CELSENTRI

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

CELSENTRI 150 mg Film-coated Tablets

CELSENTRI 300 mg Film-coated Tablets

Sugar-free

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Blue, biconvex, oval film-coated tablets debossed with ‘MVC 150’ or ‘MVC 300’ on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

CELSENTRI, in combination with other antiretroviral medicines, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral medicines (see section 4.2).

4.2 Posology and method of administration:

Therapy should be initiated by a medical practitioner 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.

- Use of CELSENTRI is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group.
- The safety and efficacy of CELSENTRI have not been established in treatment-naïve adult patients.

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 medicines (see Table 1 and section 4.5). CELSENTRI can be taken with or without food.

Table 1. Recommended Dosing Regimen

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

Concomitant Medicines	Recommended CELSENTRI Dose
• all NRTIs • enfuvirtide • nevirapine • raltegravir • tipranavir/ritonavir	

Children: The safety and efficacy of CELSENTRI in children younger than 18 years of age have not been established, therefore, use in children is not recommended (see section 5.2).

Elderly: There is limited experience in patients > 65 years of age, therefore caution should be exercised when administering CELSENTRI in elderly patients (see section 5.2).

Renal impairment: Dosage adjustment is recommended in patients with renal impairment who are receiving potent CYP3A4 inhibitors such as:

- protease inhibitors (except tipranavir/ritonavir)
- delavirdine
- ketoconazole, itraconazole, clarithromycin, nefazodone, telithromycin.

CELSENTRI should be used with caution in patients with renal impairment (CL_{cr} < 80 ml/min) who are taking potent CYP3A4 inhibitors (see section 4.4 and section 5.2).

Table 2 below provides dose interval adjustment guidelines based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors. The safety and efficacy of these dose interval adjustments have not been clinically evaluated. Therefore, clinical response to treatment should be closely monitored in these patients.

Table 2. Dose and interval adjustments for patients with renal impairment (for dose recommendations, see section 4.5, Table 3)

Recommended CELSENTRI dose interval	Creatinine clearance < 80 ml/min*
If administered without potent CYP3A inhibitors or if co-	No dose interval adjustment required (CELSENTRI

administered with tipranavir/ritonavir	300 mg every 12 hours)
If co-administered with fosamprenavir/ritonavir	CELSENTRI 150 mg every 12 hours
If co-administered with potent CYP3A inhibitors, e.g., saquinavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, atazanavir/ritonavir, ketoconazole, boceprevir, telaprevir	CELSENTRI 150 mg every 24 hours

*including subjects with ESRD requiring dialysis

Hepatic impairment: Limited data in mild and moderately hepatically impaired subjects demonstrated a small increase in the mean C_{max} of CELSENTRI, suggesting no dose adjustment is required. However, CELSENTRI should be used with caution in patients with hepatic impairment (see section 4.4 and section 5.2).

There are no data on severe hepatic impairment.

4.3 Contraindications:

Hypersensitivity to maraviroc or to any of the inactive ingredients of CELSENTRI (see section 6.1).

4.4 Special warnings and precautions for use:

HEPATOTOXICITY

Hepatotoxicity has been reported with CELSENTRI use. Evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE) prior to the development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or allergic reaction following use of CELSENTRI should be evaluated immediately.

CELSENTRI should be taken as part of an antiretroviral combination regimen. CELSENTRI should optimally be combined with other antiretrovirals to which the patient's virus is sensitive (see section 5.1).

CELSENTRI should only be used when only CCR5-tropic HIV-1 is detectable (i.e., CXCR4 or dual/mixed tropic virus not detected) as determined by an adequately validated and sensitive detection method (see section 4.1 section 4.2 and section 5.1). The viral tropism cannot be predicted by treatment history or assessment of stored samples.

Changes in viral tropism occur over time in HIV-1 infected patients.

Therefore, there is a need to start therapy shortly after a tropism test.

Dose Adjustment: Medical practitioners should ensure that appropriate dose adjustment of CELSENTRI is made when CELSENTRI is co-administered with CYP3A4 inhibitors and/or inducers since CELSENTRI concentrations and its therapeutic effects may be affected (see section 4.2 and section 4.5). Please also refer to the respective medicine information of the other antiretroviral medicines used in the combination.

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

Cardiovascular Safety: Use with caution in patients at increased risk for cardiovascular events. Eleven subjects (1,3 %) who received CELSENTRI had cardiovascular events that may be linked to coronary heart diseases including myocardial ischaemia and/or infarction during the Phase 3 studies in CCR5 tropic patients [total exposure of 526 patient-years (267 patient-years for twice daily group (BID) + 259 patient-years for once daily group (QD)], while no subjects who received placebo had such events (total exposure 99 patient-years). These subjects generally had cardiac disease or cardiac risk factors prior to CELSENTRI use, and the relative contribution of CELSENTRI to these events is not known.

