ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

CELSENTRI 150 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of maraviroc.

Excipient with known effect: each 150 mg film-coated tablet contains 0.84 mg of soya lecithin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, biconvex, oval film-coated tablets debossed with “MVC 150”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable (see section 4.2).

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients (see section 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). Other phenotypic and genotypic assays are currently being evaluated. The viral tropism cannot be safely predicted by treatment history and assessment of stored samples.

There are currently no data regarding the reuse of 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, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products (see Table 1 in section 4.5).
**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 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 patients with severe renal impairment (CLcr <30 mL/min) who are receiving potent CYP3A4 inhibitors (see sections 4.4 and 5.2).

**Hepatic impairment**
Limited data are available in patients with hepatic impairment, therefore CELSENTRI should be used with caution in this population (see sections 4.4 and 5.2).

**Paediatric population**
The safety and efficacy of CELSENTRI in children younger than 18 years of age has not been established. No data available (see section 5.2).

**Method of administration**
Oral use.
CELSENTRI can be taken with or without food.

**4.3 Contraindications**
Hypersensitivity to the active substance or to peanut or soya or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

**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 Celsentri, in most cases concomitantly with other drugs associated with these reactions. These reactions included rash, fever, and sometimes organ dysfunction and hepatic failure. Discontinue Celsentri 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 was 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 events 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) 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 be taken as part of an antiretroviral combination regimen. Maraviroc should optimally be combined with other antiretrovirals to which the patient's virus is sensitive (see section 5.1).
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. Other phenotypic and genotypic assays are currently being evaluated. 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 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Maraviroc is a substrate of cytochrome P450 CYP3A4. 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 CYP3A4 inhibitors and/or inducers. Further details for concomitantly administered medicinal products are provided below (see Table 1).

Studies in human liver microsomes and recombinant enzyme systems have shown that maraviroc does not inhibit any of the major P450 enzymes at clinically relevant concentrations (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinylestradiol and levonorgestrel, or urinary 6β-hydroxycortisol/cortisol ratio, suggesting no inhibition or induction of CYP3A4 in vivo. At higher exposure of maraviroc a potential inhibition of CYP2D6 cannot be excluded. Based on the in vitro and clinical data, the potential for maraviroc to affect the pharmacokinetics of co-administered medicinal products is low.
Renal clearance accounts for approximately 23% of total clearance of maraviroc when maraviroc is administered without CYP3A4 inhibitors. As both passive and active processes are involved, there is the potential for competition for elimination with other renally eliminated active substances. However, 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 \textit{in vitro} (IC\textsubscript{50} is 183 μM). However, maraviroc does not significantly affect the pharmacokinetics of digoxin \textit{in vivo}. It may not be excluded that maraviroc can increase the exposure to the P-glycoprotein substrate dabigatran etexilate.

**Table 1: Interactions and dose recommendations with other medicinal products**

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose of CELSENTRI used in study)</th>
<th>Effects on active substance levels</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic Enhancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Interaction not studied. Cobicistat is a potent CYP3A inhibitor.</td>
<td>CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with cobicistat containing regimen.</td>
</tr>
<tr>
<td><strong>Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine 150 mg BID (maraviroc 300 mg BID)</td>
<td>Lamivudine AUC\textsubscript{12}: ↔ 1.13 Lamivudine C\textsubscript{max}: ↔ 1.16 Maraviroc concentrations not measured, no effect is expected.</td>
<td>No significant interaction seen/expected. CELSENTRI 300 mg twice daily and NRTIs can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Tenofovir 300 mg QD (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC\textsubscript{12}: ↔ 1.03 Maraviroc C\textsubscript{max}: ↔ 1.03 Tenofovir concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td>Zidovudine 300 mg BID (maraviroc 300 mg BID)</td>
<td>Zidovudine AUC\textsubscript{12}: ↔ 0.98 Zidovudine C\textsubscript{max}: ↔ 0.92 Maraviroc concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/ritonavir 150/100mg QD (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC\textsubscript{12}: ↑ 2.86 (2.33-3.51) Maraviroc C\textsubscript{max}: ↑ 2.15 (1.71-2.69) Maraviroc C\textsubscript{12}: ↑ 4.23 (3.47-5.16) Elvitegravir AUC\textsubscript{24}: ↔ 1.07 (0.96-1.18) Elvitegravir C\textsubscript{max}: ↔ 1.01 (0.89-1.15) Elvitegravir C\textsubscript{24}: ↔ 1.09 (0.95-1.26)</td>
<td>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 ‘HIV Protease Inhibitors’).</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 3.02 (2.53, 3.57)</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.56 (2.40-2.90)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 3.02 (2.53, 3.57)</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.56 (2.40-2.90)</th>
<th>Telaprevir concentrations are not likely to be affected by maraviroc co-administration (based on historical data and the elimination pathway of telaprevir).</th>
<th>Maraviroc 150 mg twice daily when co-administered with telaprevir</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.57</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.09</th>
<th>Atazanavir concentrations not measured, no effect is expected.</th>
<th>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.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.57</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.09</th>
<th>Atazanavir concentrations not measured, no effect is expected.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Combination</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Lopinavir/ritonavir concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt; ↑ 3.95</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 1.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt; ↑ 9.77</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 4.78</td>
<td>Saquinavir/ritonavir concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir 600 mg/100 mg BID (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt; ↑ 4.05</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.29</td>
<td>Darunavir/ritonavir concentrations were consistent with historical data.</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A4 inhibitor and would be expected to increase maraviroc concentrations.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipranavir/ritonavir 500 mg/200 mg BID (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt; ↔ 1.02</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↔ 0.86</td>
<td>Tipranavir/ritonavir concentrations were consistent with historical data.</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir 700 mg/100 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt; ↑ 2.49</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 1.52</td>
<td>Maraviroc C&lt;sub&gt;12&lt;/sub&gt;: ↑ 4.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amprenavir AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.65</td>
<td>Amprenavir C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.66</td>
<td>Amprenavir C&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ritonavir AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.66</td>
<td>Ritonavir C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.61</td>
<td>Ritonavir C&lt;sub&gt;12&lt;/sub&gt;: ↔ 0.86</td>
<td></td>
</tr>
</tbody>
</table>

**Concomitant use is not recommended. Significant reductions in amprenavir C<sub>min</sub> observed may result in virological failure in patients.**

