PRODUCT MONOGRAPH

[Pr]CELSENTRI

maraviroc

Tablets 150 and 300 mg

CCR5 antagonist

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Table of Contents

[Pr]CELSENTRI
(maraviroc)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	• Film-coated tablets; 150, 300 mg maraviroc	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CELSENTRI (maraviroc), in combination with other antiretroviral agents, is indicated for adult patients infected with CCR5-tropic HIV-1.

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

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

- CELSENTRI is not recommended in patients infected with dual/mixed- or CXCR4-tropic HIV-1; efficacy in this patient population was not demonstrated in a Phase 2 Study.

Pediatrics (<18 years of age): The safety and efficacy of CELSENTRI have not been established in pediatric patients.

Geriatrics (>65 years of age): In general, caution should be exercised when administering CELSENTRI in elderly patients (see **WARNINGS AND PRECAUTIONS, Special Populations)**.

CONTRAINDICATIONS

CELSENTRI is contraindicated in patients with hypersensitivity to maraviroc or any component of this medication. For a complete listing, see the Dosage Forms,

Composition and Packaging section of this product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hepatotoxicity has been reported with CELSENTRI use. A systemic allergic reaction, including pruritic rash, eosinophilia or elevated IgE may occur prior to the development of hepatotoxicity. Patients with signs or symptoms of acute hepatitis or allergic reaction should be evaluated immediately and, if required, discontinuation of CELSENTRI treatment should be strongly considered. (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and ADVERSE REACTIONS).

General

Physicians should ensure that appropriate dose adjustment of CELSENTRI is made when CELSENTRI is coadministered with CYP3A4 inhibitors and/or inducers since maraviroc concentrations and its therapeutic effects may be affected (see **DRUG INTERACTIONS**).

Using a current sample from the patient, tropism testing should be performed prior to initiation of therapy using a highly sensitive tropism assay; however tropism assays may not detect low levels of dual/mixed or CXCR4-tropic variants. CELSENTRI did not demonstrate efficacy in a Phase 2 study of patients infected with dual/mixed or CXCR4-using virus (see **CLINICAL TRIALS**).

Ability to perform tasks that require Judgement, Motor or Cognitive Skills
There have been no studies to investigate the effect of CELSENTRI on the ability to perform tasks that require judgement, motor or cognitive skills. However, patients should be informed about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking CELSENTRI. If affected, patients should avoid potentially hazardous tasks such as driving or operating machinery.

Hepatic/Biliary/Pancreatic

Cases of hepatotoxicity and hepatic failure, some of them with allergic features, have been reported in association with CELSENTRI. An increase in hepatic adverse reactions with CELSENTRI 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. The overall incidence of hepatic adverse events and ACTG Grade 3/4 liver function test abnormalities in treatment-naïve patients was similar between CELSENTRI and efavirenz (see **ADVERSE REACTIONS).** In addition, similar cases

have been identified in the CELSENTRI postmarketing surveillance program (see **ADVERSE REACTIONS**).

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

Caution should be used when administering CELSENTRI to patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B and/or C. There are limited data in these patients (see **ADVERSE REACTIONS**, **Patients Co-infected with Hepatitis B and/or Hepatitis C Virus**). If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered.

The safety and efficacy of CELSENTRI have not been specifically studied in patients with significant underlying liver disorders. However, drug levels were increased in patients with moderate hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Cardiovascular

CELSENTRI should be used with caution in patients with a history of cardiovascular disease or who are at risk for cardiovascular events. Cases of myocardial ischemia and myocardial infarction were reported in 11 subjects (1.3%) receiving CELSENTRI in Phase 3 studies in treatment-experienced studies [total exposure 609 patient-years (300 on CELSENTRI once daily + 309 on CELSENTRI twice daily)]. These events mostly occurred in subjects with pre-existing cardiac disease or cardiac risk factors, which confounded the assessment of CELSENTRI causality.

In the Phase 2b/3 study in treatment-naïve patients, 3 subjects (0.8%) who received CELSENTRI had events related to ischemic heart diseases and 5 subjects (1.4%) who received efavirenz had such events (total exposure 506 and 508 patient-years for CELSENTRI and efavirenz, respectively).

Postural Hypotension and Syncope

CELSENTRI-related cases of postural hypotension and syncope were reported during Phase 3 studies in HIV-infected patients (treatment-naïve and treatment-experienced) who received the drug at the recommended dose (see **ADVERSE REACTIONS**). At dosing higher than the recommended dose, CELSENTRI-related cases of postural hypotension and syncope were observed during Phase 1 studies in healthy volunteers.

Patients with severe renal impairment or end-stage renal disease (ESRD) are at an increased risk of postural hypotension due to increased maraviroc exposure. Patients with impaired renal function frequently have cardiovascular co-morbidities and therefore are at an increased risk of cardiovascular adverse events triggered by postural

hypotension. The use of CELSENTRI in patients with severe renal impairment or ESRD should only be considered when no alternative treatment options are available, and they are not receiving a concomitant potent CYP3A inhibitor or inducer. If patients with severe renal impairment or ESRD experience any symptoms of postural hypotension while taking CELSENTRI 300 mg twice daily, the dose should be reduced to 150 mg twice daily (see **DOSAGE AND ADMINISTRATION**).

Caution should be used when administering CELSENTRI in patients who have a history of or risk factors for postural hypotension or patients on concomitant medications known to lower blood pressure.

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including CELSENTRI. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium-complex* (MAC), cytomegalovirus (CMV), *Pneumocystis jirovecii pneumonia* (PCP), and *tuberculosis* (TB)], which may necessitate further evaluation and treatment.

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

Potential Risk of Infection and Malignancy

The antagonistic action of CELSENTRI on the CCR5 co-receptor may impair immune function and potentially increase the risk of developing infections and/or malignancy.

The rates of certain infections (upper respiratory tract and Herpes virus) were higher in subjects receiving CELSENTRI, while others (pneumonia) were lower as compared with those in patients on placebo in Phase 3 treatment-experienced studies (see **ADVERSE REACTIONS**). The overall incidence and severity of infection and AIDS-defining category C infections were similar in the CELSENTRI and placebo treatment arms.

In the Phase 2b/3 study in treatment-naïve patients, the incidence of AIDS-defining Category C events when adjusted for exposure was 1.8 for CELSENTRI compared with 2.4 for efavirenz per 100 patient-years of exposure.

Patients receiving CELSENTRI should be carefully monitored for symptoms of infection.

There were no increased reports of malignancies in subjects treated with CELSENTRI during Phase 3 studies. Long-term follow-up is required to assess whether CELSENTRI increases the risk of malignancy. The exposure-adjusted rate for malignancies per 100 patient-years of exposure in treatment-experienced studies was 4.6 for CELSENTRI compared with 9.3 on placebo. In treatment-naïve patients, the rates were 1.0 and 2.4 per 100 patient-years of exposure for CELSENTRI and efavirenz, respectively.

Renal

Renal Impairment

CELSENTRI should not be used in patients with severe renal impairment or ESRD (CLcr <30 mL/min) who are taking potent CYP3A inhibitors or inducers. No studies have been performed in subjects with severe renal impairment or ESRD co-treated with potent CYP3A inhibitors or inducers. Hence, no dose of CELSENTRI can be recommended (see **DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Patients with impaired renal function frequently have cardiovascular co-morbidities and therefore are at an increased risk of cardiovascular adverse events triggered by postural hypotension. The use of CELSENTRI in patients with severe renal impairment or ESRD should only be considered when no alternative treatment options are available, and they are not receiving a concomitant potent CYP3A inhibitor or inducer (see **DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Recommended doses of CELSENTRI for patients with impaired renal function (CLcr ≤ 80 mL/min) are based on the results of a pharmacokinetic study conducted in healthy subjects with various degrees of renal impairment. The pharmacokinetics of maraviroc in subjects with mild and moderate renal impairment was similar to that in subjects with normal renal function (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 7 provides dosing interval adjustment guidelines for patients with renal impairment with and without coadministered potent CYP3A4 inhibitors (see **DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Severe Skin and Hypersensitivity Reactions

Hypersensitivity reactions including severe and potentially life threatening events have been reported in patients taking maraviroc, in most cases concomitantly with other drugs associated with these reactions. These reactions were characterised by features including rash, constitutional findings, and sometimes organ dysfunction and hepatic failure. Cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported (see **ADVERSE REACTIONS**). Discontinue maraviroc and other suspect agents immediately if signs or

symptoms of severe skin or hypersensitivity reactions develop. Delay in stopping maraviroc treatment or other suspect drugs after the onset of rash may result in a life-threatening reaction. Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated.

Special Populations

Pregnancy, Fertility and Reproduction: CELSENTRI has not been studied in pregnant women. CELSENTRI should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus.

There are no data on the effects of maraviroc on human fertility. Embryofetal development studies in rats and rabbits revealed no evidence of harm to the fetus from maraviroc. Pre- and post-natal developmental studies showed a slight increase in motor activity in male offspring at both weaning and as adults at the high dose, while no effects were seen in female offspring. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of maraviroc (see **TOXICOLOGY, Fertility and Reproduction**).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including CELSENTRI, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:
http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

Nursing Mothers: It is recommended that HIV-infected women not breast-feed their infants under any circumstances to avoid the transmission of HIV infection. Studies in lactating rats indicate that maraviroc is extensively excreted into rat milk. It is unknown whether maraviroc is excreted into human milk. Mothers should be instructed not to breast-feed if they are receiving CELSENTRI because of both the potential for HIV transmission and any possible undesirable effects in nursing infants.

Pediatrics (<18 years of age): The pharmacokinetics, safety and efficacy of maraviroc in pediatric patients have not been established. Therefore, maraviroc should not be used in this patient population.

Geriatrics (>65 years of age): There were insufficient numbers of subjects aged 65 and over in the clinical studies to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering CELSENTRI in elderly patients, also reflecting the greater frequency of decreased hepatic and renal function, of concomitant disease and other drug therapy.

Gender and Race: Population pharmacokinetic analysis of pooled Phase 1/2a data indicated that while gender did not affect pharmacokinetics, a typical Asian subject showed a 26.5% higher exposure than a typical Caucasian. However, a study designed to

evaluate pharmacokinetic differences between Caucasians and Singaporeans showed no differences.

Population pharmacokinetic modeling of data from the treatment-naïve patients study (MERIT) showed a 17.5% higher average concentration in the typical Black subject compared with the typical Caucasian subject. The typical female subject had a 13.7% higher average concentration compared with the typical male. In a Phase 1 study in healthy subjects, blacks were shown to have higher maraviroc exposures (17%) as compared to Caucasians with the same CYP3A5 genotype (No CYP3A5*1 alleles).

The maraviroc exposure differences are small and therefore unlikely to pose efficacy, safety or tolerability risks. Dosage adjustment is not necessary based on gender or race.

Patients co-infected with Hepatitis B and/or Hepatitis C virus: There is limited safety and efficacy data in patients co-infected with Hepatitis B and/or Hepatitis C virus. CELSENTRI should be used in caution with this population.

Dose Adjustment: Physicians should ensure that appropriate dose adjustment of CELSENTRI is made when CELSENTRI is co-administered with potent CYP3A4 inhibitors and/or inducers since concentrations of CELSENTRI and its therapeutic effects may be affected (see **DRUG INTERACTIONS** or **DOSAGE AND ADMINISTRATION**). Please also refer to the respective product monographs of the other medicinal products used in combination with CELSENTRI.

Monitoring and Laboratory Tests

Appropriate hepatic laboratory functional tests including ALT, AST, bilirubin, and GGT should be conducted prior to initiating therapy with CELSENTRI and at other time points during treatment as clinically indicated. Hepatic laboratory parameters should be obtained in any patient who develops rash, or signs/symptoms of hepatitis, or allergic reaction.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile of CELSENTRI is based on 1374 HIV-1 infected patients who received at least 1 dose of CELSENTRI during three 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 at the recommended dose 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 virus.

The median duration of therapy with CELSENTRI for subjects in these studies was 48 weeks, with the total exposure on CELSENTRI twice daily at 309 patient-years versus 111 patient-years on placebo.

During these 2 studies, approximately 50.5% of patients receiving CELSENTRI reported at least 1 treatment-related AE. The most frequently reported adverse reactions at the recommended dose, regardless of the incidence compared with optimized background therapy (OBT) alone, were diarrhea, nausea and headache.

Most of the adverse events reported were judged to be mild to moderate in severity. The most commonly reported grade 3 or 4 adverse events in subjects receiving 300 mg of CELSENTRI twice daily in these two studies were liver function analyses (5.16%) and febrile disorders (2.58%). All other grade 3 or 4 adverse events were reported in less than 2% of the subjects.

Eighty-eight subjects (20.7%) receiving 300 mg twice daily reported at least 1 SAE with 13 (3.1%) subjects with an SAE considered at least possibly treatment-related: elevated transaminases, generalised rash, mucormycosis, myositis, increased nausea and vomiting, syncope and pancytopaenia, diarrhea, syncope and orthostatic hypotension, increased hepatic enzymes, pneumonia, esophageal carcinoma, loss of consciousness, hepatic failure, bile duct cancer, and metastases to liver, bone and peritoneum.

In the two treatment-experienced studies, the rates of discontinuation due to adverse events were 4.5% in subjects receiving CELSENTRI twice daily + OBT compared with 5.3% in those receiving placebo + OBT. Adverse events that led to discontinuations in 2 or more patients are: LFTs increased/abnormal (3 on CELSENTRI twice daily), abdominal pain upper (1on CELSENTRI twice daily), rash (1 on CELSENTRI twice daily), and pyrexia (1 on CELSENTRI twice daily). In the treatment-naïve study, the rates of permanent discontinuation were lower in patients receiving CELSENTRI 300 mg twice daily compared with those receiving efavirenz.