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. However, when CELSENTRI was given at the recommended dose in HIV infected patients in Phase 3 studies, postural hypotension was seen

at a similar rate compared to placebo (approximately 0,5 %).

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

Patients with severe renal insufficiency who are treated with potent CYP3A inhibitors or boosted protease inhibitors (PIs) have an increased risk of experiencing postural hypotension due to an increase in CELSENTRI concentrations (see section 4.2, section 4.5 and section 5.2).

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

Opportunistic infections: Patients receiving CELSENTRI should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Syndrome: In HIV infected patients with severe immune deficiency at the time of institution 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 pulmonary tuberculosis, cytomegalovirus retinitis, other 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. Auto-immune disorders (such as auto-immune thyroiditis, 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 with an atypical presentation.

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.

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

An increase in hepatic adverse reactions with CELSENTRI was observed during studies of treatment-experienced subjects with HIV infection (see section 4.8).

Cases of hepatotoxicity and hepatic failure with allergic features have been reported in association with CELSENTRI. Discontinuation of CELSENTRI should be considered in any patient with signs or symptoms of acute hepatitis, in particular if drug-related hypersensitivity is suspected or with increased liver transaminases combined with rash or other systemic symptoms of potential hypersensitivity (e.g., pruritic rash, eosinophilia or elevated IgE).

There are limited data in patients with hepatitis B and/or C virus co-infection. Caution should be exercised when treating these patients with CELSENTRI. In case of concomitant antiviral therapy for hepatitis B and/or C, please refer to the relevant medicine information for these medicines.

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.

There is limited experience in patients with reduced hepatic function, therefore CELSENTRI

should be used with caution in this population (see section 4.2 and section 5.2).

Severe skin and hypersensitivity reactions: Hypersensitivity reactions including severe and potentially life-threatening events have been reported in patients taking CELSENTRI, in most cases other medicines associated with these reactions were also used. 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). Treatment with CELSENTRI and other suspected medicines should be immediately discontinued if signs or symptoms of severe skin or hypersensitivity reactions develop. Delay in stopping CELSENTRI-treatment or treatment with other suspect medicines after the onset of rash may result in a life-threatening reaction. Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated.

Renal Impairment: The safety and efficacy of CELSENTRI have not been studied in patients with renal impairment, therefore CELSENTRI should be used with caution in this population.

In the absence of metabolic inhibitors, renal clearance accounts for approximately 23 % of total clearance of CELSENTRI and hence renal impairment is not expected to significantly alter CELSENTRI exposures.

In the presence of metabolic inhibitors, renal clearance may account for up to 70 % of total clearance of CELSENTRI, hence renal impairment may result in increased CELSENTRI exposures in this case. Therefore, CELSENTRI should be used with caution in patients with renal impairment (CLcr < 80 ml/min) who are also taking potent CYP3A4 inhibitors.

Table 2 provides dose interval adjustment guidelines based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors. The safety and efficacy of these dose interval adjustments have not been clinically evaluated. Therefore, clinical response to treatment should be closely monitored in these patients (see section 4.2 and section 5.2).

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

4.5 Interactions with other medicines and other forms of interaction:

CELSENTRI is metabolized by cytochrome P450 CYP3A. CELSENTRI is also a substrate for P-glycoprotein, OATP1B1 and MRP2 in vitro. Co-administration of CELSENTRI with medicines that induce those enzymes and transporters may decrease CELSENTRI concentrations and reduce its therapeutic effects. Co-administration of CELSENTRI with medicines that inhibit those enzymes and transporters may increase CELSENTRI plasma concentrations. Dose adjustment of CELSENTRI is recommended when CELSENTRI is co-administered with CYP3A4 inhibitors and/or inducers. Further details for concomitantly administered medicines are provided below (see Table 3 and Table 1 under section 4.2).

In vitro studies have shown that CELSENTRI does not inhibit OATP1B1, MRP2 or any of the major P450 enzymes at clinically relevant concentrations (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). CELSENTRI 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 CELSENTRI a potential inhibition of CYP2D6 cannot be excluded. Based on the *in vitro* and clinical data, the potential for CELSENTRI to affect the pharmacokinetics of co-administered medicines is low.