**NNRTI + PI**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Efavirenz, lopinavir/ritonavir concentrations not measured, no effect expected.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz 600 mg QD + lopinavir/ritonavir 400mg/100 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt; ↑ 2.53</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 1.25</td>
<td>CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with efavirenz and a PI (except tipranavir/ritonavir where the</td>
</tr>
<tr>
<td>Treatment</td>
<td>Interaction Details</td>
<td>AUC Changes</td>
<td>Cmax Changes</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD + saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 5.00  Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.26  Efavirenz, saquinavir/ritonavir concentrations not measured, no effect expected.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz and atazanavir/ritonavir or darunavir/ritonavir</td>
<td>Not studied. Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir in the absence of efavirenz, an increased exposure is expected.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine and darunavir/ritonavir (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.10  Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 1.77  Etravirine AUC&lt;sub&gt;12&lt;/sub&gt;: ↔ 1.00  Etravirine C&lt;sub&gt;max&lt;/sub&gt;: ↔ 1.08  Etravirine C&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.81  Darunavir AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.86  Darunavir C&lt;sub&gt;max&lt;/sub&gt;: ↔ 0.96  Darunavir C&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.77  Ritonavir AUC&lt;sub&gt;12&lt;/sub&gt;: ↔ 0.93  Ritonavir C&lt;sub&gt;max&lt;/sub&gt;: ↔ 1.02  Ritonavir C&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine and lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ANTIBIOTICS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Interaction Details</th>
<th>AUC Changes</th>
<th>Cmax Changes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphamethoxazole/Trimethoprim 800 mg/160 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↔ 1.11  Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↔ 1.19  Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected.</td>
<td></td>
<td></td>
<td>CELSENTRI 300 mg twice daily and sulphamethoxazole/trimethoprim can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Rifampicin 600 mg QD (maraviroc 100 mg BID)</td>
<td>Maraviroc AUC: ↓ 0.37  Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.34  Rifampicin concentrations not measured, no effect expected.</td>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin + efavirenz</td>
<td>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.</td>
<td></td>
<td></td>
<td>Concomitant use of CELSENTRI and rifampicin + efavirenz is not recommended.</td>
</tr>
<tr>
<td>Drug Class</td>
<td>Drug</td>
<td>Interactions</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>--------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Rifabutin + PI</td>
<td>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.</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin, Telithromycin</td>
<td>Not studied, but both are potent CYP3A4 inhibitors and would be expected to increase maraviroc concentrations.</td>
<td>CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with clarithromycin and telithromycin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIFUNGALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (maraviroc 100 mg BID)</td>
<td>Maraviroc AUC (<em>{\text{mar}}): ↑ 5.00 Maraviroc C(</em>{\text{max}}): ↑ 3.38 Ketoconazole concentrations not measured, no effect is expected.</td>
<td>CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with ketoconazole.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Not studied. Itraconazole, is a potent CYP3A4 inhibitor and would be expected to increase the exposure of maraviroc.</td>
<td>CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with itraconazole.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Fluconazole is considered to be a moderate CYP3A4 inhibitor. Population PK studies suggest that a dose adjustment of maraviroc is not required.</td>
<td>CELSENTRI 300 mg twice daily should be administered with caution when co-administered with fluconazole.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIVIRALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV agents</td>
<td>Pegylated interferon and ribavirin have not been studied, no interaction is expected.</td>
<td>CELSENTRI 300 mg twice daily and pegylated interferon or ribavirin can be co-administered without dose adjustment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DRUG ABUSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Not studied, no interaction expected.</td>
<td>CELSENTRI 300 mg twice daily and methadone can be co-administered without dose adjustment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Not studied, no interaction expected.</td>
<td>CELSENTRI 300 mg twice daily and buprenorphine can be co-administered without dose adjustment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LIPID LOWERING MEDICINAL PRODUCTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Not studied, no interaction expected.</td>
<td>CELSENTRI 300 mg twice daily and statins can be co-administered without dose adjustment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Oral Contraceptives

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC&lt;sub&gt;e&lt;/sub&gt; Ratio</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinylestradiol 30 mcg QD (maraviroc 100 mg BID)</td>
<td>Ethinylestradiol 1.00</td>
<td>Ethinylestradiol 0.99</td>
<td>Maraviroc concentrations not measured, no interaction expected.</td>
</tr>
<tr>
<td>Levonorgestrel 150 mcg QD (maraviroc 100 mg BID)</td>
<td>Levonorgestrel 1.00</td>
<td>Levonorgestrel 1.00</td>
<td>Maraviroc concentrations not measured, no interaction expected.</td>
</tr>
</tbody>
</table>

### Sedatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC Ratio</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam 7.5 mg Single Dose (maraviroc 300 mg BID)</td>
<td>Midazolam 1.18</td>
<td>Midazolam 1.21</td>
<td>Maraviroc concentrations not measured, no interaction expected.</td>
</tr>
</tbody>
</table>

### Herbal Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort (Hypericum Perforatum)</td>
<td>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.</td>
</tr>
</tbody>
</table>

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
No meaningful clinical data on exposure during pregnancy are available. Studies in rats and rabbits showed reproductive toxicity at high exposures. Primary pharmacological activity (CCR5 receptor affinity) was limited in these species (see section 5.3). Maraviroc should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Breast-feeding**
Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. Primary pharmacological activity (CCR5 receptor affinity) was limited in these species. It is not known whether maraviroc is secreted into human milk.

It is recommended that mothers infected by HIV do not breast-feed their infants under any circumstances 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
No studies on the effects on the ability to drive and use machines have been performed. Maraviroc may cause dizziness. Patients should be instructed that if they experience dizziness they should avoid potentially hazardous tasks such as driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of maraviroc is based on 1,374 HIV-1 infected patients who has received at least one dose of maraviroc during Phase 2b/3 clinical studies. This includes 426 treatment-experienced patients and 360 treatment-naïve patients who received the recommended dose 300 mg twice daily and a further 588 treatment-experienced and treatment-naïve patients who received 300 mg once daily. 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 (≥ 1/100 to < 1/10). The reported frequencies for these events as well as the rates of discontinuation due to any adverse reactions were similar in patients receiving maraviroc in Phase 2b/3 studies compared to those receiving comparator.

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), not known (cannot be estimated from the available data). The adverse reactions and laboratory abnormalities presented below are not exposure adjusted.

The following table presents clinically important adverse reactions of moderate intensity or more occurring among patients receiving maraviroc in Phase 2b/3 studies at rates greater than rates in the comparator. Adverse reactions from clinical trials in table 2 were assessed as possibly related to study drug by investigators.
### Table 2: Clinically important adverse reactions of moderate intensity or more occurring among patients receiving maraviroc at rates greater than rates in the comparator

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

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

**Description of selected adverse reactions**

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) 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 3 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 3: 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)

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Limit</th>
<th>Maraviroc300 mg twice daily + OBT N=421* (%)</th>
<th>Placebo + OBT N=207* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>&gt;5.0x ULN</td>
<td>4.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>&gt;5.0x ULN</td>
<td>2.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>&gt;5.0x ULN</td>
<td>5.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>&gt;2.0x ULN</td>
<td>5.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Lipase</td>
<td>&gt;2.0x ULN</td>
<td>4.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>&lt;750/mm³</td>
<td>4.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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.

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 the national reporting system listed in Appendix V.

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. 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.

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.

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

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. Traditional IC50/IC90 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 nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and enfuvirtide were all susceptible to maraviroc in cell culture. Maraviroc-resistant viruses that emerged in vitro remained sensitive to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.

In vivo:
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 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-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 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 R5-virus only, maraviroc might be considered still active if the maximal percentage inhibition (MPI) value is ≥95% (Phenosense Entry assay). Residual activity in vivo for viruses with MPI-values <95% has not been determined.

Genotypic resistance: Key mutations (V3-loop) can presently not be suggested due to the high variability of the V3-sequence, and the low number of samples analysed.

**Clinical results**

**Studies in CCR5-tropic Treatment-Experienced Patients:**
The clinical efficacy of maraviroc (in combination with other antiretroviral medicinal products) on plasma HIV RNA levels and CD4+ cell counts have been investigated in two pivotal ongoing, 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 nucleoside reverse transcriptase inhibitors (NRTI), ≥1 non-nucleoside reverse transcriptase inhibitors (NNRTI), ≥2 protease inhibitors (PI), and/or enfurvirtide] or documented resistance to at least one member of each class. Patients were randomised in a 2:2:1 ratio to maraviroc 300 mg (dose 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 4: Demographic and baseline characteristics of patients (pooled studies MOTIVATE 1 and MOTIVATE 2)