Dizziness or postural dizziness occurred in 8.4% and 8.2% on CELSENTRI and placebo, respectively, with 2 subjects (0.5%) on CELSENTRI permanently discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) permanently discontinuing therapy due to dizziness.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Studies in Treatment-Experienced Patients (MOTIVATE 1 and MOTIVATE 2)

Assessment of treatment-emergent adverse events is based on the pooled data from 2 studies in treatment-experienced patients with CCR5-tropic HIV-1. The median duration

of therapy was 48 weeks for patients receiving CELSENTRI and 21 weeks for patients receiving placebo. The population was 89% male and 84% white, with mean age of 46 years (range 17-75 years). Patients received dose equivalents of 300 mg maraviroc once or twice daily.

The most common adverse events reported with twice daily therapy with CELSENTRI with frequency rates higher than placebo, regardless of causality, were cough, pyrexia, upper respiratory tract infections, rash and dizziness. In these 2 studies, the rates of discontinuation due to adverse events were 4.5% in patients receiving CELSENTRI twice daily + OBT compared with 5.3% in those receiving placebo + OBT. Most of the adverse events reported were judged to be mild to moderate in severity. The data described in Table 1 occurred with twice daily dosing of CELSENTRI.

The total number of subjects reporting infections were 233 (54.7%) and 84 (40.2%) in the group receiving CELSENTRI twice daily and the placebo group, respectively. The differences between the group receiving CELSENTRI and the placebo group may be explained by the longer treatment duration in the arm receiving CELSENTRI. The exposure-adjusted frequency (rate per 100 patient-years) of these events was similar: 133 for both CELSENTRI and placebo, respectively. Dizziness or postural dizziness occurred in 8.4% and 8.2% on CELSENTRI and placebo, respectively, with 2 patients (0.5%) on CELSENTRI permanently discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 patient on placebo (0.5%) permanently discontinuing therapy due to dizziness.

Treatment-emergent adverse events, regardless of causality, from Studies in treatment-experienced patients are summarized in Table 1. Events occurring in ≥ 2% of subjects treated with CELSENTRI twice daily and at a numerically greater incidence than placebo are included.

Table 1 Percentage of Patients at Twice Daily Dosing with Treatment-Emergent Adverse Events (All Causality) (≥ 2% on CELSENTRI +OBT[b] and at Higher Rate Compared with Placebo + OBT) Pooled Studies Week 48 in Treatment-Experienced Patients (MOTIVATE 1 and MOTIVATE 2)

	CELSENTRI + OBT Twice Daily[a] N=426 (%)	Placebo + OBT N=209 (%)
EYE DISORDERS		
Conjunctival infections, irritations, and inflammations	2.3	1.4
Ocular infections, inflammations, and associated manifestations	2.1	1.0
GASTROINTESTINAL DISORDERS		
Constipation	5.9	2.9
Stomatitis, ulceration	2.3	1.9

	CELSENTRI + OBT Twice Daily[a] N=426 (%)	Placebo + OBT N=209 (%)
Gastrointestinal signs and symptoms	2.3	1.9
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Pyrexia	12.9	8.6
Pain and discomfort	3.8	2.9
Edema	3.3	2.9
General signs & symptoms	3.1	2.4
Body temperature perception	2.1	1.9
INFECTIONS AND INFESTATIONS[c]		
Upper respiratory tract infection	22.8	12.9
Herpes Infection	7.7	4.3
Sinusitis	6.8	3.3
Bronchitis	6.6	4.8
Folliculitis	3.8	1.9
Pneumonia	2.3	5.3
Anogenital warts	2.1	1.4
Influenza	2.1	0.5
Otitis media	2.1	0.5
METABOLISM AND NUTRITION DISORDERS		
Appetite disorders	7.5	6.7
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Joint-related signs and symptoms	6.8	2.9
Muscle pains	3.1	0.5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED		
Skin neoplasms benign	3.1	1.4
NERVOUS SYSTEM DISORDERS		
Dizziness/postural dizziness	8.7	8.1
Paresthesias and dysesthesias	4.9	2.9
Sensory abnormalities	4.0	1.4
Disturbances in consciousness	3.8	2.9
Peripheral neuropathies	3.8	2.9
PSYCHIATRIC DISORDERS		
Disturbances in initiating and maintaining sleep	7.7	5.3
Depressive disorders	4.2	2.9
Anxiety Disorders	3.5	3.3

	CELSENTRI + OBT Twice Daily[a] N=426 (%)	Placebo + OBT N=209 (%)
RENAL AND URINARY DISORDERS		
Bladder and urethral symptoms	4.9	1.4
Urinary tract signs and symptoms	2.8	1.4
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Coughing and associated symptoms	13.8	5.3
Upper respiratory tract signs and symptoms	6.1	3.3
Nasal congestion and inflammations	4.2	2.9
Breathing abnormalities	3.5	2.4
Brochospasm and obstruction	2.1	1.9
Paranasal sinus disorders	2.8	0.5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	10.8	5.3
Apocrine and eccrine gland disorders	4.9	3.8
Dermal and epidermal conditions	4.5	4.3
Pruritus	3.8	1.9
Lipodystrophies	3.3	0.5
Erythemas	2.3	1.0
VASCULAR DISORDERS		
Vascular hypertensive disorders	3.1	1.9

[a] 300 mg dose equivalent
[b] OBT: optimized background therapy
[c] **MedDRA High Level Terms are shown in order to group related terms for all disorders except Infections and Infestations, which shows MedDRA Preferred Terms with the following related terms grouped:**
Bronchitis: bronchitis, acute bronchitis, bacterial bronchitis
Herpes simplex infection: genital Herpes, Herpes simplex, Herpes virus, Herpes ophthalmic, oral Herpes, proctitis Herpes,
Influenza: Influenza, influenza-like illness
Pneumonia: Pneumonia, lobar pneumonia, pneumonia bacterial, bronchopneumonia
Sinusitis: sinusitis, acute sinusitis, chronic sinusitis, sinobronchitis
Upper Respiratory Tract Infection: upper respiratory tract infection, laryngitis, laryngopharyngitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, viral respiratory tract infection

Experience after 48 weeks

The MOTIVATE studies were unblinded after Week 48, followed by an open-label phase to Week 96 and extended beyond Week 96 with an open-label observational phase for a total study duration of 5 years. The median duration of therapy was 511 days for patients receiving CELSENTRI and 144 days for patients receiving placebo. Safety results including the incidence of death, AIDS-defining events, hepatic failure, MI/cardiac

ischemia, malignancies, rhabdomyolysis, and other serious infectious events were consistent with those observed at earlier time points.

Laboratory Abnormalities

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

Table 2 Maximum Shift in Laboratory Test Values (Without Regard to Baseline) Incidence ≥ 2% of Grade 3-4 Abnormalities (ACTG Criteria) Studies in Treatment-Experienced Patients (MOTIVATE 1 and MOTIVATE 2) Pooled Analysis, 48 Weeks

Laboratory Parameter Preferred Term, %	Limit	CELSENTRI Twice daily + OBT N =421[a] %	Placebo + OBT N =207[a] %
Aspartate aminotransferase	> 5.0x ULN	4.8	2.9
Alanine aminotransferase	> 5.0x ULN	2.6	3.4
Total bilirubin	> 2.5x ULN	5.5	5.3
Amylase	> 2.0x ULN	5.7	5.8
Lipase	> 2.0x ULN	4.9	6.3
Absolute neutrophil count	< 750/mm^3	4.3	2.4

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

Study in Treatment-naïve Patients (MERIT)

Treatment-emergent Adverse Events

The median duration of therapy with CELSENTRI for treatment-naïve subjects was 672 days, with the total exposure on CELSENTRI twice daily at 506 patient-years versus 508 patient-years in the efavirenz treatment group. The most common adverse events of at least moderate severity (incidence > 5%) in a double-blind, comparative, controlled study in which 721 treatment-naïve patients received CELSENTRI 300 mg twice daily (N=360) or efavirenz 600 mg once daily (N=361) in combination with zidovudine/lamivudine (COMBIVIR) for 96 weeks were gastrointestinal events, upper respiratory tract infections, asthenia, and headaches.

Treatment-emergent adverse events that occurred in ≥ 2% of patients in either the CELSENTRI or efavirenz treatment groups and with at least moderate severity (Grades 2-4) are summarized in Table 3.

Table 3 Percentage of Subjects with Selected Treatment-Emergent Adverse Events (All Causality, ≥ 2% in Either Treatment Group and of At Least Moderate Severity). 96Weeks Data in Treatment-naïve Patients (MERIT)

	CELSENTRI 300 mg Twice Daily + Zidovudine/Lamivudine	EFAVIRENZ 600 mg Once Daily + Zidovudine/Lamivudine
	N=360 (%)	N=361 (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemias	4.0	2.0
Neutropenias	3.0	3.0
EAR AND LABYRINTH DISORDERS		
Inner ear signs and symptoms	0.6	2.0
GASTROINTESTINAL DISORDERS		
Nausea and vomiting symptoms	13.0	10.0
Diarrhea	5.0	7.0
Gastrointestinal and abdominal pains	6.0	7.0
Flatulence, bloating, and distention	3.0	2.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Asthenic conditions	10.0	8.0
Febrile disorders	3.0	2.0
INFECTIONS AND INFESTATIONS ***		
Upper respiratory tract infection	11.0	7.0
Bronchitis	8.0	4.0
Influenza	4.0	3.0
Herpes simplex infection	2.0	1.0
Bacterial infections	2.0	0.3
Sinusitis	3.0	2.0
Abdominal and GI infections	3.0	4.0
Herpes zoster/varicella	3.0	3.0
Pneumonia	3.0	2.0
Skin structures and soft tissue infections	1.0	3.0
Treponema infections	0.8	2.0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Non-site specific injuries	0.6	2.0
METABOLISM AND NUTRITION DISORDERS		
Appetite disorders	2.0	3.0

	CELSENTRI 300 mg Twice Daily + Zidovudine/Lamivudine	EFAVIRENZ 600 mg Once Daily + Zidovudine/Lamivudine
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Musculoskeletal and connective tissue signs and symptoms	4.0	6.0
Joint related signs and symptoms	2.0	1.0
NERVOUS SYSTEM DISORDERS		
Headaches	8.0	9.0
Neurological signs/symptoms	3.0	10.0
Disturbances in consciousness	3.0	3.0
Mental impairment (excl dementia and memory loss)	0.3	2.0
PSYCHIATRIC DISORDERS		
Disturbances in initiating and maintaining sleep	4.0	5.0
Parasomnias	2.0	5.0
Depressive disorders	3.0	4.0
Anxiety symptoms	2.0	2.0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Coughing and associated symptoms	2.0	2.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	2.0	6.0
Dermatitis and eczema	0.6	2.0
Pruritus	0.6	2.0
VASCULAR DISORDERS		
Vascular hypertensive disorders	2.0	2.0

Experience after 48 weeks
The MERIT study was unblinded after Week 96 and extended beyond Week 96 with an open-label observational phase for a total study duration of 5 years. Safety results were consistent with those observed at earlier time points.

Laboratory Abnormalities

Table 4 shows the treatment-emergent Grade 3-4 laboratory abnormalities that occurred in ≥2% of subjects in either treatment arm.

Table 4 Maximum Shift in Laboratory Test Values (Without Regard to Baseline) Incidence ≥ 2% of Grade 3-4 Abnormalities (ACTG Criteria) 96 Weeks Data in Treatment-Naïve Patients (MERIT Study)

Laboratory Parameter Preferred Term	Limit	CELSENTRI 300 mg Twice Daily + Zidovudine/Lamivudine N =353[a] %	Efavirenz 600 mg Once Daily + Zidovudine/Lamivudine N =350[a] %
Aspartate aminotransferase	>5.0x ULN	4.0	4.0
Alanine aminotransferase	>5.0x ULN	3.9	4.0
Creatine kinase	>10.0 x ULN	3.9	4.8
Amylase	>2.0x ULN	4.3	6.0
Absolute neutrophil count	<750/mm^3	5.7	4.9
Hemoglobin	<7.0 g/dL	2.9	2.3

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

Less Common Clinical Trial Adverse Events

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

Blood and Lymphatic System Disorders: bone marrow failure, marrow depression, coagulopathy, leukopenia, lymphadenopathy, pancytopenia

Cardiac Disorders: Unstable angina, acute cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, myocardial ischemia

Ear and Labyrinth Disorders: deafness

Eye Disorders: cataract, eyelid ptosis, glaucoma, retinal tear

Gastrointestinal Disorders: hemorrhagic diarrhea, pancreatitis, rectal hemorrhage, small intestinal obstruction, esophageal varices

Hepatobiliary Disorders: Hepatic cirrhosis, hepatic failure, cholestatic jaundice, hypertransaminasemia, jaundice, portal vein thrombosis, increased-gamma glutamyltransferase

Infections and Infestations: *Clostridium difficile* colitis, meningitis, septic shock, endocarditis, infective myositis

Metabolism and Nutrition Disorders: diabetes mellitus, tetany, weight decreased

Musculoskeletal and Connective Tissue Disorders: Myositis, osteonecrosis, rhabdomyolysis, blood creatine kinase (CK) increased, muscle spasms, pain in extremity, neck pain

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): Abdominal neoplasm, anal cancer, anaplastic large cell lymphomas T- and null-cell types, bile duct neoplasms malignant, endocrine neoplasms malignant and unspecified, basal cell carcinoma, Bowen's disease, lipoma, cholangiocarcinoma, diffuse large B-cell lymphoma, lymphoma, metastases to liver, esophageal carcinoma, seborrheic keratosis, nasopharyngeal carcinoma, squamous cell carcinoma, squamous cell carcinoma of skin, sweat gland tumor, tongue neoplasm (malignant stage unspecified)

Nervous System Disorders: Cerebrovascular accident, convulsions, facial palsy, hemianopia, loss of consciousness, visual field defect, areflexia, epilepsy, nervous system disorder, neuritis, Parkinsonism, petit mal epilepsy, polyneuropathy, tremor (excluding congenital)

Psychiatric Disorders: hallucination, auditory hallucination, suicidal ideation

Renal and Urinary Disorders: oliguria, polyuria, renal failure, acute renal failure

Respiratory, Thoracic and Mediastinal Disorders: hemoptysis, respiratory distress, respiratory failure

Skin and Subcutaneous Tissue Disorders: exfoliative dermatitis, purpura, alopecia

Vascular Disorders: aortic arteriosclerosis, peripheral embolism, vasculitis, venous thrombosis

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus

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

Post-Marketing Adverse Drug Reactions

The following events have been identified during post-approval use of CELSENTRI. Because they are reported voluntarily from a population of unknown size, estimates of frequency or causal relationship with CELSENTRI cannot be established.