Renal clearance accounts for approximately 23 % of total clearance of CELSENTRI when CELSENTRI 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 CELSENTRI. In addition, co-administration of CELSENTRI with lamivudine/zidovudine showed no effect of CELSENTRI on

lamivudine (primarily renally cleared) or zidovudine (non-P450 metabolism and renal clearance) pharmacokinetics.

CELSENTRI inhibits P-glycoprotein *in vitro* (IC_{50} is 183 µM). However, CELSENTRI does not significantly affect the pharmacokinetics of digoxin *in vivo,* suggesting that CELSENTRI neither inhibits nor induces the activity of P-glycoprotein.

Table 3. Interactions and dose recommendations with other medicines

Medicines by therapeutic areas (dose of CELSENTRI used in study)	**Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise**	**Recommendations concerning co-administration**
Anti-infectives		
Antiretrovirals		
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Lamivudine 150 mg BID (CELSENTRI 300 mg BID)	Lamivudine AUC_{12}: ↔ 1,13 (0,98; 1,32) Lamivudine C_{max}: ↔ 1,16 (0,88; 1,54) Maraviroc concentrations not measured, no effect is expected.	**CELSENTRI 300 mg twice daily** [1] No clinically significant interaction observed or expected with NRTIs.
Tenofovir 300 mg QD (CELSENTRI 300 mg BID)	Maraviroc AUC_{12}: ↔ 1,03 (0,98; 1,09) Maraviroc C_{max}: ↔ 1,03 (0,90; 1,19) Tenofovir concentrations not measured, no effect is expected.	
Zidovudine 300 mg BID (CELSENTRI 300 mg BID)	Zidovudine AUC_{12}: ↔ 0,98 (0,79; 1,22) Zidovudine C_{max}: ↔ 0,92 (0,68; 1,24) Maraviroc concentrations not measured, no effect is expected.	
Integrase Inhibitors		
Elvitegravir/ritonavir 150/100 mg QD (CELSENTRI 150 mg BID)	Maraviroc AUC_{12}: ↑ 2,86 (2,33-3,51) Maraviroc C_{max}: ↑ 2,15 (1,71-2,69) Maraviroc C_{12}: ↑ 4,23 (3,47-5,16) Elvitegravir AUC_{24}: ↔ 1,07 (0,96-1,18) Elvitegravir C_{max}: ↔ 1,01 (0,89-1,15) Elvitegravir C_{24}: ↔ 1,09 (0,95-1,26)	**CELSENTRI 150 mg twice daily** when co-administered with boosted elvitegravir
Raltegravir 400 mg BID	Maraviroc AUC_{12}: ↓ 0,86 (0,80; 0,92)	**CELSENTRI 300 mg twice**

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
(CELSENTRI 300 mg BID)	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)	**daily** [1] No clinically significant interaction observed.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz 600 mg QD (CELSENTRI 100 mg BID)	Maraviroc AUC_{12}: ↓ 0,55 (0,49; 0,62) Maraviroc C_{max}: ↓ 0,49 (0,38; 0,63) Efavirenz concentrations not measured, no effect is expected.	**CELSENTRI 600 mg twice daily** when co-administered with efavirenz in the absence of a potent CYP3A inhibitor. For combination of efavirenz and PI, see below.
Etravirine 200 mg BID (CELSENTRI 300 mg BID)	Maraviroc AUC_{12}: ↓ 0,47 (0,38; 0,58) Maraviroc C_{max}: ↓ 0,40 (0,28; 0,57) Etravirine AUC_{12}: ↔ 1,06 (0,99; 1,14) Etravirine C_{max}: ↔ 1,05 (0,95; 1,17) Etravirine C_{12}: ↔ 1,08 (0,98; 1,19)	**CELSENTRI 600 mg twice daily** when co-administered with etravirine in the absence of a potent CYP3A inhibitor. For combination of etravirine and PI, see below.
Nevirapine 200 mg BID (CELSENTRI 300 mg single dose)	Maraviroc AUC_{12}: ↔ compared to historical controls Maraviroc C_{max}: ↑ compared to historical controls Nevirapine concentrations not measured, no effect is expected.	**CELSENTRI 300 mg twice daily** [1]
Delavirdine	Limited data are available for co-administration with delavirdine. Delavirdine is a potent CYP3A inhibitor. Population PK analysis in phase 3 studies suggests dose reduction of CELSENTRI when co-administered with delavirdine gives appropriate maraviroc exposure	**CELSENTRI 150 mg twice daily**
Protease Inhibitors (PIs)		
Atazanavir 400 mg QD (CELSENTRI 300 mg	Maraviroc AUC_{12} ↑ 3,57 (3,30; 3,87) Maraviroc C_{max}: ↑ 2,09 (1,31; 4,19)	**CELSENTRI 150 mg twice daily** when co-administered