<table>
<thead>
<tr>
<th>Demographic and Baseline Characteristics</th>
<th>Maraviroc 300 mg twice daily + OBT</th>
<th>Placebo + OBT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 426</td>
<td>N = 209</td>
</tr>
<tr>
<td>Age (years), (Range, years)</td>
<td>46.3, 21-73</td>
<td>45.7, 29-72</td>
</tr>
<tr>
<td>Male Sex</td>
<td>89.7%</td>
<td>88.5%</td>
</tr>
<tr>
<td>Race (White/Black/Other)</td>
<td>85.2% / 12% / 2.8%</td>
<td>85.2% / 12.4% / 2.4%</td>
</tr>
<tr>
<td>Mean Baseline HIV-1 RNA (log_{10} copies/mL)</td>
<td>4.85</td>
<td>4.86</td>
</tr>
<tr>
<td>Median Baseline CD4+ Cell Count (cells/mm³)</td>
<td>166.8 (2.0-820.0)</td>
<td>171.3</td>
</tr>
<tr>
<td>Screening Viral Load ≥100,000 copies/mL</td>
<td>179 (42.0%)</td>
<td>84 (40.2%)</td>
</tr>
<tr>
<td>Baseline CD4+ Cell Count ≤200 cells/mm³</td>
<td>250 (58.7%)</td>
<td>118 (56.5%)</td>
</tr>
<tr>
<td>Number (Percentage) of patients with GSS score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>102 (23.9%)</td>
<td>51 (24.4%)</td>
</tr>
<tr>
<td>1</td>
<td>138 (32.4%)</td>
<td>53 (25.4%)</td>
</tr>
<tr>
<td>2</td>
<td>80 (18.8%)</td>
<td>41 (19.6%)</td>
</tr>
<tr>
<td>≥3</td>
<td>104 (24.4%)</td>
<td>59 (28.2%)</td>
</tr>
</tbody>
</table>

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/mm³) group was greater than that seen in patients failing placebo + OBT (+13.8 cells/mm³) regardless of tropism.

Table 5: Efficacy Outcomes at week 48 (pooled studies MOTIVATE 1 and MOTIVATE 2)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Maraviroc 300 mg twice daily + OBT</th>
<th>Placebo + OBT</th>
<th>Difference¹ (Confidence Interval²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA Mean change from baseline (log copies/mL)</td>
<td>-1.837</td>
<td>-0.785</td>
<td>-1.055 (-1.327, -0.783)</td>
</tr>
<tr>
<td>Percentage of patients with HIV-1 RNA &lt;400 copies/mL</td>
<td>56.1%</td>
<td>22.5%</td>
<td>Odds ratio: 4.76 (3.24, 7.00)</td>
</tr>
<tr>
<td>Percentage of patients with HIV-1 RNA &lt;50 copies/mL</td>
<td>45.5%</td>
<td>16.7%</td>
<td>Odds ratio: 4.49 (2.96, 6.83)</td>
</tr>
<tr>
<td>CD4+ cell count Mean change from baseline (cells/µL)</td>
<td>122.78</td>
<td>59.17</td>
<td>63.13 (44.28, 81.99)</td>
</tr>
</tbody>
</table>

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 6). 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 6).

Table 6: Proportion of patients achieving <50 copies/mL at Week 48 by subgroup (pooled Studies MOTIVATE 1 and MOTIVATE 2)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>HIV-1 RNA &lt;50 copies/mL</th>
<th>Maraviroc 300 mg twice daily + OBT  N=426</th>
<th>Placebo + OBT N=209</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening HIV-1 RNA (copies /mL):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>58.4%</td>
<td>26.0%</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>34.7%</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4+ (cells/µL):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>16.5%</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td>50-100</td>
<td>36.4%</td>
<td>12.0%</td>
<td></td>
</tr>
<tr>
<td>101-200</td>
<td>56.7%</td>
<td>21.8%</td>
<td></td>
</tr>
<tr>
<td>201-350</td>
<td>57.8%</td>
<td>21.0%</td>
<td></td>
</tr>
<tr>
<td>≥ 350</td>
<td>72.9%</td>
<td>38.5%</td>
<td></td>
</tr>
<tr>
<td>Number of active ARVs in OBT¹:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32.7%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44.5%</td>
<td>7.4%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>58.2%</td>
<td>31.7%</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>62%</td>
<td>38.6%</td>
<td></td>
</tr>
</tbody>
</table>

¹Based on GSS.

Studies in Non-CCR5-tropic Treatment-Experienced Patients:
Study A4001029 was an exploratory study in patients infected with dual/mixed or CXCR4 tropic HIV-1 with a similar design as the studies MOTIVATE 1 and MOTIVATE 2. In this study, neither superiority nor non-inferiority to placebo + OBT were demonstrated although there was no adverse outcome on viral load or CD4+ cell count.

Studies in Treatment-Naïve Patients
An ongoing randomised, double-blinded study (MERIT), is exploring 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 on Patients co-infected with hepatitis B and/or hepatitis C virus
The hepatic safety of maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects with HIV RNA <50 copies/mL, co-infected with Hepatitis C and/or Hepatitis B Virus was evaluated in a 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).

### 5.2 Pharmacokinetic properties

**Absorption:** the absorption of maraviroc is variable with multiple peaks. Median peak maraviroc plasma concentrations is 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 $C_{\text{max}}$ 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.

**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.

**Paediatric population:** 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 have 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$_{\text{inf}}$ (CV%) for maraviroc was as follows: healthy volunteers (normal renal function) 1348.4 ng·h/mL (61%); severe renal function 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 $C_{\text{max}}$ (CV%) was 335.6 ng/mL (87%) in healthy volunteers (normal renal function); 801.2 ng/mL (56%) in severe renal function; 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 Cmax and AUClast 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.

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 tumors 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 cholangiomas (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.
Maraviro 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 rat bone marrow micronucleus.

Maraviro 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.

Embryofetal 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 maraviro.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

High density polyethylene bottles (HDPE) with polypropylene child resistant (CR) closures and an aluminium foil/polyethylene heat induction seal containing 180 film-coated tablets.

Polyvinyl chloride (PVC) blisters with aluminium foil backing in a carton containing 30, 60, 90 film-coated tablets and multipacks containing 180 (2 packs of 90) film-coated tablets.
Not all pack sizes may be marketed.

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 Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/001
EU/1/07/418/002
EU/1/07/418/003
EU/1/07/418/004
EU/1/07/418/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th September 2007
Date of latest renewal: 20 July 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. NAME OF THE MEDICINAL PRODUCT

CELESTRONI 300 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of maraviroc.

Excipient with known effect:
Each 300 mg film-coated tablet contains 1.68 mg of soya lecithin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, biconvex, oval film-coated tablets debossed with “MVC 300”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable (see section 4.2).

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients (see section 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). Other phenotypic and genotypic assays are currently being evaluated. The viral tropism cannot be safely predicted by treatment history and assessment of stored samples.

There are currently no data regarding the reuse of 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, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products (see Table 1 in section 4.5).
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 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 patients with severe renal impairment (CLcr <30 mL/min) who are receiving potent CYP3A4 inhibitors (see sections 4.4 and 5.2).

Hepatic impairment
Limited data are available in patients with hepatic impairment, therefore CELSENTRI should be used with caution in this population (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of CELSENTRI in children younger than 18 years of age has not been established. No data available (see section 5.2).

Method of administration
Oral use.
CELSENTRI can be taken with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 CELSENTRI, in most cases concomitantly with other drugs associated with these reactions. These reactions included rash, fever, and sometimes organ dysfunction and hepatic failure. Discontinue CELSENTRI 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 was 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 events 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) 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 be taken as part of an antiretroviral combination regimen. Maraviroc should optimally be combined with other antiretrovirals to which the patient's virus is sensitive (see section 5.1).
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. Other phenotypic and genotypic assays are currently being evaluated. 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 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.

Soya lecithin

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

4.5 Interaction with other medicinal products and other forms of interaction

Maraviroc is a substrate of cytochrome P450 CYP3A4. 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 CYP3A4 inhibitors and/or inducers. Further details for concomitantly administered medicinal products are provided below (see Table 1).