Gastrointestinal Disorders: Dysphagia, swollen tongue.

Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps): Myelodysplastic syndrome

Pregnancy, Puerperium and Perinatal Conditions: Abortion spontaneous

Severe Skin and Hypersensitivity Reactions: Severe hypersensitivity reactions have been reported. These included drug rash with eosinophilia and systemic symptoms (DRESS) and severe cutaneous reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), lipodystrophy acquired

Hepatobiliary Disorders: Hepatotoxicity and hepatic failure with allergic features

Immune System: Immune Reconstitution Inflammatory Syndrome (see **WARNINGS AND PRECAUTIONS, Immune**)

Postural Hypotension: Postural hypotension that resulted in syncope has been reported.

DRUG INTERACTIONS

Overview

Maraviroc is metabolized by cytochrome P450 CYP3A4, and is also a substrate for P-glycoprotein, organic anion-transporting polypeptide (OATP) 1B1 and multidrug resistance-associated protein (MRP)2 *in vitro*. The pharmacokinetics of Maraviroc are likely to be modulated by inhibitors and inducers of CYP3A and P-gp, and may be modulated by inhibitors of OATP1B1 and MRP2. Co-administration of CELSENTRI (maraviroc) with medicinal products that induce those enzymes and transporters may decrease maraviroc concentrations and reduce its therapeutic effects. Co-administration of CELSENTRI with medicinal products that inhibit those enzymes and transporters may increase maraviroc plasma concentrations. Dose adjustment of CELSENTRI is recommended when CELSENTRI is co-administered with potent CYP3A4 inhibitors and/or inducers (see Table 5).

Drug-Drug Interactions

Effect of Maraviroc on the Pharmacokinetics of Concomitant Drugs
Maraviroc is unlikely to inhibit the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes or metabolized by OATP1B1 or MRP2 because it does not inhibit any of the seven major cytochrome P450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) or transported by OATP1B1or MRP2 because maraviroc did not inhibit activity of those enzymes and transporters at clinically relevant concentrations *In Vitro* (IC_{50} > 30 μM). Maraviroc does not induce CYP1A2 *In Vitro*. Additionally, *In Vitro* studies have shown that maraviroc is not a substrate for, and does not inhibit, any of the major renal uptake inhibitors (organic anion transporter [OAT]1, OAT3, organic cation transporter [OCT]2, novel organic cation transporter [OCTN]1, and OCTN2) at clinically relevant concentrations.

Drug interaction studies were performed with maraviroc and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions (see Table 5). Maraviroc had no effect on the pharmacokinetics of zidovudine or lamivudine, suggesting no interactions with renal clearance or non-P450 metabolism. Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinyloestradiol and levonorgestrel, no effect on the urinary 6β-hydroxycortisol/cortisol ratio, suggesting no induction of CYP3A4 *In Vivo*. Despite lack of *In Vitro* inhibition of CYP2D6, maraviroc caused an increase in debrisoquine metabolic ratio at 600 mg once daily although not at 300 mg twice daily.

Maraviroc inhibits P-glycoprotein *In Vitro* (IC_{50} is 183 μM). However. maraviroc does not significantly affect the pharmacokinetics of digoxin *In Vivo*, suggesting that maraviroc neither inhibits nor induces the activity of P-glycoprotein.

Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc
Maraviroc is a substrate of CYP3A4 and Pgp and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters. The CYP3A4/Pgp inhibitors ketoconazole, lopinavir/ritonavir, ritonavir, darunavir/ritonavir, saquinavir/ritonavir and atazanavir ± ritonavir all increased the C_{max} and AUC of maraviroc (see Table 5). The CYP3A4 inducers rifampin, efavirenz and etravirine decreased the C_{max} and AUC of maraviroc (see Table 5).

Tipranavir/ritonavir (net CYP3A4 inhibitor/Pgp inducer) did not affect the steady state pharmacokinetics of maraviroc. Substrates and inhibitors of renal clearance (cotrimoxazole and tenofovir) did not affect the pharmacokinetics of maraviroc (see Table 5).

Table 5 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction

Drug Class: Drug Name	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Clinical Comment
HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):		
Efavirenz 600 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↓ 0.55 (0.49, 0.62) Maraviroc C_{max}: ↓ 0.49 (0.38, 0.63) Maraviroc C_{min}: ↓ 0.49 (0.38, 0.63) Efavirenz concentrations not measured, no effect is expected. N = 12	Lower exposure could potentially lead to treatment failure, and therefore the dose of CELSENTRI should be increased to 600 mg BID with efavirenz in the absence of a potent CYP3A4 inhibitor.
Nevirapine 200 mg BID (maraviroc 300 mg single dose)	Maraviroc AUC_{12}: ↔ compared to historical controls Maraviroc C_{max}: ↑ compared to historical controls Maraviroc C_{min}: ND Nevirapine concentrations not measured, no effect is expected.	The combination of CELSENTRI and nevirapine, lamivudine and tenofovir can be used without dose adjustments.
Delavirdine	Not studied	Population pharmacokinetics in HIV-infected patients (n=10) determined that delavirdine behaved as a CYP3A4 inhibitor, and increased maraviroc concentrations. Therefore, the CELSENTRI dose should be decreased to 150 mg BID if used with delavirdine.
Etravirine 200 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↓ 0.47 (0.38, 0.58) Maraviroc C_{max}: ↓ 0.40 (0.28, 0.57) Maraviroc C_{min}: ↓ 0.47 (0.38, 0.58) Etravirine AUC_{12}: ↔ 1.06 (0.99, 1.14) Etravirine C_{max}: ↔ 1.05 (0.95, 1.17) Etravirine C_{min}: ↔ 1.08 (0.98, 1.19) N = 14	The CELSENTRI dose should be increased to 600 mg BID with etravirine in the absence of a PI (except tipranavir/ritonavir) or other potent CYP3A4 inhibitor.
Nucleoside Reverse Transcriptase Inhibitors (NRTI's):		
Tenofovir 300 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↔ 1.03 (0.98, 1.09) Maraviroc C_{max}: ↔ 1.04 (0.90, 1.19) Maraviroc C_{min}: ↔ 1.06 (0.94, 1.20) Tenofovir concentrations not measured, no effect is expected. N = 12	CELSENTRI 300 mg BID dose can be used.
Lamivudine 150 mg BID (maraviroc 300 mg BID)	Lamivudine AUC_{12}: ↔ 1.14 (0.98, 1.32) Lamivudine C_{max}: ↔ 1.16 (0.88, 1.54) Lamivudine C_{min}: ↑ 1.35 (1.14, 1.61) Maraviroc concentrations not measured, no effect is expected. N = 12	CELSENTRI 300 mg BID dose can be used.
Zidovudine 300 mg BID (maraviroc 300 mg	Zidovudine AUC_{12}: ↔ 0.98 (0.79, 1.22) Zidovudine C_{max}: ↔ 0.92 (0.68, 1.24) Zidovudine C_{min}: ↔ 1.22 (0.99, 1.49)	CELSENTRI 300 mg BID dose can be used.

Drug Class: Drug Name	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Clinical Comment
BID)	Maraviroc concentrations not measured, no effect is expected. N = 12	
Integrase Inhibitors		
Elvitegravir/ritonavir 150 mg/100 mg QD (maraviroc 150 mg BID)	Maraviroc AUC_{12}: ↑ 2.86 (2.33, 3.51) Maraviroc C_{max}: ↑ 2.15 (1.71, 2.69) Maraviroc C_{12}: ↑ 4.23 (3.47, 5.16) Elvitegravir AUC_{24}: ↔ 1.07 (0.96, 1.18) Elvitegravir C_{max}: ↔ 1.01 (0.89, 1.15) Elvitegravir C_{24}: ↔ 1.09 (0.95, 1.26) N = 36	Elvitegravir as a single agent is indicated only in combination with certain ritonavir boosted protease inhibitors (atazanavir, lopinavir, darunavir, fosamprenavir and tipranavir). Refer to the HIV Protease Inhibitors section in this table for the appropriate CELSENTRI dose.
Raltegravir 400 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↓ 0.86 (0.80, 0.92) Maraviroc C_{max}: ↓ 0.79 (0.67, 0.94) Maraviroc C_{min}: ↓ 0.90 (0.85, 0.96) Raltegravir AUC_{12}: ↓ 0.63 (0.44, 0.90) Raltegravir C_{max}: ↔ 0.67 (0.41, 1.08) Raltegravir C_{min}: ↓ 0.72 (0.58, 0.90) N = 17	CELSENTRI 300 mg BID and raltegravir can be co-administered without dose adjustment.
Protease Inhibitors (PIs):		
Atazanavir 400 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12} ↑ 3.57 (3.30, 3.87) Maraviroc C_{max}: ↑ 2.09 (1.72, 2.55) Maraviroc C_{min}: ↑ 4.19 (3.65, 4.80) Atazanavir concentrations not measured, no effect is expected. N = 12	The CELSENTRI dose should be decreased to 150 mg BID in the presence of atazanavir.
Atazanavir/ritonavir 300 mg/100 mg QD (maraviroc 300 mg BID)	Maraviroc AUC_{12} ↑ 4.88 (4.40, 5.41) Maraviroc C_{max}: ↑ 2.67 (2.32, 3.08) Maraviroc C_{min}: ↑ 6.67 (5.78, 7.70) Atazanavir/ritonavir concentrations not measured, no effect is expected. N = 12	The CELSENTRI dose should be decreased to 150 mg BID in the presence of atazanavir/ritonavir.
Fosamprenavir/ ritonavir 700 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↑ 2.49 (2.19 2.82) Maraviroc C_{max}: ↑ 1.52 (1.27 1.82) Maraviroc C_{12}: ↑ 4.74 (4.03 5.57) Amprenavir AUC_{12}: ↓ 0.65 (0.59 0.71) Amprenavir C_{max}: ↓ 0.66 (0.59 0.75) Amprenavir C_{12}: ↓ 0.64 (0.57 0.73) Ritonavir AUC_{12}: ↓ 0.66 (0.58 0.76) Ritonavir C_{max}: ↓ 0.61 (0.50 0.73) Ritonavir C_{12}: ↔ 0.86 (0.14 5.28)	The CELSENTRI dose should be decreased to 150 mg BID in the presence of fosamprenavir/ritonavir.

Drug Class: Drug Name	**Effects on drug levels** **Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise**	**Clinical Comment**
Fosamprenavir/ ritonavir 1400 mg/100 mg QD (maraviroc 300 mg QD)	Maraviroc AUC_{24}: ↑ 2.26 (1.99 2.58) Maraviroc C_{max}: ↑ 1.45 (1.20 1.74) Maraviroc C_{24}: ↑ 1.80 (1.53 2.13) Amprenavir AUC_{24}: ↓ 0.70 (0.64 0.77) Amprenavir C_{max}: ↓ 0.71 (0.62 0.80) Amprenavir C_{24}: ↓ 0.85 (0.75 0.97) Ritonavir AUC_{24}: ↓ 0.70 (0.61 0.80) Ritonavir C_{max}: ↓ 0.69 (0.57 0.84) Ritonavir C_{24}: ↔ 2.66 (0.41 17.23) N = 14	
Lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12} ↑ 3.95 (3.43, 4.56) Maraviroc C_{max}: ↑ 1.97 (1.66, 2.34) Maraviroc C_{min}: ↑ 9.24 (7.98, 10.70) Lopinavir/ritonavir concentrations not measured, no effect is expected. N = 11	The CELSENTRI dose should be decreased to 150 mg BID in the presence of lopinavir/ritonavir.
	Maraviroc AUC_{12} ↑ 3.83 (2.81, 5.21) Maraviroc C_{max}: ↑ 1.61 (0.99, 2.63) Maraviroc C_{min}: ↑ 6.23 (4.62, 8.41) Lopinavir/ritonavir concentrations not measured, no effect is expected. N = 8	
Saquinavir/ritonavir 1000 mg/100 mg BID (maraviroc 100 mg BID)	Maraviroc AUC_{12} ↑ 9.77 (7.87, 12.1) Maraviroc C_{max}: ↑ 4.78 (3.41, 6.71) Maraviroc C_{min}: ↑ 11.3 (8.96, 14.1) Saquinavir/ritonavir concentrations not measured, no effect is expected. N = 11	The CELSENTRI dose should be decreased to 150 mg BID in the presence of saquinavir/ritonavir.
	Maraviroc AUC_{12} ↑ 8.32 (6.11, 11.30) Maraviroc C_{max}: ↑ 4.23 (2.60, 6.88) Maraviroc C_{min}: ↑ 9.10 (6.74, 12.3) Saquinavir/ritonavir concentrations not measured, no effect is expected. N = 8	
Darunavir/ritonavir 600 mg/100 mg BID (maraviroc 150 mg BID)	Maraviroc AUC_{12} ↑ 4.05 (2.94, 5.59) Maraviroc C_{max}: ↑ 2.29 (1.46, 3.59) Maraviroc C_{min}: ↑ 8.00 (6.35, 10.1) Darunavir/ritonavir concentrations were consistent with historical data. N = 15	CELSENTRI dose should be decreased to 150 mg BID in the presence of darunavir/ritonavir.
Tipranavir/ritonavir 500 mg/200 mg BID (maraviroc 150 mg	Maraviroc AUC_{12} ↔ 1.02 (0.85, 1.23) Maraviroc C_{max}: ↔ 0.86 (0.61, 1.21) Maraviroc C_{min}: ↔ 1.80 (0.85, 1.23)	CELSENTRI 300 mg BID dose can be used.