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
BID)	Atazanavir concentrations not measured, no effect is expected.	with either a boosted or an unboosted Protease Inhibitor, except for tipranavir/ritonavir (see below for separate recommendation for tipranavir/ritonavir). CELSENTRI 150 mg twice daily has not been shown to have a clinically significant effect on PI exposure levels.
Nelfinavir	Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A inhibitor and would be expected to increase maraviroc concentrations.	
Indinavir	Limited data are available for co-administration with indinavir. Indinavir is a potent CYP3A inhibitor. Population PK analysis in phase 3 studies suggests dose reduction of maraviroc when co-administered with indinavir gives appropriate maraviroc exposure.	
Atazanavir/ritonavir 300 mg/100 mg QD (CELSENTRI 300 mg BID)	Maraviroc AUC_{12} ↑ 4,88 (3,28; 6,49) Maraviroc C_{max}: ↑ 2,67 (1,72; 2,55) Atazanavir/ritonavir concentrations not measured, no effect is expected.	
Lopinavir/ritonavir 400 mg/100 mg BID (CELSENTRI 300 mg BID)	Maraviroc AUC_{12} ↑ 3,95 (3,43; 4,56) Maraviroc C_{max}: ↑ 1,97 (1,66; 2,34) Lopinavir/ritonavir concentrations not measured, no effect is expected.	
Saquinavir/ritonavir 1000 mg/100 mg BID (CELSENTRI 100 mg BID)	Maraviroc AUC_{12} ↑ 9,77 (7,87; 12,1) Maraviroc C_{max}: ↑ 4,78 (3,41; 6,71) Saquinavir/ritonavir concentrations not measured, no effect is expected.	
Darunavir/ritonavir 600 mg/100 mg BID (CELSENTRI 150 mg BID)	Maraviroc AUC_{12} ↑ 4,05 (2,94; 5,59) Maraviroc C_{max}: ↑ 2,29 (1,46; 3,59) Darunavir/ritonavir concentrations were consistent with historical data.	
Fosamprenavir/ritonavir 700 mg/100 mg BID (CELSENTRI 300 mg BID)	Maraviroc $AUC_{12:}$ ↑ 2,49 (2,19-2,82) Maraviroc C_{max}: ↑ 1,52 (1,27-1,82) Maraviroc C_{12}: ↑ 4,74 (4,03-5,57) Amprenavir AUC_{12}: ↓ 0,65 (0,59-0,71)	

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
Fosamprenavir/ritonavir 1400 mg/100 mg QD (CELSENTRI 300 mg QD)	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) CELSENTRI C_{24}: ↑ 1,80 (1,53-2,13) Amprenavir AUC_{24}: ↓ 0,70 (0,64-0,77) Amprenavir C_{max}: ↓ 0,71 (0,62-0,80) Amprenavir C_{24}: ↓ 0,85 (0,75-0,97) Ritonavir AUC_{24}: ↓ 0,70 (0,61-0,80) Ritonavir C_{max}: ↓ 0,69 (0,57-0,84) Ritonavir C_{24}: ↔ 2,66 (0,41-17,23)	
Tipranavir/ritonavir 500 mg/200 mg BID (CELSENTRI 150 mg BID)	Maraviroc AUC_{12} ↔ 1,02 (0,85; 1,23) Maraviroc C_{max}: ↔ 0,86 (0,61; 1,21) Tipranavir/ritonavir concentrations were consistent with historical data.	**CELSENTRI 300 mg twice daily** [1]
NNRTI + PI		
Efavirenz 600 mg QD + lopinavir/ritonavir 400 mg/100 mg BID (CELSENTRI 300 mg BID)	Maraviroc AUC_{12}: ↑ 2,53 (2,24; 2,87) Maraviroc C_{max}: ↑ 1,25 (1,01; 1,55) Efavirenz, lopinavir/ritonavir concentrations not measured, no effect expected.	**CELSENTRI 150 mg twice daily** when co-administered with either efavirenz or etravirine and a Protease Inhibitor (except fosamprenavir/ritonavir where the dose should be 300 mg twice daily or tipranavir/ritonavir where the dose should be 600 mg twice daily).
Efavirenz 600 mg QD + saquinavir/ritonavir 1000 mg/ 100 mg BID (CELSENTRI 100 mg BID)	Maraviroc AUC_{12}: ↑ 5,00 (4,26; 5,87) Maraviroc C_{max}: ↑ 2,26 (1,64; 3,11) Efavirenz, saquinavir/ritonavir concentrations not measured, no effect expected.	
Efavirenz and atazanavir/ritonavir or	Not studied. Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir in the	

