooled studies MOTIVATE 1 and MOTIVATE 2)

Outcomes	Maraviroc 300 mg twice daily + OBT N=426	Placebo + OBT N=209	Difference[1] (Confidence Interval[2])
HIV-1 RNA Mean change from baseline (log copies/mL)	-1.837	-0.785	-1.055 (-1.327, -0.783)
Percentage of patients with HIV-1 RNA <400 copies/mL	56.1%	22.5%	Odds ratio: 4.76 (3.24, 7.00)

Percentage of patients with HIV-1 RNA <50 copies/mL	45.5%	16.7%	Odds ratio: 4.49 (2.96, 6.83)
CD4+ cell count Mean change from baseline (cells/µL)	122.78	59.17	63.13 (44.28, 81.99)[2]

[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%

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

Maraviroc 300 mg twice daily + OBT was superior to placebo + OBT across all subgroups of patients analysed (see Table 7). Patients with very low CD4+ count at baseline (i.e. <50 cells/µL) had a less favourable outcome. This subgroup had a high degree of bad prognostic markers, i.e. extensive resistance and high baseline viral loads. However, a significant treatment benefit for maraviroc compared to placebo + OBT was still demonstrated (see Table 7).

Table 7: Proportion of patients achieving <50 copies/mL at Week 48 by subgroup (pooled Studies MOTIVATE 1 and MOTIVATE 2)

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

[1]Based on GSS.

Studies in Treatment-Experienced Adult Patients Infected with Non-CCR5-tropic Virus

Study A4001029 was an exploratory study in patients infected with dual/mixed or CXCR4 tropic HIV-1 with a similar design as the studies MOTIVATE 1 and MOTIVATE 2. Use of maraviroc was not associated with a significant decrease in HIV 1 RNA compared with placebo in these subjects and no adverse effect on CD4+ cell count was noted.

Studies in Treatment-Naïve Adult Patients Infected with CCR5-tropic Virus

A randomised, double-blinded study (MERIT), explored maraviroc versus efavirenz, both in combination with zidovudine/lamivudine (n=721, 1:1). After 48 weeks of treatment, maraviroc did not reach non-inferiority to efavirenz for the endpoint of HIV-1 RNA < 50 copies/mL (65.3 vs. 69.3 % respectively, lower confidence bound -11.9%). More patients treated with maraviroc discontinued due to lack of efficacy (43 vs.15) and among patients with lack of efficacy, the proportion acquiring NRTI resistance (mainly lamivudine) was higher in the maraviroc arm. Fewer patients discontinued maraviroc due to adverse events (15 vs. 49).

Studies in Adult Patients Co-infected with Hepatitis B and/or Hepatitis C virus

The hepatic safety of maraviroc in combination with other antiretroviral agents in CCR5-tropic HIV-1-infected subjects with HIV RNA <50 copies/mL, co-infected with Hepatitis C and/or Hepatitis B Virus was evaluated in a multicentre, randomized, double blinded, placebo-controlled study. 70 subjects (Child-Pugh Class A, n=64; Child-Pugh Class B, n=6) were randomized to the maraviroc group and 67 subjects (Child-Pugh Class A, n=59; Child-Pugh Class B, n=8) were randomized to the placebo group.

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

Studies in Treatment-Experienced Paediatric Patients Infected with CCR5-tropic Virus

Study A4001031 is an open-label, multicenter trial in paediatric patients (aged 2 years to less than 18 years) infected with CCR5-tropic HIV-1, determined by the enhanced-sensitivity Trofile assay.
Subjects were required to have HIV-1 RNA greater than 1,000 copies per mL at Screening.

All subjects (n = 103) received maraviroc twice daily and OBT. Maraviroc dosing was based on body surface area and doses were adjusted based on whether the subject was receiving potent CYP3A inhibitors and/or inducers.

In paediatric patients with a successful tropism test, dual mixed/CXCR4-tropic virus was detected in around 40% of screening samples (8/27, 30% in 2-6 year-olds, 31/81, 38% in 6-12 year-olds and 41/90, 46% in 12-18 year-olds), underscoring the importance of tropism testing also in the paediatric population.

The population was 52% female and 69% black, with mean age of 10 years (range: 2 years to 17 years). At baseline, mean plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL (range 2.4 to 6.2 $\log_{10}$ copies per mL), mean CD4+ cell count was 551 cells/mm^3 (range 1 to 1654 cells/mm^3) and mean CD4+ % was 21% (range 0% to 42%).