Studies in human liver microsomes and recombinant enzyme systems have shown that maraviroc does not inhibit any of the major P450 enzymes at clinically relevant concentrations (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinylestradiol and levonorgestrel, or urinary 6β-hydroxycortisol/cortisol ratio, suggesting no inhibition or induction of CYP3A4 in vivo. At higher exposure of maraviroc a potential inhibition of CYP2D6 cannot be excluded. Based on the in vitro and clinical data, the potential for maraviroc to affect the pharmacokinetics of co-administered medicinal products is low.
Renal clearance accounts for approximately 23% of total clearance of maraviroc when maraviroc is administered without CYP3A4 inhibitors. As both passive and active processes are involved, there is the potential for competition for elimination with other renally eliminated active substances. However, 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 (IC₅₀ 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 1: Interactions and dose recommendations with other medicinal products

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose of CELSENTRI used in study)</th>
<th>Effects on active substance levels</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic Enhancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Interaction not studied.</td>
<td>CELSENTRI dose should be decreased to 150 mg twice daily when co-administered with cobicistat containing regimen.</td>
</tr>
<tr>
<td>Lamivudine 150 mg BID (maraviroc 300 mg BID)</td>
<td>Lamivudine AUC₁₂: ↔ 1.13 Lamivudine Cₘₐₓ: ↔ 1.16 Maraviroc concentrations not measured, no effect is expected.</td>
<td>No significant interaction seen/expected. CELSENTRI 300 mg twice daily and NRTIs can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Tenofovir 300 mg QD (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC₁₂: ↔ 1.03 Maraviroc Cₘₐₓ: ↔ 1.03 Tenofovir concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td>Zidovudine 300 mg BID (maraviroc 300 mg BID)</td>
<td>Zidovudine AUC₁₂: ↔ 0.98 Zidovudine Cₘₐₓ: ↔ 0.92 Maraviroc concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/ritonavir 150/100mg QD (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC₁₂: ↑ 2.86 (2.33-3.51) Maraviroc Cₘₐₓ: ↑ 2.15 (1.71-2.69) Maraviroc C₁₂: ↑ 4.23 (3.47-5.16) Elvitegravir AUC₂₄: ↔ 1.07 (0.96-1.18) Elvitegravir Cₘₐₓ: ↔ 1.01 (0.89-1.15) Elvitegravir C₂₄: ↔ 1.09 (0.95-1.26)</td>
<td>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 ‘HIV Protease Inhibitors’).</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Maraviro AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.55</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.49</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Etravirine 200 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.47</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.40</td>
</tr>
<tr>
<td>Nevirapine 200 mg BID (maraviroc 300 mg Single Dose)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↔ compared to historical controls</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ compared to</td>
</tr>
</tbody>
</table>

**HCV Protease Inhibitors**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.02 (2.53, 3.59)</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 3.33 (2.54, 4.36)</th>
<th>Maraviroc C&lt;sub&gt;12&lt;/sub&gt;: ↑ 2.78 (2.40-3.23)</th>
<th>Boceprevir concentrations are not likely to be affected by maraviro co-administration (based on historical data and the elimination pathway of boceprevir).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir 750 mg TID (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 9.49 (7.94, 11.34)</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 7.81 (5.92, 10.32)</td>
<td>Telaprevir concentrations are not likely to be affected by maraviro co-administration (based on historical data and the elimination pathway of telaprevir).</td>
<td>Maraviroc 150 mg twice daily when co-administered with telaprevir</td>
</tr>
</tbody>
</table>

**HIV Protease Inhibitors (PIs)**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.57</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.09</th>
<th>Atazanavir concentrations not measured, no effect is expected.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir 400 mg QD (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 4.88</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.67</td>
<td>Atazanavir/ritonavir concentrations not measured, no effect is expected.</td>
<td>Atazanavir/ritonavir 300 mg/100 mg QD (maraviroc 300 mg BID)</td>
</tr>
</tbody>
</table>

|| Raltegravir 400 mg BID (maraviroc 300 mg BID) | Maraviroc AUC<sub>12</sub>: ↓ 0.86 | Maraviroc C<sub>max</sub>: ↓ 0.79 | Raltegravir AUC<sub>12</sub>: ↓ 0.63 | Raltegravir C<sub>max</sub>: ↓ 0.67 | Raltegravir C<sub>12</sub>: ↓ 0.72 | No clinically significant interaction seen. CELSENTRI 300 mg twice daily and raltegravir can be co-administered without dose adjustment. |

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.55</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.49</th>
<th>Efavirenz concentrations not measured, no effect is expected.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine 200 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.47</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.40</td>
<td>Etravirine AUC&lt;sub&gt;12&lt;/sub&gt;: ↔ 1.06</td>
<td>Etravirine is only approved for use with boosted protease inhibitors. For combination with etravirine + PI, see below.</td>
</tr>
<tr>
<td>Nevirapine 200 mg BID (maraviroc 300 mg Single Dose)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↔ compared to historical controls</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ compared to historical controls</td>
<td>Nevirapine concentrations not measured, no effect is expected.</td>
<td>Comparison to exposure in historical controls suggests that CELSENTRI 300 mg twice daily and nevirapine can be co-administered without dose adjustment.</td>
</tr>
</tbody>
</table>

**HCV Protease Inhibitors**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.02 (2.53, 3.59)</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 3.33 (2.54, 4.36)</th>
<th>Maraviroc C&lt;sub&gt;12&lt;/sub&gt;: ↑ 2.78 (2.40-3.23)</th>
<th>Boceprevir concentrations are not likely to be affected by maraviro co-administration (based on historical data and the elimination pathway of boceprevir).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir 750 mg TID (maraviroc 150 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 9.49 (7.94, 11.34)</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 7.81 (5.92, 10.32)</td>
<td>Telaprevir concentrations are not likely to be affected by maraviro co-administration (based on historical data and the elimination pathway of telaprevir).</td>
<td>Maraviroc 150 mg twice daily when co-administered with telaprevir</td>
</tr>
</tbody>
</table>

**HIV Protease Inhibitors (PIs)**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 3.57</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.09</th>
<th>Atazanavir concentrations not measured, no effect is expected.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir 400 mg QD (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;: ↑ 4.88</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 2.67</td>
<td>Atazanavir/ritonavir concentrations not measured, no effect is expected.</td>
<td>Atazanavir/ritonavir 300 mg/100 mg QD (maraviroc 300 mg BID)</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Lopinavir/ritonavir Concentrations</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)</td>
<td>↑ 3.95</td>
<td>↑ 1.97</td>
<td>Not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td>Saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)</td>
<td>↑ 9.77</td>
<td>↑ 4.78</td>
<td>Not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir 600 mg/100 mg BID (maraviroc 150 mg BID)</td>
<td>↑ 4.05</td>
<td>↑ 2.29</td>
<td>Consistent with historical data.</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td></td>
<td>Limited data are available for co-administration with nelfinavir. Nelfinavir is a potent CYP3A4 inhibitor and would be expected to increase maraviroc concentrations.</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Tipranavir/ritonavir 500 mg/200 mg BID (maraviroc 150 mg BID)</td>
<td>↔ 1.02</td>
<td>↔ 0.86</td>
<td>Consistent with historical data.</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir 700 mg/100 mg BID (maraviroc 300 mg BID)</td>
<td>↑ 2.49</td>
<td>↑ 1.52</td>
<td>Concomitant use is not recommended. Significant reductions in amprenavir C&lt;sub&gt;min&lt;/sub&gt; observed may result in virological failure in patients.</td>
<td></td>
</tr>
</tbody>
</table>

**NNRTI + PI**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Maraviroc AUC&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Maraviroc C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Efavirenz, lopinavir/ritonavir Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz 600 mg QD + lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)</td>
<td>↑ 2.53</td>
<td>↑ 1.25</td>
<td>Not measured, no effect expected.</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD + saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)</td>
<td>↑ 5.00</td>
<td>↑ 2.26</td>
<td>Not measured, no effect expected.</td>
</tr>
</tbody>
</table>