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
darunavir/ritonavir	absence of efavirenz, an increased exposure is expected.	
Etravirine and darunavir/ritonavir (CELSENTRI 150 mg BID)	Maraviroc $AUC_{12:}$ ↑ 3,10 (2,57; 3,74) Maraviroc C_{max}: ↑ 1,77 (1,20; 2.60) Etravirine AUC_{12}: ↔ 1,00 (0,86; 1,15) Etravirine C_{max}: ↔ 1,08 (0,98; 1,20) Etravirine C_{12}: ↓ 0,81 (0,65; 1,01) Darunavir AUC_{12}: ↓ 0,86 (0,76; 0,96) Darunavir C_{max}: ↔ 0,96 (0,84; 1,10) Darunavir C_{12}: ↓ 0,77 (0,69; 0,85) Ritonavir AUC_{12}: ↔ 0,93 (0,75; 1,16) Ritonavir C_{max}: ↔ 1,02 (0,80; 1,30) Ritonavir C_{12}: ↓ 0,74 (0,63; 0,86)	
Etravirine and lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir	Not studied. Based on the extent of inhibition by lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir in the absence of etravirine, an increased exposure is expected.	
Antibiotics		
Sulphamethoxazole/Trimethoprim 800 mg/160 mg BID (CELSENTRI 300 mg BID)	Maraviroc AUC_{12}: ↔ 1,11 (1,01; 1,21) Maraviroc C_{max}: ↔ 1,19 (1,04; 1,37) Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected.	**CELSENTRI 300 mg twice daily** [1]
Rifampicin 600 mg QD (CELSENTRI 100 mg BID)	Maraviroc AUC_{12}: ↓ 0,37 (0,33; 0,41) Maraviroc C_{max}: ↓ 0,34 (0,26; 0,43) Rifampicin concentrations not measured, no effect expected.	**CELSENTRI 600 mg twice daily** when co-administered with rifampicin in the absence of a potent CYP3A inhibitor. This dose adjustment has not been studied in HIV patients.
Rifabutin + PI	Not studied. Rifabutin is considered to be a weaker inducer than rifampicin. When combining rifabutin	**CELSENTRI 150 mg twice daily** when co-administered

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
	with protease inhibitors that are potent inhibitors of CYP3A a net inhibitory effect on maraviroc is expected.	with rifabutin and a PI (except tipranavir/ritonavir where the dose should be 300 mg twice daily).
Clarithromycin, Telithromycin	Not studied, but both are potent CYP3A inhibitors and would be expected to increase maraviroc concentrations.	**CELSENTRI 150 mg twice daily**
Antifungals		
Ketoconazole 400 mg QD (CELSENTRI 100 mg BID)	Maraviroc AUC_{12}: ↑ 5,00 (3,98; 6,29) Maraviroc C_{max}: ↑ 3,38 (2,38; 4,78) Ketoconazole concentrations not measured, no effect is expected.	**CELSENTRI 150 mg twice daily**
Itraconazole	Not studied. Itraconazole, is a potent CYP3A inhibitor and would be expected to increase the exposure of maraviroc.	**CELSENTRI 150 mg twice daily**
Fluconazole	Fluconazole is considered to be a moderate CYP3A inhibitor. Population PK studies suggest that a dose adjustment of CELSENTRI is not required.	**CELSENTRI 300 mg twice daily** [1] No clinically significant interaction expected with fluconazole
Antivirals		
HCV medicines		
Boceprevir 800 mg TID (CELSENTRI 150 mg BID)	Maraviroc AUC12 ↑ 3.02 (2,53, 3.59) Maraviroc C_{max}: ↑ 3.33 (2,54, 4.36) Maraviroc C12: ↑ 2,78 (2,40 3,23) Boceprevir concentrations were consistent with historical data.	**CELSENTRI 150 mg twice daily when co-administered with boceprevir**
Pegylated interferon and ribavirin	Pegylated interferon and ribavirin have not been studied, no interaction is expected.	**CELSENTRI 300 mg twice daily**[1]
Telaprevir 750 mg TID	Maraviroc AUC12 ↑ 9,49 (7,94, 11,34) Maraviroc C_{max}: ↑ 7,81 (5,.92, 10,32)	**CELSENTRI 150 mg twice daily when co-administered**