At 48 weeks, using a missing, switch or discontinuation equals failure analysis, 48% of subjects treated with maraviroc and OBT achieved plasma HIV-1 RNA less than 48 copies/mL and 65% of subjects achieved plasma HIV-1 RNA less than 400 copies per mL. The mean CD4+ cell count (percent) increase from baseline to Week 48 was 247 cells/mm^3 (5%).

5.2 Pharmacokinetic properties

Absorption

The absorption of maraviroc is variable with multiple peaks. Median peak maraviroc plasma concentrations are attained at 2 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. The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg. Maraviroc is a substrate for the efflux transporter P-glycoprotein.

Co-administration of a 300 mg tablet with a high fat breakfast reduced maraviroc C_{max} and AUC by 33% and co-administration of 75 mg of oral solution with a high fat breakfast reduced maraviroc AUC by 73% in adult healthy volunteers. Studies with the tablets demonstrated a reduced food-effect at higher doses.

There were no food restrictions in the adult studies (using tablet formulations) or in the paediatric study (using both tablet and oral solution formulations). The results did not indicate any relevant efficacy or safety concern related to either fed or fasted dosing conditions. Therefore, maraviroc tablets and oral solution can be taken with or without food at the recommended doses in adults, adolescents and children aged 2 years and older and weighing at least 10 kg (see section 4.2).

Distribution

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

Biotransformation

Studies in humans and *in vitro* studies using human liver microsomes and expressed enzymes have demonstrated that maraviroc is principally metabolized by the cytochrome P450 system to metabolites that are essentially inactive against HIV-1. *In vitro* studies indicate that CYP3A4 is the major enzyme responsible for maraviroc metabolism. *In vitro* studies also indicate that polymorphic enzymes CYP2C9, CYP2D6 and CYP2C19 do not contribute significantly to the metabolism of maraviroc.

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

Elimination

A mass balance/excretion study was conducted using a single 300 mg dose of ^{14}C-labeled maraviroc. Approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the faeces over 168 hours. Maraviroc was the major component present in urine (mean of 8% dose) and faeces (mean of 25% dose). The remainder was excreted as metabolites. After intravenous administration (30 mg), the half-life of maraviroc was 13.2 h, 22% of the dose was excreted unchanged in the urine and the values of total clearance and renal clearance were 44.0 L/h and 10.17 L/h respectively.

Special patient populations:

Paediatric population

Intensive pharmacokinetics of maraviroc were evaluated in 50 treatment-experienced, CCR5-tropic, HIV-1 infected paediatric patients aged 2 to 18 years (weight 10.0 to 57.6 kg) in the dose-finding stage of clinical trial A4001031. Doses were given with food on intensive pharmacokinetic evaluation days and optimised to achieve an average concentration over the dosing interval (C_{avg}) of greater than 100 ng/mL; otherwise, maraviroc was given with or without food. The initial dose of maraviroc was scaled from adult doses using a body surface area (BSA) of 1.73 m^2 to children and adolescent BSA (m^2)-based bands. In addition, dosing was based on whether subjects were receiving potent CYP3A inhibitors (38/50), potent CYP3A inducers (2/50) or other concomitant medicinal products that are not potent CYP3A inhibitors or potent CYP3A inducers (10/50) as part of OBT. Sparse pharmacokinetics were evaluated in all subjects including the additional 47 subjects receiving potent CYP3A inhibitors that did not take part in the dose-finding stage. The impact of potent CYP3A inhibitors and/or inducers on maraviroc pharmacokinetic parameters in paediatric patients was similar to that observed in adults.

BSA (m2)-based bands have been modified to weight (kg)-based bands to simplify dosing and reduce dosing errors (see section 4.2). Use of weight (kg)-

based doses in treatment-experienced HIV-1-infected paediatrics results in maraviroc exposures similar to those observed in treatment-experienced adults receiving recommended doses with concomitant medications. The pharmacokinetics of maraviroc in paediatric patients below 2 years of age have not been established (see section 4.2).

Elderly

Population analysis of the Phase 1/2a and Phase 3 studies (16-65 years of age) has been conducted and no effect of age has been observed (see section 4.2).