Drug Class: Drug Name	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Clinical Comment
BID)	Tipranavir/ritonavir concentrations were consistent with historical data. N = 12	
Saquinavir 1200 mg TID (maraviroc 100 mg BID)	Maraviroc AUC_{12} ↑ 4.25 (3.47, 5.19) Maraviroc C_{max}: ↑ 3.32 (2.45, 4.49) Maraviroc C_{min}: ↑ 4.50 (3.77, 5.38) Saquinavir concentrations not measured, no effect is expected. N = 12	The CELSENTRI dose should be decreased to 150 mg BID in the presence of saquinavir.
Ritonavir 100 mg BID (maraviroc 100 mg BID)	Maraviroc AUC_{12} ↑ 2.61 (1.92, 3.56) Maraviroc C_{max}: ↔ 1.28 (0.79, 2.09) Maraviroc C_{min}: ↑ 4.55 (3.37, 6.13) Ritonavir concentrations not measured, no effect is expected. N = 8	The CELSENTRI dose should be decreased to 150 mg BID in the presence of ritonavir.
Nelfinavir	Not studied	Nelfinavir is considered to be a potent CYP3A4 inhibitor and would be expected to increase maraviroc concentration. The CELSENTRI dose should therefore be decreased to 150 mg BID in the presence of nelfinavir.
NNRTI + PI:		
Efavirenz 600 mg QD + lopinavir/ritonavir 400 mg/100 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↑ 2.53 (2.24, 2.87) Maraviroc C_{max}: ↑ 1.25 (1.01, 1.55) Maraviroc C_{min}: ↑ 6.29 (4.72, 8.39) Efavirenz, lopinavir/ritonavir concentrations not measured, no effect expected. N = 11	The CELSENTRI dose should be decreased to 150 mg BID in the presence of lopinavir/ritonavir + efavirenz (except fosamprenavir/ritonavir where the dose should be 300 mg BID or tipranavir/ritonavir where the dose should be 600 mg BID).
Efavirenz 600 mg QD + saquinavir/ritonavir 1000mg/100mg BID (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↑ 5.00 (4.26, 5.87) Maraviroc C_{max}: ↑ 2.26 (1.64, 3.11) Maraviroc C_{min}: ↑ 8.42 (6.46, 10.97) Efavirenz, saquinavir/ritonavir concentrations not measured, no effect expected. N = 11	The CELSENTRI dose should be decreased to 150 mg BID in the presence of saquinavir/ritonavir + efavirenz (except fosamprenavir/ritonavir where the dose should be 300 mg BID or tipranavir/ritonavir where the dose should be 600 mg BID).
Etravirine 200 mg BID + Darunavir/ritonavir 600 mg/ 100 mg BID (maraviroc 150 mg BID)	Maraviroc AUC_{12}: ↑ 3.10 (2.57, 3.74) Maraviroc C_{max}: ↑ 1.77 (1.20, 2.60) Maraviroc C_{min}: ↑ 5.27 (4.51, 6.15) Etravirine AUC_{12}: ↔ 1.00 (0.86, 1.15) Etravirine C_{max}: ↔ 1.08 (0.98, 1.20) Etravirine C_{min}: ↓ 0.81 (0.65, 1.01) Darunavir AUC_{12}: ↓ 0.86 (0.76, 0.96)	The CELSENTRI dose should be decreased to 150 mg BID in the presence of etravirine + darunavir/ritonavir (except fosamprenavir/ritonavir where the dose should be 300 mg BID or tipranavir/ritonavir where the dose should be 600 mg BID).

Drug Class: Drug Name	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Clinical Comment
	Darunavir C_{max}: ↔ 0.96 (0.84, 1.10) Darunavir C_{min}: ↓ 0.77 (0.69, 0.85) Ritonavir AUC_{12}: ↔ 0.93 (0.75, 1.16) Ritonavir C_{max}: ↔ 1.02 (0.80, 1.30) Ritonavir C_{min}: ↓ 0.74 (0.63, 0.86) N = 10	
Efavirenz 600 mg QD + Didanosine EC 250 mg QD + Tenofovir 300 mg QD (maraviroc 300 mg single dose)	Maraviroc AUC_{12}: ↓ 0.48[a] (0.31, 0.75) Maraviroc C_{max}: ↔ 0.76[a] (0.47, 1.25) Maraviroc C_{min}: ND N = 8	Lower maraviroc exposure could potentially lead to treatment failure, and therefore the combination of CELSENTRI and efavirenz + didanosine + tenofovir should not be used without a dosage increase to 600 mg BID for CELSENTRI.
Efavirenz and atazanavir/ritonavir or darunavir/ritonavir	Not studied	Based on the extent of inhibition by atazanavir/ritonavir or darunavir/ritonavir in the absence of efavirenz, an increased exposure is expected. Therefore, the CELSENTRI dose should be decreased to 150 mg BID when co-administered with either efavirenz or etravirine and a Protease Inhibitor (except fosamprenavir/ritonavir where the dose should be 300 mg BID or tipranavir/ritonavir where the dose should be 600 mg BID).
Etravirine and lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir	Not studied	Based on the extent of inhibition by lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir in the absence of etravirine, an increased exposure is expected. Therefore, the CELSENTRI dose should be decreased to 150 mg BID when co-administered with either efavirenz or etravirine and a protease inhibitor (except fosamprenavir/ritonavir where the dose should be 300 mg BID or tipranavir/ritonavir where the dose should be 600 mg BID).
Other HIV Combinations:		
Efavirenz 600 mg QD + Lamivudine/ zidovudine 150mg/ 300 mg BID (maraviroc 300 mg single dose)	Maraviroc AUC_{12}: ↓ 0.46[a] (0.30, 0.72) Maraviroc C_{max}: ↓ 0.67[a] (0.41, 1.09) Maraviroc C_{min}: ND N = 8	Lower maraviroc exposure could potentially lead to treatment failure, and therefore in the presence of efavirenz + lamivudine/zidovudine. The CELSENTRI dose should therefore be increased to 600 mg BID.

Drug Class: Drug Name	**Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise**	**Clinical Comment**
Nevirapine 200 mg BID + Lamivudine 300 mg QD + Tenofovir 300 mg QD (maraviroc 300 mg single dose)	Maraviroc AUC_{12}: ↔ 1.01[a] (0.65, 1.55) Maraviroc C_{max}: ↔ 1.54[a] (0.94, 2.51) Maraviroc C_{min}: ND N = 8	CELSENTRI 300 mg BID dose can be used.
Lopinavir/ritonavir 400/ 100 mg BID + Lamivudine 150 mg BID + Stavudine 40 mg BID (maraviroc 300 mg single dose)	Maraviroc AUC_{12}: ↑ 2.65[a] (1.61, 4.35) Maraviroc C_{max}: ↑ 1.80[a] (1.03, 3.14) Maraviroc C_{min}: ND N = 5	The CELSENTRI dose should be decreased to 150 mg BID in the presence of lopinavir/ritonavir + lamivudine + stavudine.
Antifungals / Antibacterials:		
Ketoconazole 400 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↑ 5.01 (3.98, 6.29) Maraviroc C_{max}: ↑ 3.38 (2.38, 4.78) Maraviroc C_{min}: ↑ 3.75 (3.01, 4.69) Ketoconazole concentrations not measured, no effect is expected. N = 12	The CELSENTRI dose should be decreased to 150 mg BID in the presence of ketoconazole.
Itraconazole	Not studied	Similar to ketoconazole (see Table 6) itraconazole is a potent CYP3A4 inhibitor and would be expected to increase the exposure of CELSENTRI. The CELSENTRI dose should therefore be decreased to 150 mg BID in the presence of itraconazole.
Voriconazole	Not studied	Voriconazole is considered to be a moderate CYP3A4 inhibitor and the CELSENTRI dose of 300 mg BID should be administered with caution.
Fluconazole	Not studied	Fluconazole is considered to be a moderate CYP3A4 inhibitor and the CELSENTRI dose of 300 mg BID should be administered with caution.
Rifampin 600 mg QD (maraviroc 100 mg BID)	Maraviroc AUC_{12}: ↓ 0.37 (0.33, 0.41) Maraviroc C_{max}: ↓ 0.34 (0.26, 0.43) Maraviroc C_{min}: ↓ 0.22 (0.17, 0.28) Rifampicin concentrations not measured, no effect expected. N = 12	Lower exposure could potentially lead to treatment failure, and therefore in the presence of rifampin the CELSENTRI dose should be increased to 600 mg BID. This dose adjustment has not been studied in HIV patients.
Sulfamethoxazole/ trimethoprim 800 mg/160 mg BID (maraviroc 300 mg BID)	Maraviroc AUC_{12}: ↔ 1.11 (1.01, 1.21) Maraviroc C_{max}: ↔ 1.19 (1.04, 1.37) Maraviroc C_{min}: ↔ 0.90 (0.80, 1.00) Sulphamethoxazole/trimethoprim concentrations not measured, no effect expected. N = 15	CELSENTRI 300 mg BID dose can be used.

Drug Class: Drug Name	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Clinical Comment
Clarithromycin	Not studied	Similar to ketoconazole (see Table 6) clarithromycin is a potent CYP3A4 inhibitor and is expected to increase the exposure of CELSENTRI. The CELSENTRI dose should therefore be decreased to 150 mg BID in the presence of clarithromycin.
Rifabutin + Protease Inhibitor	Not studied	Rifabutin is considered to be a weaker inducer than rifampin. When combining rifabutin with protease inhibitors that are potent inhibitors of CYP3A4, a net inhibitory effect on maraviroc is expected. Therefore, the CELSENTRI dose should be decreased to 150 mg BID when co-administered with rifabutin and a protease inhibitor (except tipranavir/ritonavir where the dose should be 300 mg twice daily.
Analgesics:		
Midazolam 7.5 mg single dose (maraviroc 300 mg BID)	Midazolam. AUC: ↔ 1.18 (1.04, 1.34) Midazolam. C_{max}: ↔ 1.21 (0.92, 1.60) Midazolam C_{min}: ND Maraviroc concentrations not measured, no interaction expected. N = 12	In the presence of maraviroc, an increase of 18% for midazolam exposure (AUC) was observed, indicating that maraviroc is not an inhibitor of the CYP3A4 enzyme.
Methadone	Not studied	No interaction is expected.
Buprenorphine	Not studied	No interaction is expected.
Phosphodiesterase-5 Inhibitors:		
Sildenafil	Not studied	Though no pharmacokinetic interaction is expected, both CELSENTRI and the PDE-5 inhibitors have reported hypotension adverse effects, as such the CELSENTRI dose of 300 mg BID should be administered with caution.
Oral Contraceptives:		
Ethinylestradiol 30 mcg QD (maraviroc 100 mg BID)	Ethinylestradiol AUC_{12}: ↔ 1.00 (0.95, 1.05) Ethinylestradiol C_{max}: ↔ 0.98 (0.91, 1.06) Ethinylestradiol C_{min}: ↑ 1.16 (1.08, 1.26) Maraviroc concentrations not measured, no interaction expected. N = 15	In the presence of maraviroc, there was no observed change in the exposure (AUC) of ethinylestradiol, suggesting no potential for an interaction with this oral contraceptive.
Levonorgestrel 150 mcg QD (maraviroc 100 mg BID)	Levonorgestrel AUC_{12}: ↔ 0.98 (0.92, 1.04) Levonorgestrel C_{max}: ↔ 1.00(0.93, 1.08) Levonorgestrel C_{min}: ↔ 0.99 (0.93, 1.06) Maraviroc concentrations not measured, no interaction expected. N = 15	In the presence of maraviroc, there was no observed change in the exposure (AUC) of levonorgestrel, suggesting no potential for an interaction with this oral contraceptive.

Drug Class: Drug Name	Effects on drug levels Geometric mean ratio [90% Confidence Interval (CI)] if not stated otherwise	Clinical Comment
Antivirals:		
HCV Agents		
Pegylated interferon and ribavirin	Pegylated interferon and ribavirin have not been studied, no interaction is expected.	CELSENTRI 300 mg BID dose can be used.
Anticonvulsants:		
Carbamazepine Phenobarbital Phenytoin	Not studied, but these are potent CYP3A inducers and would be expected to decrease maraviroc concentrations.	The CELSENTRI dose should be increased to 600 mg twice daily when co-administered with carbamazepine, phenobarbital or phenytoin in the absence of a potent CYP3A inhibitor.
Lipid Lowering Medicinal Products:		
Statins	Not studied	No interaction is expected.
Antiarrhythmics		
Digoxin 0.25 mg single dose (maraviroc 300 mg BID)	Digoxin AUC_t: ↔ 1.00 (0.88, 1.14) Digoxin C_{max}: ↔ 1.04 (0.84, 1.29) Maraviroc concentrations not measured, no interaction expected. N = 12	CELSENTRI 300 mg BID dose can be used.

[a] in HIV patients, compared with historical controls
ND: Not determined

Drug-Food Interactions
Coadministration of a 300 mg tablet with a high fat breakfast reduced maraviroc Cmax and AUC by 33% in healthy volunteers. There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc (see **CLINICAL TRIALS**). Therefore, maraviroc can be taken with or without food at the recommended dose (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions
Concomitant use of maraviroc and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Coadministration of maraviroc with St. John's wort is expected to substantially decrease maraviroc concentrations and may result in suboptimal levels of maraviroc and lead to loss of virologic response and possible resistance to maraviroc.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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

Dosing Considerations

CELSENTRI must be taken every day in combination with other antiretroviral agents. The recommended dose is 300 mg twice daily but adjustments are recommended based on the patient's concomitant medications. CELSENTRI can be taken with or without food.

Recommended Dose and Dosage Adjustment

Adults: The recommended dose of CELSENTRI is 300 mg twice daily. A dose adjustment may be needed due to the potential for drug interactions (see Table 6 and **DRUG INTERACTIONS, Drug-Drug Interactions**, Table 5).