**CELSENTRI dose**

- When co-administered with efavirenz and a PI (except tipranavir/ritonavir where the dose should be 600 mg twice daily), concomitant use of CELSENTRI and fosamprenavir/ritonavir is not recommended.
<table>
<thead>
<tr>
<th>Interaction</th>
<th>Clinical Impact</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz and atazanavir/ritonavir or darunavir/ritonavir</td>
<td>Not studied. Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir in the absence of efavirenz, an increased exposure is expected.</td>
<td></td>
</tr>
<tr>
<td>Etravirine and darunavir/ritonavir (maraviroc 150 mg BID)</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Etravirine and lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>ANTIBIOTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphamethoxazole/Trimethoprim 800 mg/160 mg BID (maraviroc 300 mg BID)</td>
<td>Maraviroc AUC: ↑ 3.10 Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↑ 1.77 Etravirine AUC: ↔ 1.00 Etravirine C&lt;sub&gt;max&lt;/sub&gt;: ↔ 1.08 Darunavir AUC: ↓ 0.86 Darunavir C&lt;sub&gt;max&lt;/sub&gt;: ↔ 0.96 Ritonavir AUC: ↔ 0.93 Ritonavir C&lt;sub&gt;max&lt;/sub&gt;: ↔ 1.02 Ritonavir C&lt;sub&gt;12&lt;/sub&gt;: ↓ 0.77 Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected.</td>
<td>CELSENTRI 300 mg twice daily can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Rifampicin 600 mg QD (maraviroc 100 mg BID)</td>
<td>Maraviroc AUC: ↓ 0.37 Maraviroc C&lt;sub&gt;max&lt;/sub&gt;: ↓ 0.34 Rifampicin concentrations not measured, no effect expected.</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin + efavirenz</td>
<td>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.</td>
<td>Concomitant use of CELSENTRI and rifampicin + efavirenz is not recommended.</td>
</tr>
<tr>
<td>Rifabutin + PI</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Drug Class</td>
<td>Drug</td>
<td>Interaction Details</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>ANTIFUNGALS</strong></td>
<td><strong>Ketoconazole 400 mg QD (maraviroc 100 mg BID)</strong></td>
<td>Maraviroc AUC_{tau}: ↑ 5.00 Maraviroc C_{max}: ↑ 3.38 Ketoconazole concentrations not measured, no effect is expected.</td>
</tr>
<tr>
<td></td>
<td><strong>Itraconazole</strong></td>
<td>Not studied. Itraconazole, is a potent CYP3A4 inhibitor and would be expected to increase the exposure of maraviroc.</td>
</tr>
<tr>
<td></td>
<td><strong>Fluconazole</strong></td>
<td>Fluconazole is considered to be a moderate CYP3A4 inhibitor. Population PK studies suggest that a dose adjustment of maraviroc is not required.</td>
</tr>
<tr>
<td><strong>ANTIVIRALS</strong></td>
<td><strong>HCV agents</strong></td>
<td>Pegylated interferon and ribavirin have not been studied, no interaction is expected.</td>
</tr>
<tr>
<td><strong>DRUG ABUSE</strong></td>
<td><strong>Methadone</strong></td>
<td>Not studied, no interaction expected.</td>
</tr>
<tr>
<td></td>
<td><strong>Buprenorphine</strong></td>
<td>Not studied, no interaction expected.</td>
</tr>
<tr>
<td><strong>LIPID LOWERING MEDICINAL PRODUCTS</strong></td>
<td><strong>Statins</strong></td>
<td>Not studied, no interaction expected.</td>
</tr>
<tr>
<td></td>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td>Digoxin. AUC_{r}: ↔ 1.00 Digoxin. C_{max}: ↔ 1.04 Maraviroc concentrations not measured, no interaction expected.</td>
</tr>
<tr>
<td></td>
<td><strong>ETHINYLESTRADIOL 30 mcg QD (maraviroc 100 mg BID)</strong></td>
<td>Ethinylestradiol. AUC_{r}: ↔ 1.00 Ethinylestradiol. C_{max}: ↔ 0.99 Maraviroc concentrations not measured, no interaction expected.</td>
</tr>
</tbody>
</table>

The effect of maraviroc on digoxin at the dose of 600 mg BID has not been studied.
Levonorgestrel 150 mcg QD  
(maraviroc 100 mg BID)  
Levonorgestrel. AUC 12: ↔ 0.98  
Levonorgestrel. C<sub>max</sub>: ↔ 1.01  
Maraviroc concentrations not measured, no interaction expected.  
**CEFENTRI 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<sub>max</sub>: ↔ 1.21  
Maraviroc concentrations not measured, no interaction expected.  
**CEFENTRI 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.**

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
No meaningful clinical data on exposure during pregnancy are available. Studies in rats and rabbits showed reproductive toxicity at high exposures. Primary pharmacological activity (CCR5 receptor affinity) was limited in these species (see section 5.3). Maraviroc should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Breast-feeding**
Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. Primary pharmacological activity (CCR5 receptor affinity) was limited in these species. It is not known whether maraviroc is secreted into human milk.

It is recommended that mothers infected by HIV do not breast-feed their infants under any circumstances 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

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

### 4.8 Undesirable effects

**Summary of the safety profile**
The safety profile of maraviroc is based on 1,374 HIV-1 infected patients who received at least one dose of maraviroc during Phase 2b/3 clinical studies. This includes 426 treatment-experienced patients and 360 treatment-naïve patients who received the recommended dose 300 mg twice daily and a further 588 treatment-experienced and treatment-naïve patients who received 300 mg once daily for at least 24 weeks. 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 (≥ 1/100 to < 1/10). The reported frequencies for these events as well as the rates of discontinuation due to any adverse reactions were similar in patients receiving maraviroc in Phase 2b/3 studies compared to those receiving comparator.

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 <1/1000), or not known (cannot be estimated from the available data). The adverse reactions and laboratory abnormalities presented below are not exposure adjusted.

The following table presents clinically important adverse reactions of moderate intensity or more occurring among patients receiving maraviroc in Phase 2b/3 studies at rates greater than rates in the comparator. Adverse reactions from clinical trials in table 2 were assessed as possibly related to study drug by investigators.
Table 2: Clinically important adverse reactions of moderate intensity or more occurring among patients receiving maravirocat rates greater than rates in the comparator.

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

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

Description of selected adverse reactions

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) 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 3 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 3: 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)

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Limit</th>
<th>Maraviroc 300 mg twice daily + OBT N =421* (%)</th>
<th>Placebo + OBT N =207* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>&gt;5.0x ULN</td>
<td>4.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>&gt;5.0x ULN</td>
<td>2.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>&gt;5.0x ULN</td>
<td>5.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>&gt;2.0x ULN</td>
<td>5.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Lipase</td>
<td>&gt;2.0x ULN</td>
<td>4.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>&lt;750/mm³</td>
<td>4.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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

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 the national reporting system listed in Appendix V.

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. 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.

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
medicines. 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.

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

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. Traditional IC50/IC90 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 nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and enfuvirtide were all susceptible to maraviroc in cell culture. Maraviroc-resistant viruses that emerged in vitro remained sensitive to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.

In vivo:
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 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-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 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 R5-virus only, maraviroc might be considered still active if the maximal percentage inhibition (MPI) value is ≥95% (Phenosense Entry assay). Residual activity in vivo for viruses with MPI-values <95% has not been determined.

**Genotypic resistance:** Key mutations (V3-loop) can presently not be suggested due to the high variability of the V3-sequence, and the low number of samples analysed.