Renal impairment

A study compared the pharmacokinetics of a single 300 mg dose of maraviroc in subjects with severe renal impairment (CLcr < 30 mL/min, n=6) and end stage renal disease (ESRD) to healthy volunteers (n=6). The geometric mean AUC_{inf} (CV%) for maraviroc was as follows: healthy volunteers (normal renal function) 1348.4 ng·h/mL (61%); severe renal impairment 4367.7 ng·h/mL (52%); ESRD (dosing after dialysis) 2677.4 ng·h/mL (40%); and ESRD (dosing before dialysis) 2805.5 ng·h/mL (45%). The C_{max} (CV%) was 335.6 ng/mL (87%) in healthy volunteers (normal renal function); 801.2 ng/mL (56%) in severe renal impairment; 576.7 ng/mL (51%) in ESRD (dosing after dialysis) and 478.5 ng/mL (38%) in ESRD (dosing before dialysis). Dialysis had a minimal effect on exposure in subjects with ESRD. Exposures observed in subjects with severe renal impairment and ESRD were within the range observed in single maraviroc 300 mg dose studies in healthy volunteers with normal renal function. Therefore, no dose adjustment is necessary in patients with renal impairment receiving maraviroc without a potent CYP3A4 inhibitor (see sections 4.2, 4.4 and 4.5).

In addition, the study compared the pharmacokinetics of multiple dose maraviroc in combination with saquinavir/ritonavir 1000/100 mg BID (a potent CYP3A4 inhibitor) for 7 days in subjects with mild renal impairment (CLcr >50 and ≤80 mL/min, n=6) and moderate renal impairment (CLcr ≥30 and ≤50 mL/min, n=6) to healthy volunteers (n=6). Subjects received 150 mg of maraviroc at different dose frequencies (healthy volunteers – every 12 hours; mild renal impairment – every 24 hours; moderate renal impairment – every 48 hours). The average concentration (Cavg) of maraviroc over 24 hours was 445.1 ng/mL, 338.3 ng/mL, and 223.7 ng/mL for subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively. The Cavg of maraviroc from 24-48 hours for subjects with moderate renal impairment was low (Cavg: 32.8 ng/mL). Therefore, dosing frequencies of longer than 24 hours in subjects with renal impairment may result in inadequate exposures between 24-48 hours.

Dose adjustment is necessary in patients with renal impairment receiving maraviroc with potent CYP3A4 inhibitors (see sections 4.2 and 4.4 and 4.5).

Hepatic impairment

Maraviroc is primarily metabolized and eliminated by the liver. A study compared the pharmacokinetics of a single 300 mg dose of maraviroc in patients with mild (Child-Pugh Class A, n=8), and moderate (Child-Pugh Class B, n=8) hepatic impairment compared to healthy subjects (n=8). Geometric mean ratios for C_{max} and AUC_{last} were 11% and 25% higher respectively for subjects with mild hepatic impairment, and 32% and 46% higher respectively for subjects with moderate hepatic impairment compared to subjects with normal hepatic function. The effects of moderate hepatic impairment may be underestimated due to limited data in patients with decreased metabolic capacity and higher renal clearance in these subjects. The results should therefore be interpreted with caution. The pharmacokinetics of maraviroc has not been studied in subjects with severe hepatic impairment (see sections 4.2 and 4.4).

Race

No relevant difference between Caucasian, Asian and Black subjects has been observed. The pharmacokinetics in other races has not been evaluated.

Gender

No relevant differences in pharmacokinetics have been observed.

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 genotype conferring poor maraviroc metabolism (no CYP3A5*1 allele), 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 C_{avg} 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

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

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

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

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

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

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

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

Pre- and post-natal developmental studies were performed in rats at doses up to 27-fold the estimated free clinical AUC for a 300 mg twice daily dose. A slight increase in motor activity in high-dose male rats at both weaning and as adults was noted, while no effects were seen in females. Other developmental parameters of these offspring, including fertility and reproductive performance, were not affected by the maternal administration of maraviroc.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (anhydrous)
Sodium citrate dihydrate
Sucralose
Sodium benzoate (E211)
Strawberry flavouring
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

After first opening: 60 days

6.4 Special precautions for storage

Store below 30 ºC. Discard 60 days after first opening. The discard date of the oral solution should be written on the carton in the space provided. The date should be written as soon as the bottle has been opened for first use.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle, with a child resistant closure, containing 230 mL maraviroc 20 mg/mL solution. The pack also includes a low density polyethylene or thermoplastic elastomeric press in bottle adapter, and a 10 ml oral applicator comprised of a polypropylene barrel (with mL graduations) and a polyethylene plunger.

The oral applicator is provided for accurate measurement of the prescribed dose of oral solution.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
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London

WC1A 1DG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 35728/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

27/06/2025