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
(CELSENTRI 150 mg BID)	Maraviroc C12: ↑ 10,17 (8,73 11,85) Telaprevir concentrations were consistent with historical data.	**with telaprevir**
Anticonvulsants		
Carbamazepine Phenobarbital Phenytoin	Not studied, but these are potent CYP3A inducers and would be expected to decrease maraviroc concentrations.	CELSENTRI 600 mg twice daily when co-administered with carbamazepine, phenobarbital or phenytoin in the absence of a potent CYP3A inhibitor
Drug Abuse		
Methadone	Not studied, no interaction expected.	**CELSENTRI 300 mg twice daily** [1]
Buprenorphine	Not studied, no interaction expected.	**CELSENTRI 300 mg twice daily** [1]
Lipid Lowering Medicinal Products		
Statins	Not studied, no interaction expected.	**CELSENTRI 300 mg twice daily** [1]
Antiarrhythmics		
Digoxin 0,25 mg single dose (CELSENTRI 300 mg BID)	Digoxin. $AUC_{t:}$ ↔ 1,00 Digoxin. C_{max}: ↔ 1,04 Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily** [1]
Oral contraceptives		
Ethinylestradiol 30 mcg QD (CELSENTRI 100 mg BID)	Ethinylestradiol. $AUC_{12:}$ ↔ 1,00 (0,95; 1,05) Ethinylestradiol. C_{max}: ↔ 0,99 (0,91; 1,06) Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily** [1]
Levonorgestrel 150 mcg QD (CELSENTRI 100 mg	Levonorgestrel. $AUC_{12:}$ ↔ 0,98 (0,92; 1,04) Levonorgestrel. C_{max}: ↔ 1,01 (0,93; 1,08) Maraviroc concentrations not measured, no	**CELSENTRI 300 mg twice daily** [1]

Medicines by therapeutic areas (dose of CELSENTRI used in study)	Effects on medicine levels Geometric mean ratio [90 % Confidence Interval (CI)] if not stated otherwise	Recommendations concerning co-administration
BID)	interaction expected.	
Benzodiazepines		
Midazolam 7,5 mg single dose (CELSENTRI 300 mg BID)	Midazolam. AUC: ↔ 1,18 (1,04; 1,34) Midazolam. C_{max}: ↔ 1,21 (0,92; 1,60) Maraviroc concentrations not measured, no interaction expected.	**CELSENTRI 300 mg twice daily** [1]
Herbal Products		
St John's Wort	Co-administration of CELSENTRI 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 CELSENTRI.	Concomitant use of CELSENTRI 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 CELSENTRI according to Table 3.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety in pregnancy and lactation has not been demonstrated.

Breastfeeding:

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. Based on animal data, it is expected that CELSENTRI will be secreted into human milk.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. CELSENTRI may cause dizziness. Patients should be instructed that if they experience dizziness,

they should avoid potentially hazardous tasks such as driving, cycling, or operating machinery.

4.8 Undesirable effects:

Clinical trial data:

CELSENTRI has been studied in 1374 HIV-1 infected patients who received at least one dose of CELSENTRI during three Phase 3 clinical studies. This includes 426 treatment-experienced patients and 360 treatment-naïve patients who received 300 mg twice daily and a further 414 treatment-experienced and 174 treatment-naïve patients who received 300 mg once daily. The safety profile of CELSENTRI is based on 786 HIV-1 infected patients who received CELSENTRI 300 mg twice daily. Assessment of treatment related adverse reactions is based on pooled data from two Phase 3 studies in treatment-experienced adult patients (MOTIVATE 1 and MOTIVATE 2) and one study in treatment-naïve adult patients (MERIT) in CCR5-tropic, HIV-1 infected patients.

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 (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000). The adverse reactions and laboratory abnormalities presented below are not exposure adjusted.

Treatment-experienced:

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

Table 4. Adverse reactions of all intensities occurring among treatment-experienced patients receiving CELSENTRI 300 mg twice daily + optimised background therapy (OBT) with an incidence of ≥ 1 % and at a higher incidence than patients receiving placebo + OBT alone (pooled studies MOTIVATE-1 and MOTIVATE-2)

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

Laboratory abnormalities in treatment-experienced:

Table 5. Clinically significant Grade 3 or 4 laboratory test abnormalities (ACTG criteria) reported in treatment-experienced patients receiving CELSENTRI 300 mg twice

daily + OBT with an incidence of ≥ 1 % and at a higher incidence than patients receiving placebo + OBT alone (pooled studies MOTIVATE-1 and MOTIVATE-2)