Table 6 Recommended Dosing Regimen

Concomitant Medications	Dose of CELSENTRI
Potent CYP3A4 inhibitors (with or without a CYP3A4 inducer) including, but not limited to: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin	150 mg twice daily
Potent CYP3A4 inducers (without a potent CYP3A4 inhibitor) including, but not limited to: • efavirenz • rifampin • etravirine • carbamazepine, phenobarbital, and phenytoin	600 mg twice daily
Other concomitant medications, including all other antiretrovirals that are not potent CYP3A4 inhibitors or potent CYP3A4 inducers, including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide	300 mg twice daily

Pediatrics (<18 years of age): The pharmacokinetics, safety and efficacy of maraviroc in pediatric patients have not been established. Therefore, maraviroc should not be used in this patient population.

Geriatrics (>65 years of age): There were insufficient numbers of subjects aged 65 and over in the clinical studies to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering CELSENTRI in elderly patients, also reflecting the greater frequency of decreased hepatic and renal function, of concomitant disease and other drug therapy.

Renal Impairment: CELSENTRI should not be used in patients with severe renal impairment or ESRD (CLcr < 30 mL/min) who are taking potent CYP3A inhibitors or inducers (see **WARNINGS AND PRECAUTIONS**).

No dose adjustment is necessary for renally impaired patients, including patients with ESRD, requiring dialysis, not receiving a potent CYP3A4 inhibitor in combination with

CELSENTRI. Table 7 below provides dosing interval adjustment guidelines for patients based on renal function and concomitant medications.

Table 7 Dose and interval adjustments for patients with renal impairment

Concomitant Medications	Dose of CELSENTRI Based on Renal Function				
	Normal (CLcr >80 mL/min)	**Mild (CLcr >50 and ≤ 80 mL/min)**	**Moderate (CLcr ≥ 30 and ≤ 50 mL/min)**	**Severe (CLcr <30 mL/min)**	**End Stage Renal Disease (ESRD)**
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin • other potent CYP3A inhibitors	150 mg twice daily	150 mg twice daily	150 mg twice daily	NR	NR
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: • efavirenz • rifampin • etravirine • carbamazepine, phenobarbital, phenytoin	600 mg twice daily	600 mg twice daily	600 mg twice daily	NR	NR
Other concomitant medications, including: • tipranavir/ritonavir • nevirapine • raltegravir • all NRTIs • enfuvirtide	300 mg twice daily	300 mg twice daily	300 mg twice daily	300 mg twice daily[a]	300 mg twice daily[a]

NR=Not recommended

[a] The dose of CELSENTRI should be reduced to 150 mg twice daily if there are any symptoms of postural hypotension (see **WARNINGS AND PRECAUTIONS**).

Missed Dose

If a dose is missed, patients should take the next dose as soon as possible. A dose should not be doubled.

OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

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. Administration of activated charcoal may be used to aid in removal of unabsorbed drug. Since maraviroc is moderately protein bound, dialysis may be beneficial in removal of this medicine.

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

Prolongation of the QT interval was seen in dogs and monkeys at plasma concentrations 6 and 12 times, respectively, to those expected in humans at the maximum recommended dose of 300 mg twice daily. However, no significant QT prolongation was seen in the Phase 3 clinical studies using the recommended doses of maraviroc or in a specific pharmacokinetic study to evaluate the potential of maraviroc to prolong the QT interval (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Effects on Electrocardiogram**).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Maraviroc is a member of a therapeutic class called CCR5 antagonists. Maraviroc selectively binds to the human chemokine CCR5 co-receptor and inhibits the interaction of the envelope glycoprotein (gp120) from CCR5-tropic HIV-1 strains with CCR5 co-receptor. Binding of gp120 to CCR5 co-receptor is an essential step in the HIV-1 entry process for CCR5-tropic viruses (i.e. viruses that use only CCR5 co-receptor for entry). Maraviroc has no activity against viruses that can use CXCR4 as their co-receptor. These CXCR4-using viruses include dual-tropic viruses (which can use either CCR5 or CXCR4 co-receptors), mixed-tropic viruses (which consist of a mixture of CCR5-tropic and CXCR4-tropic viruses) or CXCR4-tropic viruses (which can use only CXCR4 co-receptor for entry).

Pharmacodynamics

Maraviroc inhibits the replication of CCR5-tropic laboratory strains and clinical isolates of HIV-1 in models of acute T-cell infection (see **DETAILED PHARMACOLOGY**, **Antiviral Activity in Cell Culture**).

Exposure Response Relationship in Treatment-Experienced Subjects

The relationship between maraviroc modeled plasma trough concentration (C_{min}) (1to 9 samples per patient taken on up to 7 visits) and virologic response (<400 copies/mL viral RNA at 24 weeks, discontinuation=failure) was evaluated in 594 treatment-experienced HIV-1-infected subjects with varied optimized background antiretroviral regimens in treatment-experienced patients studies (MOTIVATE 1 and MOTIVATE 2). Table 8 illustrates the proportion of subjects with virologic success (%) at 24 weeks within each C_{min} quartile for maraviroc 150 mg twice daily and 300 mg twice daily compared with equivalent placebo plus optimized background therapy.

Table 8 Treatment-Experienced Subjects with Virologic Success by C_{min} Quartile (Q1-Q4)

	150 mg Twice Daily (with CYP3A inhibitors)			300 mg Twice Daily (without CYP3A inhibitors)		
	n	Median C_{min}	% Subjects with Virologic Success	n	Median C_{min}	% Subjects with Virologic Success
Placebo	160	-	30.6	35	-	28.6
Q1	78	33	52.6	22	13	50.0
Q2	77	87	63.6	22	29	68.2
Q3	78	166	78.2	22	46	63.6
Q4	78	279	74.4	22	97	68.2

The C_{min} exposure response relationships shown in Table 8 above are specific to 300 mg twice daily dosing given in the absence of potent CYP3A4/Pgp inhibitors and 150 mg twice daily in the presence of potent CYP3A4/Pgp inhibitors. Near maximal response is achieved between C_{min} Quartiles 2 and 4.

Exposure Response Relationship in Treatment-Naïve Subjects

The relationship between maraviroc modeled plasma trough concentration (C_{min}) (1-12 samples per patient taken on up to 8 visits) and virologic response (<50 copies/mL viral RNA at 48 weeks, discontinuation=failure) was evaluated in 294 treatment-naïve HIV-1-infected subjects receiving maraviroc 300 mg twice daily in combination with zidovudine/lamivudine in treatment-naïve patients study (MERIT). Table 9 illustrates the proportion of subjects with virologic success (%) within each C_{min} quartile.

Table 9 Treatment-Naïve Subjects with Virologic Success by C_{min} Quartile (Q1-Q4)

	300 mg Twice Daily		
	n	Median C_{min}	% Subjects with Virologic Success
Q1	75	23	57.3
Q2	72	39	72.2
Q3	73	56	74.0
Q4	74	81	83.8

The relationship between low C_{min} and lack of virologic success shown in Q1 in Table 9 is explained by poor adherence to antiretroviral treatment. Fifteen of 32 subjects (47%) in Q1 who were classed as failures (discontinuation=failure) at 48 weeks had no measurable maraviroc concentration on one or more visits indicating poor adherence to treatment.

Pharmacokinetics

Healthy volunteer (Phase 1) and Phase 2a asymptomatic patient exposures are derived from non-compartmental analysis using full pharmacokinetic profiles while the Phase 2b/3 patient exposures are derived from population modeling of sparse samples after outpatient dosing.

Table 10 Mean Maraviroc Pharmacokinetic Parameters

Patient Population	Maraviroc Dose	N	AUC_{12} (ng.hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Healthy volunteers (Phase 1)	300 mg twice daily	64	2,908	888	43.1
Asymptomatic HIV patients (Phase 2a)	300 mg twice daily	8	2,550	618	33.6
Treatment-experienced HIV patients (Phase 3)[a]	300 mg twice daily	94	1,513	266	37.2
	150 mg twice daily (+ CYP3A inhibitor)	375	2,463	332	101
Treatment-naïve HIV patients (Phase 2b/3)[a]	300 mg twice daily	344	1,865	287	60

[a] Estimated exposures from modeling Phase 3 data may differ from noncompartmental analysis of Phase 1/2a study data due to methodology, sparse sampling, food effects, compliance and concomitant medications

Absorption: Peak maraviroc plasma concentrations are attained 0.5 to 4 hours following single oral doses of 1-1,200 mg administered to uninfected 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.

Effect of Food on Oral Absorption: Coadministration of a 300 mg tablet with a high-fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers. There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc

(see **CLINICAL TRIALS**). Therefore, maraviroc can be taken with or without food at the recommended dose (see **DOSAGE AND ADMINISTRATION**).

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

Preclinical data in the rat indicate CSF exposure with concentrations ~10% of free plasma concentrations.

Metabolism: Studies in humans and *In Vitro* studies using human liver microsomes and expressed enzymes have demonstrated that maraviroc is principally 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 (~ 42% drug related radioactivity) following a single oral dose of 300 mg [^{14}C]-maraviroc to healthy male volunteers. The most significant circulating metabolite in humans is a secondary amine (~ 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 drug related radioactivity.

Elimination: The terminal half-life of maraviroc following oral dosing to steady-state in healthy subjects was 14 to 18 hours. 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 feces over 168 hours. Maraviroc was the major component present in urine (mean of 8% dose) and feces (mean of 25% dose). The remainder was excreted as metabolites.

Effects on Electrocardiogram: A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female volunteers was conducted with 3 single oral doses of maraviroc and moxifloxacin. The placebo-adjusted mean maximum increases in QTc from baseline after 100, 300 and 900 mg of maraviroc were –2.3, -0.6, and 1.0 msec, respectively, and 12.9 msec for moxifloxacin 400 mg. No subject in any group had an increase in QTc of ≥ 60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. No clinically significant QT prolongation was seen in the studies in treatment-experienced and treatment-naïve subjects with HIV using the recommended doses of maraviroc.

Special Populations and Conditions

Hepatic Impairment: Maraviroc is primarily metabolized and eliminated by the liver. A study compared the pharmacokinetics of a single 300mg dose of CELSENTRI in patients with mild (Child-Pugh Class A, n=8), and moderate (Child-Pugh Class B, n=8) hepatic

impairment compared with 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 with subjects with normal hepatic function. The pharmacokinetics of maraviroc have not been studied in subjects with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Renal Impairment: A study compared the pharmacokinetics of a single 300 mg dose of CELSENTRI in subjects with severe renal impairment (CLcr <30 mL/min, n=6) and ESRD to healthy volunteers (n=6). Dialysis had a minimal effect on exposure in subjects with ESRD (Table 11). Exposures observed in subjects with severe renal impairment and ESRD were within the range observed in single CELSENTRI 300 mg dose studies in healthy volunteers with normal renal function (Table 11). Therefore, no dose adjustment is necessary in patients with renal impairment receiving CELSENTRI without a potent CYP3A4 inhibitor. If patients with severe renal impairment or ESRD experience any symptoms of postural hypotension while taking CELSENTRI 300 mg twice daily, the dosage should be reduced to 150 mg twice daily (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Table 11 Mean (CV%) Maraviroc Pharmacokinetic Parameters for Subjects with Normal Renal Function, Severe Renal Impairment, or ESRD Treated with a Single Dose of 300 mg MVC

	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)
Normal Renal Function	1348.4 (61%)	335.6 (87%)
Severe Renal Impairment	4367.7 (52%)	801.2 (56%)
ESRD (dosing pre-dialysis)	2805.5 (45%)	478.5 (38%)
ESRD (dosing post-dialysis)	2677.4 (40%)	576.7 (51%)

In addition, the pharmacokinetics of CELSENTRI in combination with saquinavir/ritonavir 1,000/100 mg twice daily (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 with normal renal function (n=6) were studied. Subjects received 150 mg of CELSENTRI at different dose frequencies (healthy volunteers – every 12 hours; mild renal impairment – every 24 hours; moderate renal impairment – every 48 hours) (see Table 12).

Based on the data from this study, no adjustment in dose is recommended for CELSENTRI in patients with mild or moderate renal impairment when used in combination with a potent CYP3A inhibitor or inducer.

No studies have been performed in subjects with severe renal impairment or ESRD who received potent CYP3A inhibitors or inducers concomitantly. Therefore, no dosage for CELSENTRI can be recommended (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Table 12 Mean (CV%) Maraviroc Pharmacokinetic Parameters for Subjects with Normal Renal Function, Mild or Moderate Renal Impairment Treated with Multiple Doses of 150 mg MVC + SQV/r 1,000/100 mg twice daily

	N	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)
Normal Renal Function MVC 150 mg twice daily + SQV/r 1,000/100 mg twice daily	6	5341.5 (27%)	950.9 (23%)
Mild Renal Impairment (CLcr >50 and ≤80 mL/min) MVC 150 mg once daily + SQV/r 1,000/100 mg twice daily	6	8118.7 (35%)	1150.7 (32%)
Moderate Renal Impairment (CLcr ≥30 and ≤50 mL/min) MVC 150 mg once every other day + SQV/r 1,000/100 mg twice daily	6	6193.3 (27%)	674.2 (38%)

Pharmacogenomics: A study showed that differences in CYP3A5 genotype on maraviroc exposure in different racial groups are not considered clinically significant and no maraviroc dose adjustment according to CYP3A5 genotype and race is needed.

STORAGE AND STABILITY

CELSENTRI film-coated tablets should be stored at 15º to 30ºC in a USP tight container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form and Packaging:

Dosage Form:
150 and 300 mg tablets are blue, biconvex, oval, film-coated tablets plain on one side and debossed with “MVC 150” or “MVC 300” on the other.

Packaging:
CELSENTRI 150 mg and 300 mg tablets are supplied in high density polyethylene bottles (HDPE) with polypropylene child resistant (CR) closures and an aluminium foil/polyethylene heat induction sealcontaining 30, 60, 120 and 180 film-coated tablets.

CELSENTRI 150 mg and 300 mg tablets are supplied in polyvinyl chloride (PVC) blisters with aluminium foil backing in a carton containing 30, 60, 90 and 180 (2 x 90) film-coated tablets.