**Clinical results**

**Studies in CCR5-tropic Treatment-Experienced Patients:**
The clinical efficacy of maraviroc (in combination with other antiretroviral medicinal products) on plasma HIV RNA levels and CD4+ cell counts have been investigated in two pivotal ongoing, 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 nucleoside reverse transcriptase inhibitors (NRTI), ≥1 non-nucleoside reverse transcriptase inhibitors (NNRTI), ≥2 protease inhibitors (PI), and/or enfuvirtide] or documented resistance to at least one member of each class. Patients were randomised in a 2:2:1 ratio to maraviroc 300 mg (dose 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 4: Demographic and baseline characteristics of patients (pooled studies MOTIVATE 1 and MOTIVATE 2)

<table>
<thead>
<tr>
<th>Demographic and Baseline Characteristics</th>
<th>Maraviroc 300 mg twice daily + OBT N = 426</th>
<th>Placebo + OBT N = 209</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (Range, years)</td>
<td>46.3/21-73</td>
<td>45.7/29-72</td>
</tr>
<tr>
<td>Male Sex</td>
<td>89.7%</td>
<td>88.5%</td>
</tr>
<tr>
<td>Race (White/Black/Other)</td>
<td>85.2% / 12% / 2.8%</td>
<td>85.2% / 12.4% / 2.4%</td>
</tr>
<tr>
<td>Mean Baseline HIV-1 RNA (log10 copies/mL)</td>
<td>4.85</td>
<td>4.86</td>
</tr>
<tr>
<td>Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)</td>
<td>166.8/(2.0-820.0)</td>
<td>171.3/(1.0-675.0)</td>
</tr>
<tr>
<td>Screening Viral Load $&gt;100,000$ copies/mL</td>
<td>179 (42.0%)</td>
<td>84 (40.2%)</td>
</tr>
<tr>
<td>Baseline CD4+ Cell Count $&lt;200$ cells/mm^3</td>
<td>250 (58.7%)</td>
<td>118 (56.5%)</td>
</tr>
<tr>
<td>Number (Percentage) of patients with GSS score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>102 (23.9%)</td>
<td>51 (24.4%)</td>
</tr>
<tr>
<td>1</td>
<td>138 (32.4%)</td>
<td>53 (25.4%)</td>
</tr>
<tr>
<td>2</td>
<td>80 (18.8%)</td>
<td>41 (19.6%)</td>
</tr>
<tr>
<td>$\geq$3</td>
<td>104 (24.4%)</td>
<td>59 (28.2%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Maraviroc 300 mg twice daily + OBT N=426</th>
<th>Placebo + OBT N=209</th>
<th>Difference(^1) (Confidence Interval(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA Mean change from baseline (log copies/mL)</td>
<td>-1.837</td>
<td>-0.785</td>
<td>-1.055 (-1.327, -0.783)</td>
</tr>
<tr>
<td>Percentage of patients with HIV-1 RNA &lt;400 copies/mL</td>
<td>56.1%</td>
<td>22.5%</td>
<td>Odds ratio: 4.76 (3.24, 7.00)</td>
</tr>
<tr>
<td>Percentage of patients with HIV-1 RNA &lt;50 copies/mL</td>
<td>45.5%</td>
<td>16.7%</td>
<td>Odds ratio: 4.49 (2.96, 6.83)</td>
</tr>
<tr>
<td>CD4+ cell count Mean change from baseline (cells/µL)</td>
<td>122.78</td>
<td>59.17</td>
<td>63.13 (44.28, 81.99)(^2)</td>
</tr>
</tbody>
</table>

\(^1\) 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 6). 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 6).

### Table 6: Proportion of patients achieving <50 copies/mL at Week 48 by subgroup (pooled Studies MOTIVATE 1 and MOTIVATE 2)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>HIV-1 RNA &lt;50 copies/mL</th>
<th>Maraviroc300 mg twice daily</th>
<th>Placebo + OBT N=209</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening HIV-1 RNA (copies/mL):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>58.4%</td>
<td>26.0%</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>34.7%</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4+ (cells/µL):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>16.5%</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td>50-100</td>
<td>36.4%</td>
<td>12.0%</td>
<td></td>
</tr>
<tr>
<td>101-200</td>
<td>56.7%</td>
<td>21.8%</td>
<td></td>
</tr>
<tr>
<td>201-350</td>
<td>57.8%</td>
<td>21.0%</td>
<td></td>
</tr>
<tr>
<td>≥350</td>
<td>72.9%</td>
<td>38.5%</td>
<td></td>
</tr>
<tr>
<td>Number of active ARVs in OBT¹:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32.7%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44.5%</td>
<td>7.4%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>58.2%</td>
<td>31.7%</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>62%</td>
<td>38.6%</td>
<td></td>
</tr>
</tbody>
</table>

¹Based on GSS.

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

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

### Studies in Treatment-Naïve Patients

An ongoing randomised, double-blinded study (MERIT), is exploring 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 on Patients co-infected with hepatitis B and/or hepatitis C virus

The hepatic safety of maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects with HIV RNA <50 copies/mL, co-infected with Hepatitis C and/or Hepatitis B Virus was evaluated in a multicentre, randomised, 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).

5.2 Pharmacokinetic properties

**Absorption:** the absorption of maraviroc is variable with multiple peaks. Median peak maraviroc plasma concentrations is 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 $C_{\text{max}}$ 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.

**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.

**Paediatric population:** 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:** a study compared the pharmacokinetics of a single 300 mg dose of maraviroc in subjects with severe renal impairment ($\text{CLcr} < 30 \text{ mL/min, n=6}$) and end stage renal disease (ESRD) to healthy volunteers (n=6). The geometric mean AUC$_{\text{inf}}$ (CV%) for maraviroc was as follows: healthy volunteers (normal renal function) 1348.4 ng·h/mL (61%); severe renal function 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 $C_{\text{max}}$ (CV%) was 335.6 ng/mL (87%) in healthy volunteers (normal renal function); 801.2 ng/mL (56%) in severe renal function; 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 Cmax and AUClast 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.

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 tumors 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 rat 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.

Embryofetal 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

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

High density polyethylene bottles (HDPE) with polypropylene child resistant (CR) closures and an aluminium foil/polyethylene heat induction seal containing 180 film-coated tablets.

Polyvinyl chloride (PVC) blisters with aluminium foil backing in a carton containing 30, 60, 90 film-coated tablets and multipacks containing 180 (2 packs of 90) film-coated tablets.
Not all pack sizes may be marketed.

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 Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/006
EU/1/07/418/007
EU/1/07/418/008
EU/1/07/418/009
EU/1/07/418/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th September 2007
Date of latest renewal: 20 July 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the drug active substances

(Process A and B) Drug substance release testing:
Pfizer Ireland Pharmaceuticals
Ringaskiddy Drug Substance Plant
PO Box 140, Ringaskiddy, County Cork, Ireland

(Process B only) Drug substance release testing:
n.v. Ajinomoto Omnichem s.a.
Cooppallaan 9, B-9230 Wetteren, Belgium

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

Bottle label - 150 mg film-coated tablets

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELSENTRI 150 mg film-coated tablets</td>
</tr>
<tr>
<td>maraviroc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains 150 mg of maraviroc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains soya lecithin: see leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP {MM-YYYY}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
</table>
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/001

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Celsentri 150 mg
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label - 300 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CELSENTRI 300 mg film-coated tablets
maraviroc

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg of maraviroc.

3. LIST OF EXCIPIENTS

Contains soya lecithin: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY }

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/006

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Celsentri 300 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton for blister pack containing 150 mg maraviroc film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT
CELSENTRI 150 mg film-coated tablets
maraviroc

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 150 mg of maraviroc.

3. LIST OF EXCIPIENTS
Contains soya lecithin: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
30 film-coated tablets
60 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS
### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd  
980 Great West Road  
Brentford  
Middlesex  
TW8 9GS  
United Kingdom

### 12. MARKETING AUTHORISATION NUMBER(S)

- EU/1/07/418/002  
- EU/1/07/418/003  
- EU/1/07/418/004

### 13. BATCH NUMBER

Lot {number}

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

Celsentri 150 mg
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton for blister pack containing 300 mg maraviroc film-coated tablets

### 1. NAME OF THE MEDICINAL PRODUCT
CELESETRI 300 mg film-coated tablets
maraviroc

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 300 mg of maraviroc.