Laboratory Parameter	Abnormality range	Grade	CELSENTRI twice daily + OBT N=421[1] (%)	OBT alone N=207 (%)
Lipase	> 2 x ULN – 5 x ULN	3	10/171 (5,8)	9/93 (9,7)
	> 5 x ULN	4	3/173 (1,7)	0/93 (0)
Absolute Neutrophil Count	0,5 - 0,75 x 10^3/mm^3	3	13/420 (3,1)	6/207 (2,9)
	< 0,5 x 10^3/mm^3	4	5/420 (1,2)	0/207 (0)
Bilirubin	> 2,5 x ULN – 5 x ULN	3	24/421 (5,7)	10/207 (4,8)
	> 5 x ULN	4	4/421 (1,0)	3/207 (1,4)
AST	> 5 x ULN – 10 x ULN	3	19/421 (4,5)	7/207 (3,4)
	> 10 x ULN	4	6/421 (1,4)	1/207 (0,5)

[1]Percentages based on total patients evaluated for each laboratory parameter
ULN=upper limit of normal

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

Treatment-naïve:

Table 6 and Table 7 summarises adverse reaction and laboratory test abnormalities from the Phase III Treatment Naïve MERIT study.

Table 6. Adverse reactions of moderate intensity or greater occurring among treatment-naïve patients receiving CELSENTRI 300 mg twice daily with an incidence of ≥ 1 % (MERIT)

System Organ Class	Adverse Reaction	Frequency
Blood and lymphatic system disorders	Anaemia	Common
Metabolism and nutrition disorders	Anorexia	Common
Psychiatric disorders	Depression, abnormal dreams, insomnia	Common
Nervous system disorders	Dizziness, headache, somnolence	Common
Gastrointestinal disorders	Abdominal pain, constipation, dyspepsia, flatulence, nausea, diarrhoea, vomiting	Common
Hepatobiliary disorders	ALT increased, AST increased	Common
Musculoskeletal and connective tissue disorders	Neck pain	Common
General disorders and administration site conditions	Fatigue, asthenia	Common

Table 7. Clinically significant Grade 3 or 4 laboratory test abnormalities (ACTG criteria) reported in treatment-naïve patients receiving CELSENTRI 300 mg twice daily with an incidence of ≥ 1 % (MERIT)

Laboratory parameter	Abnormality range	Grade	CELSENTRI 300 mg twice daily N=360[1] (%)
ALT	> 5,0 x ULN – 10,0 x ULN	3	11/353 (3,1)
	> 10,0 x ULN	4	3/353 (0,8)
AST	> 5,0 x ULN – 10,0 x ULN	3	8/353 (2,3)
	> 10,0 x ULN	4	6/353 (1,7)
Creatine kinase	> 10,0 x ULN – 20,0 x ULN	3	10/353 (2,8)
	> 20,0 x ULN	4	4/353 (1,1)
Serum amylase	> 2,0 x ULN – 5,0 x ULN	3	14/352 (4,0)
	> 5,0 x ULN	4	1/352 (0,3)
Haemoglobin	6,5 – 6,9 g/dL	3	2/352 (0,6)
	< 6,5 g/dL	4	8/352 (2,3)
Absolute neutrophil count	500 - 749/mm^3	3	15/352 (4,3)
	< 500/mm^3	4	5/352 (1,4)

[1] Percentages based on total patients evaluated for each laboratory parameter

ULN: Upper Limit of Normal

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

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Post-marketing data:

Severe hypersensitivity reactions have been reported. These included drug rash with eosinophilia

and systemic symptoms (DRESS), severe cutaneous reactions (SJS and TEN) as well as hepatotoxicity and hepatic failure with allergic features.

Postural hypotension which can result in syncope has been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reactions Reporting Form,'** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

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.

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.

5. PHARMACOLOGICAL PROPERTIES:

A 20.2.8 Antiviral agents

5.1 Pharmacodynamic properties:

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 cell culture:

The serum adjusted EC90 value in 43 primary CCR5-tropic HIV-1 clinical isolates was 0,57 (0,06-10,7) ng/ml without significant changes between different subtypes tested. Maraviroc has no antiviral activity in cell culture against viruses which can use CXCR4 as their entry co-receptor (dual-tropic or CXCR4-tropic viruses, collectively termed 'CXCR4-using' virus below). The antiviral activity of maraviroc against HIV-2 has not been evaluated.

When used with other antiretroviral medicines in cell culture, the combination of maraviroc was not antagonistic with a range of nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), protease inhibitors (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 exclusively use drug-bound CCR5 (CCR5-tropic virus).