Composition:

CELSENTRI is available as film-coated tablets for oral administration containing either 150 or 300 mg of maraviroc and the following inactive ingredients: dibasic calcium phosphate (anhydrous), magnesium stearate, microcrystalline cellulose, sodium starch glycolate. The film-coat [OpadryII Blue (85G20583)] contains FD&C blue #2 aluminum lake, polyethylene glycol (macrogol 3350), polyvinyl alcohol, soya lecithin, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

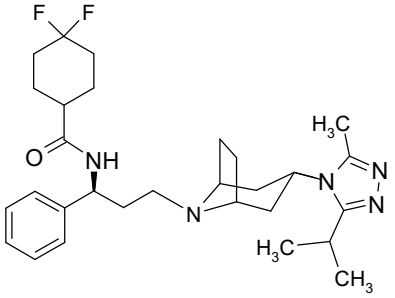
Proper name: Maraviroc

Chemical name: 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl} cyclohexanecarboxamide.

Molecular formula: $C_{29}H_{41}F_2N_5O$

Molecular weight: 513.67 Daltons

Structural formula:



Physicochemical Properties

Description: Maraviroc is a white to pale colored powder.

Solubility: At 37°C, maraviroc is highly soluble across the physiological pH range (pH 1.0 to 7.5)

pk_a: Maraviroc has pK_a values of 3.3 and 7.3. The lower pK_a value corresponds to protonation of the 1,2,4-triazole ring. The higher pK_a value corresponds to protonation of tropane nitrogen.

CLINICAL TRIALS

Overview

The clinical efficacy and safety of CELSENTRI are derived from analyses of 48-week data from 3 ongoing studies in adult subjects infected with CCR5-tropic HIV-1: in antiretroviral treatment-experienced adult patients infected with CCR5-tropic HIV-1 (MOTIVATE 1 and MOTIVATE 2) and in treatment-naïve subjects (MERIT). These studies are supported by a 48-week study in antiretroviral treatment-experienced adult patients infected with dual/mixed-tropic HIV-1, 1029.

Studies in CCR5-tropic virus infected, Treatment-Experienced Patients (MOTIVATE 1 and MOTIVATE 2)

Studies in treatment-experienced patients are ongoing, double-blind, randomized, placebo-controlled, multicenter studies in patients infected with CCR5-tropic HIV-1. Patients were required to have an HIV-1 RNA of greater than 5,000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes [≥ 1 nucleoside reverse transcriptase inhibitors (NRTI), ≥ 1 non-nucleoside reverse transcriptase inhibitors (NNRTI), ≥ 2 protease inhibitors (PI), and/or enfuvirtide] or documented resistance or intolerance to at least 1 member of each class. All patients received an optimized background regimen consisting of 3 to 6 antiretroviral agents (excluding low-dose ritonavir) selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements. In addition to the optimized background regimen, patients were then randomized in a 2:2:1 ratio to CELSENTRI 300 mg once daily, CELSENTRI 300 mg twice daily, or placebo. Doses were adjusted based on background therapy (see **DOSAGE AND ADMINISTRATION,** Table 6).

In the pooled analysis for studies in treatment-experienced patients, the demographics and baseline characteristics of the treatment groups were comparable (Table 11 and Table 12). Table 13 compares the demographic characteristics of the patients in the CELSENTRI + OBT and placebo + OBT arms.

Table 13 Demographic Characteristics of Patients in Studies with Treatment-Experienced Patients (MOTIVATE 1 and MOTIVATE 2)

Studies MOTIVATE 1 and MOTIVATE 2 (Pooled Analysis)		
Demographic Characteristics	**CELSENTRI twice daily[a] + OBT N = 426**	**Placebo + OBT N = 209**
Age (years) (Range, years)	46.3 21-73	45.7 29-72
Sex		
Male	382 (89.7%)	185 (88.5%)
Female	44 (10.3%)	24 (11.5%)
Race		
White	363 (85.2%)	178 (85.2%)
Black	51 (12.0%)	26 (12.4%)
Other	12 (2.8%)	5 (2.4%)
Subjects with Previous Enfuvirtide Use	143 (33.6%)	60 (28.7%)
Subjects with Enfuvirtide as Part of OBT	182 (42.7%)	90 (43.1%)
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.9	4.9
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	166.8 (2.0-820.0)	170.8 (1.0-675.0)
Patients with Screening Viral Load ≥ 100,000 copies/mL	179 (42.0%)	84 (40.2%)
Patients with Baseline CD4+ Cell Count ≤ 200 cells/mm^3)	250 (58.7%)	118 (56.5%)

[a] 300 mg dose equivalent

Table 14 compares the baseline characteristics of the patients on CELSENTRI + OBT with those on placebo + OBT.

Table 14 Baseline Characteristics of Patients in Treatment-Experienced Studies (MOTIVATE 1 and MOTIVATE 2)

Studies MOTIVATE 1 and MOTIVATE 2 (Pooled Analysis)		
	CELSENTRI twice daily[c] + OBT N =426	**Placebo + OBT N = 209**
Percentage of patients with Overall Susceptibility Score (OSS):[a]		
0	57 (13%)	35 (17%)
1	136 (32%)	43 (21%)
2	103 (24%)	59 (28%)
≥ 3	126 (30%)	67 (32%)
Percentage of patients with enfuvirtide resistance mutations	90/424 (21%)	44/209 (21%)
Median Number of Resistance-Associated:[b]		
PI mutations	10	10
NNRTI mutations	1	1
NRTI mutations	6	6

[a] OSS -Sum of active drugs in OBT based on combined information from genotypic and phenotypic testing.
[b] Resistance mutations based on IAS guidelines
[c] 300 mg dose equivalent

The week 48 results for the pooled studies in treatment-experienced patients are shown in Table 15.

Table 15 Outcomes of Randomized Treatment at Week 48 - Pooled Studies in Treatment-Experienced Patients (MOTIVATE 1 and MOTIVATE 2)

Outcome	CELSENTRI twice daily[b] + OBT N=426	Placebo+ OBT N=209	Confidence Interval[a]
Mean change from baseline HIV-1 RNA to wk 48	-1.84	-0.78	(1.33, -0.78)
< 400 copies/mL at week 48	239 (56.1%)	47 (22.5%)	Odds ratio: 4.76 (3.24, 7.00)
< 50 copies/mL at week 48	194 (45.5%)	35 (16.7%)	Odds ratio: 4.49 (2.96, 6.83)
Mean increase in CD4+ count	124.07 cells/mm^3	60.93 cells/mm^3	(44.28, 81.99)
Virologic Responders Confirmed reduction in HIV-1 RNA ≥1$\log_{10}$ OR < 400 copies/mL through week 48	270 (63.4%)	61 (29.2%)	(2.98, 6.07)
Discontinuations due to Insufficient Clinical Response	97 (22.8%)	113 (54.1%)	
Discontinuations due to Adverse Events	19 (4.5%)	11 (5.3%)	
Discontinuations for Other Reasons	27 (6.3%)	18 (8.6%)	
Patients with treatment-emergent CDC Category C events	22 (5.2%)	16 (7.7%)	
Deaths (during study or within 28 days of last dose)	10 (2.3%)[c]	1 (0.5%)	

[a] For all efficacy endpoints, the confidence intervals were 95%, except for HIV-1 RNA change from baseline which was 97.5%.
[b] 300 mg dose equivalent
[c] Includes 1 patient discontinued from double-blind placebo for insufficient response and started on open-label therapy with CELSENTRI.

After 48 weeks of therapy, the proportion of subjects with HIV-1 RNA <400 copies/mL receiving CELSENTRI compared with placebo was 56% and 22%, respectively. The mean changes in plasma HIV-1 RNA from baseline to week 48 were -1.84 $\log_{10}$ copies/mL for subjects receiving CELSENTRI + OBT compared with -0.78 $\log_{10}$ copies/mL for subjects receiving OBT only. The mean increase in CD4+ cell counts was higher on CELSENTRI twice daily + OBT (124 cells/mm^3) than on placebo + OBT (60 cells/mm^3).

Study in Treatment-Naïve Patients (MERIT)

The Treatment-Naïve study is a randomized, double-blind, multicenter study in subjects infected with CCR5-tropic HIV-1 classified by the TROFILE tropism assay. Subjects were required to have plasma HIV-1 RNA ≥ 2,000 copies/mL and could not have: 1) previously received any antiretroviral therapy for > 14 days, 2) an active or recent opportunistic infection or a suspected primary HIV-1 infection, or 3) phenotypic or genotypic resistance to zidovudine, lamivudine, or efavirenz. Subjects were randomized in a 1:1:1 ratio to CELSENTRI 300 mg once daily, CELSENTRI 300 mg twice daily, or efavirenz 600 mg once daily, each in combination with zidovudine/lamivudine. The efficacy and safety of CELSENTRI are based on the comparison of CELSENTRI twice daily versus efavirenz. In a pre-planned interim analysis at 16 weeks, CELSENTRI 300 mg once daily failed to meet the pre-specified criteria for demonstrating non-inferiority and was discontinued.

The demographic and baseline characteristics of patients in the maraviroc and efavirenz treatment groups were comparable (Table 16). Subjects were stratified by screening HIV-1 RNA levels and by geographic region. The median CD4+ cell counts and mean HIV-1 RNA at baseline were similar for both treatment groups.

Table 16 Demographic and Baseline Characteristics of Subjects in the Treatment-Naïve Study[a] (MERIT)

	CELSENTRI 300 mg Twice Daily + Zidovudine/Lamivudine N=360	Efavirenz 600 mg Once Daily + Zidovudine/Lamivudine N=361
Age (years)		
Mean (SD)	36.7 (9.4)	37.4 (9.8)
Range	20-69	18-77
Gender n (%)		
Male	256 (71.1)	259 (71.7)
Female	104 (28.9)	102 (28.3)
Race, n (%)		
White	204 (56.7)	198 (54.8)
Black	123 (34.2)	133 (36.8)
Asian	6 (1.7)	5 (1.4)
Other	27 (7.5)	25 (6.9)
Median CD4+ cell count (cells/µL)	241 (5-1,422)	254 (8-1,053)
Median HIV-1 RNA (log $_{10}$ copies/mL)	4.9 (3.1-6.8)	4.9 (2.9 – 6.7)

[a] Data from Full Analysis Set. Similar results were observed for the Per Protocol population.

The treatment outcomes through week 48 for the treatment-naïve study (MERIT) are shown in Table 17.

Table 17 Outcomes of Randomized Treatment at Week 48 in Treatment-Naïve Patients (MERIT)[a]

Outcome at Week 48	CELSENTRI 300 mg Twice Daily + Zidovudine/Lamivudine N=360	Efavirenz 600 mg Once Daily + Zidovudine/Lamivudine N=361	Difference in Proportions[c] Maraviroc vs Efavirenz (%)	
			Difference	Lower Bound of 1-sided 97.5% CI
Responder[b]				
< 400 copies/mL	70.6%	73.1%	-3.0	-0.095
< 50 copies/mL	65.3%	69.3%	-4.2	-0.109
Virologic Failure (TLOVR)[d]				
< 400 copies/mL	27.7%	5.3%		
< 50 copies/mL	32.0%	8.8%		
Rebound[d]				
< 400 copies/mL	20.8%	16.0%		
< 50 copies/mL	19.7%	14.7%		
Never suppressed[d]				
< 400 copies/mL	0	0		
< 50 copies/mL	5.7%	2.0%		
Death[e]	1 (0.3)	2(0.6)		
Discontinuations				
Adverse events (all causality)	15 (4.1)	49 (13.6)		
Insufficient response	43 (11.9)	15 (4.2)		
Other reasons	38 (10.5)	27 (7.5)		

[a] Data obtained with Original Tropism Assay
[b] Patients achieved and maintained confirmed HIV-1 RNA through week 48, Full Analysis Set
[c] Adjusted for randomization strata
[d] Based on Time to Loss of Virologic Response (TLOVR) algorithm, Full Analysis Set.
[e] Death during study or within 28 days of the last dose at week 48.

The primary efficacy endpoints were defined as the percentage of subjects with HIV-1 RNA undetectable by the standard and ultra sensitive methods (< 400 copies/mL and < 50 copies/mL). After 48 weeks of combination therapy with zidovudine/lamivudine, CELSENTRI 300 mg twice daily demonstrated non-inferiority to efavirenz 600 mg once daily in the proportion of patients with undetectable viral load measured at < 400 copies/mL but not at < 50 copies/mL (lower bound of 97.5% CI > -10% for non-inferiority). The median increase from baseline in CD4+ cell counts at week 48 was 157 cells/mm^3 for the arm receiving CELSENTRI compared with 127 cells/mm^3 for the efavirenz arm ($p < 0.01$).

The treatment outcomes at 96 weeks for the treatment-naïve patients study (MERIT) are shown in Table 18. Treatment outcomes are based on reanalysis of the screening samples using a more sensitive tropism assay, Enhanced sensitivity TROFILE HIV tropism assay, which became available after the week 48 analysis. Approximately 15% of the subjects identified as CCR5-tropic virus in the original analysis had CXCR4-using virus. Screening with the enhanced sensitivity version of the TROFILE tropism assay reduced the number of maraviroc virologic failures with CXCR4-using virus at failure to 12 compared with 24 when screening with the original TROFILE HIV tropism assay.

Table 18 Study Outcome at Week 96 Using Enhanced Sensitivity Assay[a]

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

[a] The total number of subjects (Ns) in Table 16 represents the subjects who had a CCR5-tropic virus in the reanalysis of screening samples using the more sensitive tropism assay. This reanalysis reclassified approximately 15% of subjects shown in Table 14 as having CXCR4-using virus. These numbers are different than those presented in Table 14 because the numbers in Table 14 reflect the subjects with CCR5-tropic virus according to the original tropism assay.
[b] Week 48 results: Virologic responders (< 400): 228/311 (73%) in CELSENTRI, 219/303 (72%) in efavirenz
Virologic responders (< 50): 213/311 (69 %) in CELSENTRI, 207/303 (68%) in efavirenz
[c] Other reasons for discontinuation include lost to follow-up, withdrawn, protocol violation, and other.