### 3. LIST OF EXCIPIENTS
Contains soya lecithin: see leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS
- 30 film-coated tablets
- 60 film-coated tablets
- 90 film-coated tablets

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE
EXP {MM-YYYY }

### 9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/007
EU/1/07/418/008
EU/1/07/418/009

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Celsentri 300 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Outer wrapper label on multi packs of 180 (2 packs of 90 film-coated tablets) wrapped in transparent foil - including the blue box - 150 mg film-coated tablets

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celsentri 150 mg film-coated tablets</td>
</tr>
<tr>
<td>maraviroc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains 150 mg of maraviroc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains soya lecithin: see leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multipack: 180 (2 packs of 90) film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP {MM-YYYY }</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
</table>
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/005

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Celsentri 150 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Outer wrapper label on multi packs of 180 (2 packs of 90 film-coated tablets) wrapped in transparent foil - including the blue box - 300 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT
Celsentri 300 mg film-coated tablets
maraviroc

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 300 mg of maraviroc.

3. LIST OF EXCIPIENTS
Contains soya lecithin: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
Multipack: 180 (2 packs of 90) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP {MM-YYYY }

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

ViiV Healthcare UK Ltd  
980 Great West Road  
Brentford  
Middlesex  
TW8 9GS  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/418/010

13. **BATCH NUMBER**

Lot {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Celsentri 300 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

2x carton for blister pack containing 150 mg maraviroc film-coated tablets

---

**1. NAME OF THE MEDICINAL PRODUCT**

Celsentri 150 mg film-coated tablets
maraviroc

---

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 150 mg of maraviroc.

---

**3. LIST OF EXCIPIENTS**

Contains soya lecithin: see leaflet for further information.

---

**4. PHARMACEUTICAL FORM AND CONTENTS**

90 film-coated tablets. Component of a multipack, cannot be sold separately.

---

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

---

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

---

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

---

**8. EXPIRY DATE**

EXP {MM-YYYY}

---

**9. SPECIAL STORAGE CONDITIONS**

---

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

---
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/005

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Celsentri 150 mg
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

2x carton for blister pack containing 300 mg maraviroc film-coated tablets

### 1. NAME OF THE MEDICINAL PRODUCT

Celsentri 300 mg film-coated tablets
maraviroc

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg of maraviroc.

### 3. LIST OF EXCIPIENTS

Contains soya lecithin: see leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS

90 film-coated tablets. Component of a multipack, cannot be sold separately.

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP {MM-YYYY }

### 9. SPECIAL STORAGE CONDITIONS

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/418/010

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Celsentri 300 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister Pack of 10 tablets of 150 mg maraviroc film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELSENTRI 150 mg film-coated tablets</td>
</tr>
<tr>
<td>maraviroc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViiV Healthcare (logo)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP {MM-YYYY}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot: {number}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 10 tablets of 300 mg maraviroc film-coated tablets

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELSENTRI 300 mg film-coated tablets</td>
</tr>
<tr>
<td>maraviroc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViiV Healthcare (logo)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP {MM-YYYY}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot: {number}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet:

1. What CELSENTRI is and what it is used for
2. What you need to know before you take CELSENTRI
3. How to take CELSENTRI
4. Possible side effects
5. How to store CELSENTRI
6. Contents of the pack and other information

1. What CELSENTRI is and what it is used for

CELSENTRI is used to treat Human Immunodeficiency Virus type-1 (HIV-1) in adults.

CELSENTRI contains a medicine called maraviroc. Maraviroc belongs to a group of medicines called CCR5 antagonists. CELSENTRI works by blocking a receptor called CCR5 which HIV uses to enter and infect your blood cells.

CELSENTRI must be taken in combination with other medicines which are also used to treat the HIV infection. These medicines are all called anti-HIV medicines or antiretrovirals.

CELSENTRI, as part of combination therapy, reduces the amount of virus in your body, and keeps it at a low level. This helps your body to increase the CD4 cell count in your blood. CD4 cells are a type of white blood cell that are important in helping your body to fight infection.

2. What you need to know before you take CELSENTRI

Do not take CELSENTRI if you are allergic to maraviroc or to peanut or soya or to any of the other ingredients of CELSENTRI (listed in section 6).

Warnings and precautions

Your doctor must take blood samples to test whether CELSENTRI is an appropriate treatment for you.

Before taking this medicine, make sure that your doctor knows if you have or in the past had any of the following:

- problems with your liver including chronic hepatitis B or C as there is only limited experience in patients with liver problems. Your liver function may need to be closely monitored. If you notice
symptoms of hepatitis (loss of appetite, fever, feeling sick/being sick and/or yellowing of skin or eyes), rash and/or itching, you should stop taking CELSENTRI and inform your doctor immediately.

- had low blood pressure, low blood pressure on standing and/or if you are taking any medicines to lower blood pressure

- tuberculosis or serious fungal infections as due to the way CELSENTRI works on certain immune cells, CELSENTRI could potentially increase the risk of developing infections. However, there has been no evidence of an increase in the occurrence of AIDS-related infections associated with the use of CELSENTRI in clinical studies

- any kidney problems particularly if you are taking certain antibiotics (clarithromycin, telithromycin), antifungal medicines (ketoconazole, itraconazole) and/or protease inhibitors (except for tipranavir/ritonavir)

- problems with your heart or circulatory system as there is only limited experience in patients with serious problems of this type.

**Check with your doctor** if you think any of these apply to you.

**Look out for important symptoms**
Some people taking CELSENTRI develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you’re taking CELSENTRI, these include the following:

- Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index, among other factors, may increase the risk of developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. **Inform your doctor** if you notice any of these symptoms.

- Some patients with AIDS and a history of opportunistic infection (an infection that can occur when your immune system is impaired), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment.

**Contact you doctor immediately** to seek necessary treatment if you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity.

**Protect other people**
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

**Elderly people**
CELSENTRI has only been used in limited numbers of patients 65 years or older. If you belong to this age group please discuss with your doctor if you can use CELSENTRI.

**Children and adolescents**

The use of CELSENTRI in people under the age of 18 has not been proven. Therefore CELSENTRI is not recommended for use in children and adolescents.

**Other medicines and CELSENTRI**

**Tell your doctor or pharmacist if you’re taking any other medicines, or if you’ve taken any recently, including herbal medicines or other medicines you bought without a prescription.**

Remember to tell your doctor or pharmacist if you begin taking a new medicine while you’re taking CELSENTRI.

Some medicines may change the amount of CELSENTRI in the body when they are taken at the same time as CELSENTRI. These include other medicines to treat HIV or hepatitis C infection (e.g. atazanavir, cobicistat, darunavir, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, boceprevir, telaprevir), antibiotics (clarithromycin, telithromycin, rifampicin, rifabutin) and antifungal medicines (ketoconazole, itraconazole, fluconazole).

Tell your doctor if you are taking any of these medicines. This will allow your doctor to prescribe the right dose of CELSENTRI for you.

Medicines containing St. John’s Wort (*Hypericum perforatum*) are likely to prevent CELSENTRI from working properly and should not be taken together with CELSENTRI.

**Pregnancy**

If you are pregnant, if you become pregnant or if you are planning to become pregnant, talk to your doctor about the risks and benefits to you and your baby of taking CELSENTRI during your pregnancy. The safe use of CELSENTRI in pregnancy has not been proven.