Resistance in cell culture:

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

Phenotypic resistance:

Concentration response curves for the maraviroc-resistant viruses were characterised by curves that did not reach 100 % inhibition in assays using serial dilutions of maraviroc (<100 % maximal percentage inhibition (MPI)). Traditional EC_{50} fold-change was not a useful parameter to measure

phenotypic resistance, as those values were sometimes unchanged despite significantly reduced sensitivity.

Genotypic resistance:

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

Cross-resistance:

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

Resistance in patients:

Treatment-naïve patients:

The resistance profile in treatment-naïve patients has not been characterised.

Treatment-experienced patients:

In the pivotal studies (MOTIVATE 1 and MOTIVATE 2) 7,6 % of patients had a change in tropism result from CCR5-tropic to CXCR4-tropic or dual/mixed-tropic between screening and baseline (a period of 4-6 weeks).

Failure with CXCR4-using virus: CXCR4-using virus was detected at failure in approximately 60 % of subjects who failed treatment on maraviroc, as compared to 6 % of subjects who experienced treatment failure in the 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 subjects (16 subjects from the maraviroc arms and 4 subjects from the OBT alone arm) in whom CXCR4-using virus was detected. This analysis indicated that CXCR4-using virus emerged from a pre-existing CXCR4-using reservoir not detected at baseline, rather than from mutation of CCR5-tropic virus present at baseline. An analysis of tropism following failure of maraviroc therapy with CXCR4-using virus, demonstrated

that the virus population reverted back to CCR5 tropism in the majority of patients during follow up after discontinuation of maraviroc. Out of 44 patients studied, the virus population in 30 reverted back to exclusively CCR5-tropism during a median follow-up of 203 days; 14 patients continued to have detectable CXCR4-using virus. However, the follow-up period in these patients was shorter (median 16 days). At time of failure with CXCR4-using virus, the resistance pattern to other antiretrovirals appears similar to that of the CCR5-tropic population at baseline, based on available data. Hence, in the selection of a treatment regimen, it should be assumed that viruses forming part of the previously undetected CXCR4-using population (i.e., minor viral population) harbours the same resistance pattern as the CCR5-tropic population.

Failure with CCR5-tropic virus:

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

Genotypic resistance: the resistance profile of virus from treatment-experienced subjects has not been fully characterised. Specific mutations associated with reduced susceptibility to maraviroc have been identified in viruses from individual patients but for each patient there was a unique pattern of mutations.

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 % in healthy volunteers.

There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc (see section 5.1). Therefore, maraviroc can be taken with or without food at the recommended doses (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.

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 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-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 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.

Children: The pharmacokinetics of maraviroc in paediatric patients 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: The pharmacokinetics of maraviroc have not been studied in patients with renal impairment. However, renal clearance contributes approximately 23 % of maraviroc total clearance in the absence of CYP3A4 inhibitors, therefore the impact of renal impairment on maraviroc elimination should be minimal. In the presence of metabolic inhibitors, renal clearance may account for up to 70 % of total clearance of maraviroc and hence renal impairment may result in increased maraviroc exposures in this case (see section 4.2 and section 4.4).

Hepatic impairment: Maraviroc is primarily metabolised 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 pharmacokinetics of maraviroc have not been studied in subjects with severe hepatic impairment (see section 4.2 and section 4.4).

Race: Population pharmacokinetic analysis of pooled Phase 1/2a data indicated exposure was 26,5 % higher in Asians (n = 95) as compared to non-Asians (n = 318). However, a study designed to evaluate pharmacokinetic differences between Caucasians (n = 12) and Asians (n = 12) showed no difference between these two populations. Only 14 Black subjects were included in the population pharmacokinetic analysis. No dosage adjustment is necessary on the basis of race.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Dibasic calcium phosphate (anhydrous), FD&C blue #2 aluminium lake, magnesium stearate,

microcrystalline cellulose, polyethylene glycol (macrogol 3350), polyvinyl alcohol, sodium starch glycollate, soya lecithin, talc and titanium dioxide.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf-life:

60 months.

6.4 Special precautions for storage:

Store at or below 30 °C.

6.5 Nature and contents of container:

CELSENTRI 150 mg and 300 mg tablets are supplied in clear polyvinyl chloride (PVC) blisters with aluminium lidding foil backing or child-resistant aluminium/polyethylene terephthalate (PET) lidding foil backing, in a carton containing 60 film-coated tablets for the 150 mg and 300 mg strengths.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

CELSENTRI 150 mg: 42/20.2.8/0941

CELSENTRI 300 mg: 42/20.2.8/0942

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

1 March 2013

10. DATE OF REVISION OF TEXT:

12 November 2020

GDS19

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