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

A reanalysis of the screening samples from the study in treatment-naïve patients (MERIT Study) using a more sensitive tropism assay (TROFILE-ES) which became available after the week 48 analysis was completed showed approximately 15% of the patients identified as CCR5-tropic virus in the primary analysis had non-CCR5-tropic virus. Excluding these patients resulted in the lower one-sided 97.5% confidence bound of the treatment

difference between CELSENTRI and efavirenz being above -10% for both < 400 and < 50 copies/mL (Table 19).

Table 19 Efficacy Endpoints – Percentage of Subjects with Viral Load < 400 and < 50 copies/mL at Weeks 48 and 96 Using Original TROFILEAssay and Enhanced Sensitivity TROFILE Assay (ESTA)

Parameter Unit=copies/mL	CELSENTRI 300 mg Twice Daily + Zidovudine/Lamivudine n (%)	Efavirenz 600 mg Once Daily + Zidovudine/Lamivudine n (%)	Difference in % of Subjects[a]; CELSENTRI 300 mg Twice Daily vs. Efavirenz 600 mg Once Daily	
			Difference (%)[a]	LB of 1-sided 97.5% CI
FAS Original TROFILE	N = 360	N = 361		
< 400 at Week-48	254 (70.6)	264 (73.1)	-3.0	-9.5
< 50 at Week-48	235 (65.3)	250 (69.3)	-4.2	-10.9
< 400 at Week-96	221 (61.4)	233 (64.5)	-3.2	-10.2
< 50 at Week-96	205 (56.9)	226 (62.6)	-5.8	-12.8
FAS ESTA	N = 311	N = 303		
< 400 at Week-48	228 (73.3)	219 (72.3)	0.6	-6.4
< 50 at Week-48	213 (68.5)	207 (68.3)	-0.2	-7.4
< 400 at Week-96	199 (64.0)	195 (64.4)	-0.4	-7.9
< 50 at Week-96	183 (58.8)	190 (62.7)	-3.9	-11.5

n=number of responders; N=number of subjects in the treatment group in the indicated population; FAS=full analysis set; LB and CI=Lower bond of confidence interval;
[a] Adjusted for randomization strata- positive values favor CELSENTRI

Tropism

In both treatment-experienced and treatment-naïve subjects, detection of CXCR4-using virus prior to initiation of therapy has been associated with a reduced virologic response to maraviroc.

Treatment-Experienced (MOTIVATE 1 and MOTIVATE 2)

Failure With CXCR4-using Virus: In the majority of cases, treatment failure on CELSENTRI was associated with detection of CXCR4 using (i.e., CXCR4- or dual/mixed-tropic) virus which was not detected by the tropism assay prior to treatment. CXCR4-using virus was detected at failure in 54.8% of subjects who failed treatment on CELSENTRI, as compared with 7.2% of subjects who experienced treatment failure in the placebo arm. To investigate the likely origin of the on-treatment CXCR4-using virus, a detailed clonal analysis was conducted on virus from 20 representative subjects (16

subjects from the arms receiving CELSENTRI and 4 subjects from the placebo arm) in whom CXCR4-using virus was detected at treatment failure. From analysis of amino acid sequence differences and phylogenetic data, CXCR4-using virus in these subjects emerged from a low level of pre-existing CXCR4-using virus not detected by the tropism assay (which is population-based) prior to treatment rather than from a co-receptor switch from CCR5-tropic virus to CXCR4-using virus resulting from mutation in the virus.

Detection of CXCR4-using virus prior to initiation of therapy has been associated with a reduced virological response to maraviroc. Furthermore, at week 48 subjects failing CELSENTRI twice daily with CXCR4-using virus had a lower median increase in $CD4^+$ cell counts from baseline (+41 cells/mm^3) than those subjects failing with CCR5-tropic virus (+162 cells/mm^3). The median increase in $CD4^+$ cell count in patients failing in the placebo arm was +6.5 cells/mm^3.

Failure With CCR5-tropic Virus (Phenotypic resistance) in patients with CCR5-tropic virus at time of treatment failure with CELSENTRI, virus with reduced sensitivity to maraviroc was detected in 22 out of 59 patients. A clinically-validated cut-off value for reduced virological response has not yet been established. Therefore, continued use of CELSENTRI after treatment failure cannot be generally recommended regardless of the viral tropism seen.

Genotypic resistance profile of virus from treatment-experienced subjects has not yet been fully characterized. Specific mutations associated with reduced susceptibility to maraviroc have been identified in viruses from 16 patients but for each patient there was a unique pattern of mutations.

Treatment-Naïve (MERIT)

In the pivotal study, 3.5% of patients had a change in tropism result from CCR5-tropic virus to CXCR4-using or dual-mixed virus between screening and baseline (a period of 4-6 weeks).

Failure with CXCR4 using virus at week 96: In the analysis of Week 96 data, using a time to loss of virologic response (HIV-1 RNA <50 copies/mL) endpoint, CXCR4-using virus was detected at failure in approximately 28% of subjects with CCR5-tropic virus at baseline and who failed treatment on CELSENTRI, as compared with none of the subjects who experienced treatment failure in the efavirenz arm. Based on a re-analysis when subjects with CXCR4-using virus at screening, detected using an enhanced sensitivity tropism assay, were censored from the analysis, of the subjects with CCR5-tropic virus at baseline and who failed treatment on CELSENTRI, CXCR4-using virus was detected in 17% as compared with none in the Efavirenz arm. Screening with the enhanced sensitivity tropism assay reduces the number of maraviroc virologic failures due to CXCR4-using virus. A detailed clonal analysis was conducted in two previously antiretroviral treatment-naïve subjects enrolled in a Phase 2a monotherapy study and who had CXCR4-using virus observed after 10 day treatment with CELSENTRI. Consistent with the detailed clonal analysis conducted in treatment-experienced subjects, the CXCR4-using variant was found to be pre-existing prior to starting therapy.

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

Subjects who had CCR5-tropic virus at baseline and failed therapy with CELSENTRI with CXCR4- using virus had a median increase in $CD4^+$ cell counts from baseline of +97 cells/mm^3 while those subjects failing with CCR5-tropic virus had an increase of +147 cells/mm^3. The median increase in $CD4^+$ cell count in patients failing in the efavirenz arm was +69 cells/mm^3.

Study in Patients with CXCR4-using HIV

Study 1029 was an exploratory, randomized, double-blind, multicenter trial to determine the safety and efficacy of CELSENTRI in patients infected with CXCR4-using HIV-1. The inclusion/exclusion criteria were similar to those for studies in treatment-experienced patients above and the patients were randomized in a 1:1:1 ratio to CELSENTRI once daily, CELSENTRI twice daily, or placebo.

There was no significant difference in the efficacy between the arm receiving CELSENTRI and the placebo arm, however patients receiving CELSENTRI exhibited an increase in their absolute CD4+ cell counts from baseline (+79) as compared with subjects on placebo (+51).

DETAILED PHARMACOLOGY

Microbiology

Mechanism of Action

Maraviroc is a member of a therapeutic class called CCR5 co-receptor antagonists. Maraviroc selectively binds to the human chemokine CCR5 co-receptor present on the cell membrane, preventing the interaction of HIV-1 gp120 and CCR5 co-receptor necessary for CCR5-tropic HIV-1 to enter cells. The entry of CXCR4-using HIV-1 into cells is not inhibited by maraviroc.

Antiviral Activity in Cell Culture

Maraviroc inhibits the replication of CCR5-tropic virus laboratory strains and clinical isolates of HIV-1 in models of acute peripheral blood leukocyte infection. The *In Vitro* IC_{50} (50% inhibitory concentration) for maraviroc against HIV-1 group M isolates (subtypes A to J and circulating recombinant from AE) and group O isolates ranged from 0.1 to 4.5 nM (0.05 to 2.3 ng/mL) in cell culture. 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.

The serum adjusted EC_{90} value in 43 primary CCR5-tropic HIV-1 clinical isolates was 0.57 (0.06 – 10.7) ng/mL without significant changes between different subtypes tested. Maraviroc has no antiviral activity in cell culture against viruses that can use CXCR4 as their entry co-receptor. The antiviral activity of maraviroc against HIV-2 has not been evaluated.

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

Resistance in Cell Culture

HIV-1 variants with reduced susceptibility to maraviroc have been selected *In Vitro*, following serial passage of 2 CCR5-tropic viruses. The maraviroc-resistant viruses remained CCR5-tropic and there was no conversion from a CCR5-tropic virus to a CXCR4-using virus. Two amino acid residue substitutions in the V3-loop region of the HIV-1 envelope glycoprotein (gp160), A316T, and I323V (numbering by alignment to the HIV-1 strain HXB2) were identified by site directed mutagenesis and were shown to be necessary for the maraviroc-resistant phenotype in the HIV-1 isolate CC1/85. In contrast, a 3-amino acid residue deletion in the V3 loop, ΔQAI (positions 315 to 317, numbering by alignment to the HIV-1 strain HXB2), was associated with the maraviroc-resistant phenotype in the RU570 isolate. Concentration-response curves for the maraviroc resistant viruses were characterized phenotypically by curves that did not reach 100% inhibition in drug assays using serial dilutions of maraviroc. The relevance of the specific gp120 mutations observed in isolates CC1/85 and RU570 to maraviroc susceptibility in other viruses is not known.

Cross-resistance in Cell Culture

Maraviroc had antiviral activity against HIV-1 clinical isolates resistant to NNRTIs, NRTIs, PIs, and the fusion inhibitor enfuvirtide in cell culture (EC_{50} values ranged from 0.7 to 8.9 nM (0.36 to 4.57 ng/mL)). Maraviroc-resistant viruses that emerged in cell culture remained susceptible to the enfuvirtide and the protease inhibitor saquinavir.

Clinical Resistance

Virologic failure on maraviroc can result from genotypic and phenotypic resistance to maraviroc, through outgrowth of undetected CXCR4-using virus present before maraviroc treatment (see **CLINICAL TRIALS, Tropism**), through resistance to background therapy drugs (Table 18), or due to low exposure to maraviroc (see **ACTION AND CLINICAL PHAMACOLOGY**).

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

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

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

Genotypic resistance of virus was evaluated with a clonal analysis of the V3 loop amino acid sequences performed in patients failing MVC with evidence of reduced MVC susceptibility. The V3 loop sequences of the pre-treatment and the on-treatment viruses generally differed between subjects. Unique patterns of multiple amino acid substitutions in the V3-loop of gp120 were detected in each of these viruses, however all had changes at either position 308 or 323. The contribution of mutations in other regions of gp120 to maraviroc resistance has not been investigated.

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

<u>Antiretroviral treatment-experienced subjects</u>
Week 48 data from treatment-experienced subjects failing maraviroc-containing regimens with CCR5-tropic virus (n=58) have identified 22 viruses that had decreased susceptibility to maraviroc characterized in phenotypic drug assays by concentration-response curves that did not reach 100% inhibition. Additionally, CCR5-tropic virus from 2 of these treatment failure subjects had ≥ 3-fold shifts in EC_{50} values for maraviroc at the time of failure.

Fifteen of these viruses were sequenced in the gp120 encoding region and multiple amino acid substitutions with unique patterns in the heterogeneous V3 loop region were detected. Changes at either amino acid position 308 or 323 (HXB2 numbering) were seen in the V3 loop in 7 of the subjects with decreased maraviroc susceptibility. Substitutions outside the V3 loop of gp120 may also contribute to reduced susceptibility to maraviroc.

Antiretroviral treatment-naïve subjects

Treatment-naïve subjects receiving CELSENTRI had more virologic failures and more treatment-emergent resistance to the background regimen drugs compared with those receiving efavirenz (Table 20).

Table 20 Development of Resistance to Maraviroc or Efavirenz and Background Drugs in Antiretroviral Treatment-naïve patients study (MERIT) with CCR5-Tropic Virus at Screening Using Enhanced Sensitivity TROFILE Assay

	Maraviroc	Efavirenz
Total N in Dataset (As-Treated)	273	241
Total Virologic Failures (As-Treated)	85(31%)	56 (23%)
Evaluable Virologic Failures with Post Baseline Genotypic and Phenotypic Data	73	43
• Lamivudine Resistance	39 (53%)	13 (30%)
• Zidovudine Resistance	2 (3%)	0
• Efavirenz Resistance	--	23 (53%)
• Phenotypic Resistance to Maraviroc[a]	19 (26 %)	

[a] Includes subjects failing with CXCR4 or dual/mixed tropism because these viruses are not intrinsically susceptible to maraviroc.

In an as-treated analysis of treatment-naïve subjects at 96 weeks, 32 subjects failed a maraviroc-containing regimen with CCR5-tropic virus and had a tropism result at failure; 7 of these subjects had evidence of maraviroc phenotypic resistance defined as concentration-response curves that did not reach 95% inhibition. A clonal analysis of the V3 loop amino acid envelope sequences was performed from 6 of the 7 subjects. Changes in V3 loop amino acid sequence differed between each of these different subjects, even for those infected with the same virus clade suggesting that that there are multiple diverse pathways to maraviroc resistance. The subjects who failed with CCR5-tropic virus and without a detectable maraviroc shift in susceptibility were not evaluated for genotypic resistance.

Of the 32 maraviroc virologic failures failing with CCR5-tropic virus, 20(63%) also had genotypic and/or phenotypic resistance to background drugs in the regimen (lamivudine, zidovudine).

TOXICOLOGY

Acute/Chronic Toxicity

The no observed adverse effect level (NOAEL) was found to be 750 mg/kg in the mouse and 100 mg/kg in the rat. The LD in both rats and mice is > 2000 mg/kg.

Repeat-Dose Toxicity Studies

Repeat-dose studies in CD-1 mice were associated with mortality and slight to mild degenerative changes to the superficial epithelium of the cecum at oral daily doses of 1,000 and 2,000 mg/kg and no adverse effects at 750 mg/kg. The AUC at the NOAEL provides an exposure 68-fold greater than that at the therapeutic dose. Maraviroc was also well tolerated in rasH2 transgenic mice at daily doses of 200, 800 and 1,500 mg/kg for up to 6 months.

In a 1-month oral range-finding study in male rats at daily doses of 100, 300, and 1500 mg/kg, the dose of 1500 mg/kg induced clinical signs of salivation, diarrhea, decreases in body weight and food consumption, dilatation of colon and cecum (probably secondary to diarrhea) and pituitary vacuolation. In addition, 2 rats had moderate increases in liver enzymes, associated in 1 rat with liver necrosis. The NOAEL was 300 mg/kg. In a 6-month study, dose levels of 30, 100, 300 and 900 mg/kg were well tolerated. Body weight in males treated with 900 mg/kg was reduced at the end of the treatment and reversibility periods. The liver was confirmed as the principal target organ, with changes in the bile duct (vacuolation from 100 mg/kg and hyperplasia from 300 mg/kg) and hepatocytes (altered cell foci and multinucleated cells at 900 mg/kg). Some hepatic changes in males treated with 300 and 900 mg/kg were still present after a 3-month reversibility period. Thyroid follicular cell hypertrophy at 300 and 900 mg/kg was shown to be reversible. An exploratory study to investigate thyroid function in rats showed that liver enzyme induction may have contributed to this change. The NOAEL is 100 mg/kg, providing an AUC exposure 8-fold greater than that at the therapeutic dose.

In dogs, maraviroc produced a range of clinical signs: emesis from 5 mg/kg, salivation, reddening of the skin and conjunctiva and mydriasis from 10 mg/kg, protruding nictitating membrane, lacrimation from 15 mg/kg and partially closed eyes from 40 mg/kg. Multiple bouts of emesis from 150 mg/kg and body weight loss at this dose are considered to set the maximum tolerated dose, at an exposure multiple of 23 (C_{max}) or 28 (AUC). There were inconsistent reductions in blood pressure in dogs at 50 and 250 mg/kg, and increases in QTc interval from 15 mg/kg. Consequently, the NOAEL is 5 mg/kg in dogs, providing a C_{max} exposure 2-fold greater than that at the therapeutic dose.

Studies in monkeys indicated that the daily dose of 800 mg/kg was not well tolerated. Animals treated with this dose were euthanized due to severe clinical signs (prostration, decreased activity, loss of balance, and vomiting) and cardiovascular effects (QT prolongation, decreased heart rate, and lowered diastolic blood pressure). Treatment at 400 mg/kg produced similar, though less severe, findings. After treatment for 9 months, body weight in males was reduced at 120 mg/kg (8%) and 400 mg/kg (11%). At 400 mg/kg (given as a divided dose), decreases in blood pressure, heart rate and increases in QTc interval were measured. At this dose, C_{max} exposures were 11-12 fold higher than seen at the therapeutic dose. Based on these cardiovascular changes the NOAEL is 120 mg/kg in monkeys, providing a C_{max} exposure 5-fold greater than that at the therapeutic dose.

Fertility and Reproduction

A fertility study was conducted to evaluate the effects of maraviroc on mating performance, the fertility of adult male and female rats and the development of the embryos during the pre- and post-implantation stages. The NOAEL for adult male and female rats was 300 mg/kg. There were no effects on fertility up to 1,000 mg/kg in either sex.

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. The only effect in the offspring was a slight increase in motor activity in male offspring rats at both weaning and as adults at the high dose, while no effects were seen in female offspring. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of maraviroc.

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 the oral embryofetal development study in rats at daily doses of 100, 300, and 1,000 mg/kg, the high dose was slightly toxic to pregnant females (decreased body weight and food consumption). There were no effects on reproductive parameters, embryofetal development or growth. The NOAEL was 300 mg/kg for the pregnant females and 1,000 mg/kg for the foetuses. In the oral embryofetal development study in rabbits at daily doses of 30, 75, and 200 mg/kg, death was observed at the high dose. There were no associated clinical signs or macroscopic findings. Treatment with maraviroc had no effect on reproductive parameters. An increased incidence of external anomalies was observed at the high dose. Thus, the NOAEL was 75 mg/kg (approximately 7-fold higher than seen at the therapeutic dose) for the pregnant females and fetuses.

Carcinogenesis and Mutagenesis

Carcinogenic potential was assessed in a 24-month study using Sprague-Dawley rats and in a 6-month study with Tg (rasH2) hemizygous mice. In rats, daily doses of 50, 100, 500 and 900 mg/kg were administered to males for 104 weeks and to females for 96 weeks (due to high mortality in female control rats). There was no adverse treatment effect on survival. Maraviroc produced a toxicologically significant decrease in mean body weight in the males at 500 and 900 mg/kg and in females at 900 mg/kg. An increased incidence of follicular cell adenoma of the thyroid was observed in both males and females of the high dose group (900 mg/kg; 21 times higher than that found at the human therapeutic dose of 300 mg twice daily). This may be associated with adaptive liver changes. A rare tumour, cholangiocarcinoma, was observed in the liver of 2 male rats at 900 mg/kg. The incidence was slightly higher than that observed in a large database of control animals (3/1850) and in the control group of a concurrent study (1/65).

In Tg(rasH2) mice, daily doses of 200, 800 and 1500 mg/kg did not produce hyperplastic, neoplastic inflammatory or degenerative changes. The free plasma AUC exposure in Tg mice at 1500 mg/kg was 54-times higher than that found at the human therapeutic dose.

Maraviroc is not considered to be genotoxic based on *In Vitro* (bacterial mutation, chromosome aberration in human lymphocytes) and *In Vivo* (mouse bone marrow micronucleus) tests.

Immunotoxicology

Immunotoxicologic potential was assessed in a 4-week oral immunotoxicology study in monkeys at daily doses of 30, 100 and 300 mg/kg (15, 50, 150 mg/kg twice daily). Treatment with maraviroc did not affect lymphocyte subset distribution, NK cell activity, phagocytosis activity, oxidative burst or humoral primary (IgM) and secondary (IgG) immune responses against KLH. There were no adverse pathological changes to the immune system. CCR5 co-receptors occupancy by maraviroc was complete at all timepoints at 300 mg/kg/day, while at 30 mg/kg/day CCR5 co-receptors occupancy was complete at the 1 hour post-dose time point only (receptor occupancy was approx. 79% at 7 and 24 hours after dosing).

Local Tolerance

In topical studies, maraviroc produced very slight dermal irritation at 2000 mg/kg in rats, which resolved on day 5, but no dermal irritation in rabbits.

Maraviroc produced very slight ocular irritation in an eye irritation study in rabbits and no evidence of skin sensitization in a local lymph node assay in mice.

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PART III: CONSUMER INFORMATION

[Pr]CELSENTRI
(maraviroc)

This leaflet is part III of a three-part "Product Monograph" published when CELSENTRI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CELSENTRI. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.

ABOUT THIS MEDICATION

What the medication is used for: CELSENTRI is an oral tablet used for the treatment of HIV-1 (Human Immunodeficiency Virus type 1) infection in adults, in combination with other anti-HIV drugs. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). CELSENTRI is a type of anti-HIV drug called a CCR5 antagonist.

CELSENTRI can reduce the amount of HIV in the blood (called "viral load") and increase the number of CD4 (T) cells. This may keep your immune system healthy, so it can help fight infection.

CELSENTRI is used with other anti-HIV medicines in adults with CCR5-tropic HIV-1 infection.

CELSENTRI does not cure HIV infection or AIDS. People taking CELSENTRI may still develop infections or other conditions associated with HIV infection. Although CELSENTRI is not a cure for HIV or AIDS, CELSENTRI can help reduce your risks of getting illnesses associated with HIV infection (AIDS and opportunistic infection).

CELSENTRI does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of contact with any body fluids such as semen, vaginal secretions, or blood. Never re-use or share needles.

This medicine is prescribed for your particular condition. Do not use it for any other condition. Do not give CELSENTRI to other people, even if they have the same symptoms you have. It may harm them.

What it does: CELSENTRI works by blocking a receptor called CCR5 that a type of HIV uses to enter cells in your blood called CD4 or T-cells. This virus type is called CCR5-tropic HIV. Your doctor may take blood samples to determine if you have been infected with CCR5-tropic HIV and determine if CELSENTRI is an appropriate treatment for you.

When it should not be used: If you are allergic (hypersensitive) to maraviroc or any of the other ingredients of CELSENTRI (see **What the important nonmedicinal ingredients are**).

CELSENTRI is not recommended for use in children.

What the medicinal ingredient is: The active ingredient is maraviroc.

What the important nonmedicinal ingredients are: Other non-medicinal ingredients present in CELSENTRI film-coated tablets include: microcrystalline cellulose, dibasic calcium phosphate, sodium starch glycolate, magnesium stearate.

Film-coat: aluminum lake (FD&C blue #2), macrogol 3350, polyvinyl alcohol, soya lecithin, talc, and titanium dioxide.

What dosage forms it comes in: CELSENTRI comes in oval-shaped, blue, film-coated tablets in 150 mg and 300 mg strengths.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Liver problems

Liver problems (liver toxicity) have happened in patients taking CELSENTRI. An allergic reaction may happen before liver problems occur. Stop taking CELSENTRI and call your doctor right away if you get any of the following symptoms:

- an itchy rash on your body (allergic reaction)
- your skin or eyes look yellow and/or dark (tea-colored) urine
- vomiting and/or upper right stomach area (abdominal) pain

You should see your doctor right away but continue taking CELSENTRI if you have any of the following other symptoms: nausea, fever, flu-like symptoms, fatigue.

BEFORE you use CELSENTRI talk to your doctor or pharmacist if:

- You have liver problems or are infected with Hepatitis B and/or Hepatitis C, as your liver function may need to be closely monitored.
- You have a history of low blood pressure or low blood pressure on standing (postural hypotension) and/or if you are taking any medication to lower blood pressure.
- You have heart disease
- You have a history of any kidney problems.
- You are pregnant, planning to become pregnant, or become pregnant while taking CELSENTRI. It is not known if CELSENTRI can harm your unborn child. You and your doctor will need to decide if taking CELSENTRI is right for you. If you take CELSENTRI while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- You are breast-feeding. You should not breast-feed if you are HIV-positive because of the chance of passing HIV to your baby. Also, it is not known if CELSENTRI can pass into your breast milk and if it can harm your baby. Talk with your doctor about the best way to feed your baby.

Other warnings:

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your CELSENTRI supply starts to run low, ask your doctor or pharmacist for a refill. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time.
- You should never stop taking CELSENTRI or your other HIV medicines without talking with your doctor.
- Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking CELSENTRI. These reactions included rash, fever and sometimes organ dysfunction and liver failure. 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
    - Blisters and peeling skin, particularly around the mouth, nose, eyes and genitals
    - Symptoms of liver problems such as a general feeling of being sick or unwell, feeling very tired, loss of appetite, stomach pain, itching, yellowing of the skin and eyes, dark urine, drowsiness and confusion.

  Contact a doctor immediately. Stop taking CELSENTRI.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Your doctor may need to adjust your dose of CELSENTRI depending on which other medications you are taking. Do not start or stop any other medications without your doctor or pharmacist's approval.

The following medications are known to interact or may interact with CELSENTRI and your doctor may adjust the dosage of CELSENTRI:

- clarithromycin, ketoconazole, itraconazole, rifampin
- delavirdine
- atazanavir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz, etravirine, lopinavir/ritonavir, saquinavir, saquinavir/ritonavir, nelfinavir, fosamprenavir/ritonavir and other anti-HIV combinations
- anticonvulsant medicines (carbamazepine, phenobarbital, phenytoin)
- St. John's Wort (Hypericum perforatum) should not be used as it may reduce the amount of CELSENTRI in the blood and reduce the effectiveness of this medication.

Tell your doctor if you are taking fluconazole.

PROPER USE OF THIS MEDICATION

Usual adult dose: CELSENTRI should be taken every day as prescribed in combination with other medicines used to treat HIV. The recommended dose of CELSENTRI in adults is 300 mg twice daily. However, a dose adjustment may be needed due to the potential for interactions with other medicinal products. Further adjustment may be necessary if you also have kidney problems. CELSENTRI can be taken with or without food. CELSENTRI comes in a tablet form and should be swallowed with plenty of liquid (e.g. water). Do not chew the tablets.

Overdose:

If you are concerned that you may have taken too much CELSENTRI, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, CELSENTRI can cause side effects, although not everybody gets them.

The most common side effects include: cough, fever, upper respiratory tract infections, rash, muscle-related symptoms (such as muscle pain, aches or soreness), abdominal pain, dizziness, constipation, itching, difficulty sleeping, diarrhea, nausea, and headache.

Tell your doctor promptly about these or other symptoms. If the condition persists or worsens, seek medical attention.

Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment. Look for any other symptoms such as:

- High temperature (fever), redness, rash or swelling
- Fatigue
- Joint or muscle pain
- Numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- Palpitations (chest pain) or rapid heart rate
- Yellowing of the skin or eyes

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

If you experience dizziness or fainting while taking CELSENTRI, do not drive or operate heavy machinery.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	- Possible chance of infection		√	
	- Breathing abnormalities		√	
Uncommon	- Heart problems including heart attack			√
	- Immune Reconstitution Inflammatory Syndrome (your immune system may get stronger and could begin to fight other infections)		√	
	- Low blood pressure when standing up (postural hypotension) can cause dizziness or fainting	√		
Rare	-A severe or life-threatening skin reaction (see WARNINGS AND PRECAUTIONS)			√

This is not a complete list of side effects. For any unexpected effects while taking* CELSENTRI*, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C and 30°C, in the original package. **Do not take CELSENTRI after the expiry date shown on the package. Keep out of the reach of children. This medicine has been prescribed for your medical problem. Do not give it to anyone else. Discuss all your questions about your health with your doctor. If you have questions about CELSENTRI ask your doctor, nurse or pharmacist.**

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: **Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.**

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.viivhealthcare.com
or by contacting the sponsor, ViiV Healthcare ULC at:
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