**Breast-feeding**

**Women who are HIV-positive must not breast-feed**, because HIV infection can be passed on to the baby in breast milk.

It is not known whether the ingredients in Celsentri can also pass into your breast milk. If you are breast-feeding, or thinking about breast-feeding:

→ **Talk to your doctor immediately.**

**Driving and using machines**

CELSENTRI may cause dizziness. If you experience dizziness while taking CELSENTRI do not drive and do not operate any tools or machines.

**CELSENTRI contains soya lecithin.**

If you are allergic to peanut or soya do not use this medicinal product.

**3. How to take CELSENTRI**

You should keep taking CELSENTRI until your doctor tells you to stop. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
People with kidney problems

If you have a kidney problem, your doctor may alter your dose. **Talk to your doctor** if this applies to you.

The usual dose of CELSENTRI is **150 mg, 300 mg or 600 mg twice per day** depending on other medicines that you are taking at the same time as CELSENTRI. Always take the dose recommended by your doctor.

**CELSENTRI can be taken with or without food.** CELSENTRI should always be taken by mouth.

CELSENTRI must be taken in combination with other medicines used to treat HIV. Please refer to the Package Leaflets of these other medicines for guidance on how to take them.

If you take more CELSENTRI than you should

If you accidentally take more than the prescribed dose of CELSENTRI, contact your doctor or the nearest hospital right away. You may feel dizzy or light-headed when you stand or sit up quickly. This is due to a sudden fall in your blood pressure. If this happens, lie down until you feel better. When you get up, do so as slowly as possible.

If you forget to take CELSENTRI

If you miss a dose of CELSENTRI, take the missed dose as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

If you stop taking CELSENTRI

Taking your medicines at the right time every day is important as it makes sure the HIV infection does not increase in your body. Therefore, unless your doctor tells you to stop treatment, it is important to keep taking CELSENTRI correctly, as described above.

If you have any further questions on the use of this medicine, ask your doctor or your pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you notice anything unusual about your health.

Conditions you need to look out for include the following

Liver Problems

These have been reported rarely and may affect up to 1 in 1,000 people taking CELSENTRI. Signs include:

- loss of appetite
- feeling sick/being sick
- yellowing of skin or eyes
- skin rash or itching
- feeling very tired
• stomach pain or tenderness
• dark urine
• drowsiness and confusion
• fever

⇒ Contact a doctor immediately if you get these symptoms. Stop taking CELSENTRI.

Serious allergic or skin reactions

Although rare (may affect up to 1 in 1,000 people taking CELSENTRI), severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking CELSENTRI. If you get any of the following symptoms while you’re taking CELSENTRI:
• swelling of the face, lips or tongue
• difficulty breathing
• widespread skin rash
• fever
• blisters and peeling skin, particularly around the mouth, nose, eyes and genitals

⇒ Contact a doctor immediately. Stop taking CELSENTRI.

Common side effects (may affect up to 1 in 10 people):
• diarrhoea, feeling sick, stomach ache, flatulence, indigestion
• headache, problems sleeping, depression
• rash, feeling weak, anaemia
• loss of appetite
• increase of liver enzymes; these can be seen in the results of blood tests and can be a sign of reduced function or damage of the liver.

Uncommon side effects (may affect up to 1 in 100 people):
• pneumonia, fungal infection of the oesophagus
• fits
• an increase in a substance which may be found in blood tests when muscles are inflamed or damaged
• kidney failure, passing protein in urine

Rare side effect (may affect up to 1 in 1000 people):
• reduction in number of blood cells
• chest pain caused by reduced blood flow to the heart
• decrease in the size of muscle
• some types of cancer like cancer of the oesophagus and bile duct
• feeling dizzy, faint or light headed when standing up

Other side effects of combination therapy for HIV

You may have problems with your bones
Some people taking combination therapy for HIV develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone.
The frequency is unknown, but you may be more likely to get this condition if you:
• have been taking combination therapy for a long time
• are also taking anti-inflammatory medicines called corticosteroids
• drink alcohol
• have a very weak immune system
• are overweight

Signs to look out for include:

• stiffness in the joints
• aches and pains (especially in the hip, knee or shoulder)
• difficulty moving

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CELSENTRI

Keep out of the sight and reach of children.

Do not use CELSENTRI after the expiry date which is stated on the carton, blister or bottle label. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What CELSENTRI contains

• The active ingredient in CELSENTRI is maraviroc. Each film-coated tablet contains either 150 mg or 300 mg of maraviroc.

• The other ingredients are:

  Tablet core: cellulose microcrystalline, calcium hydrogen phosphate anhydrous, sodium starch glycolate, magnesium stearate

  Film-coat: poly (vinyl alcohol), titanium dioxide, macrogol 3350, talc, soya lecithin, indigo carmine aluminium lake (E132).

What CELSENTRI looks like and contents of the pack

CELSENTRI film-coated tablets are blue coloured with “MVC 150” or “MVC 300”.

CELSENTRI 150 mg and 300 mg film-coated tablets are supplied in bottles of 180 tablets or in blister packs of 30, 60, 90 film-coated tablets and multipacks containing 180 (2 packs of 90) film-coated tablets.

Not all pack sizes may be marketed in all countries.
Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:

ViiV Healthcare UK Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GS United Kingdom.

The Manufacturer is:

Pfizer Manufacturing Deutschland GmbH, Betriebsstätte Freiburg, Mooswaldallee 1, 79090 Freiburg, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
ViiV Healthcare sprl/bvba .
Tél/Tel: + 32 (0) 10 85 65 00

**Lietuva**
GlaxoSmithKline Lietuva UAB
Tel: + 370 5 264 90 00
info.lt@gsk.com

**България**
ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

**Luxembourg/Luxemburg**
ViiV Healthcare sprl/bvba
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 65 00

**Česká republika**
GlaxoSmithKline s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

**Magyarország**
GlaxoSmithKline Kft.
Tel.: + 36 1 225 5300

**Danmark**
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

**Malta**
GlaxoSmithKline Malta
Tel: + 356 21 238131

**Deutschland**
ViiV Healthcare GmbH
Tel.: + 49 (0)89 203 0038-10
viiv.med.info@viivhealthcare.com

**Nederland**
ViiV Healthcare BV
Tel: + 31 (0)30 6986060
contact-nl@viivhealthcare.com

**Eesti**
GlaxoSmithKline Eesti OÜ
Tel: + 372 6676 900
estonia@gsk.com

**Norge**
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

**Ελλάδα**
GlaxoSmithKline A.E.B.E.
Τηλ.: + 30 210 68 82 100

**Österreich**
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

**España**
Laboratorios ViiV Healthcare, S.L.
Tel: + 34 902 051 260
es-ci@viivhealthcare.com

**Polska**
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000
France
ViiV Healthcare SAS
Tél.: + 33 (0)1 39 17 6969
Infomed@viivhealthcare.com

Portugal
VIIVHIV HEALTHCARE, UNIPESSOAL, LDA.
Tel: + 351 21 094 08 01
viiv.fi.pt@viivhealthcare.com

Hrvatska
GlaxoSmithKline d.o.o.
Tel: + 385 1 6051 999

România
GlaxoSmithKline (GSK) S.R.L.
Tel: + 4021 3028 208

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 (0)1 280 25 00
medical.x.si@gsk.com

Ísland
Vistor hf.
Sími: + 354 535 7000

Slovenská republika
GlaxoSmithKline Slovakia s. r. o.
Tel: + 421 (0)2 48 26 11 11
recepcia.sk@gsk.com

Italia
ViiV Healthcare S.r.l.
Tel: + 39 (0)45 9212611

gsceyprus@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30
Finland.tuoteinfo@gsk.com

Κύπρος
GlaxoSmithKline (Cyprus) Ltd
Tηλ: + 357 22 39 70 00
gskcyprus@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

Latvija
GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

United Kingdom
ViiV Healthcare UK Ltd
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: