Maraviroc

Brand Name: Selzentry
Drug Class: Entry and Fusion Inhibitors

Drug Description

Maraviroc, also known as Selzentry, is a chemokine receptor antagonist that acts as an entry inhibitor. It is designed to prevent HIV infection of CD4 cells by blocking chemokine receptor 5 (CCR5), a coreceptor necessary for HIV entry, from binding to HIV. [1]

HIV/AIDS-Related Uses

Maraviroc, a first-in-its-class, selective, CCR5-coreceptor antagonist, was granted accelerated regulatory review in the United States and Europe in February 2007.[2] In April 2007, the FDA's Antiviral Drugs Evaluation Committee unanimously recommended accelerated approval of maraviroc for treatment-experienced patients.[3] Maraviroc received accelerated approval by the FDA on August 6, 2007. The accelerated approval was based on 24-week, interim data from two ongoing trials.[4] [5] After evaluation of longer-term safety and efficacy data, the FDA granted full approval of maraviroc on November 25, 2008.[6]

Maraviroc is approved for use in combination with other antiretroviral (ARV) medications for the treatment of CCR5-tropic HIV-1 (R5 virus) in adults whose viral loads remain detectable despite existing ARV treatment or who have multiple-drug--resistant virus. Among treatment-experienced patients, approximately 50% to 60% have R5 virus. Maraviroc is not approved for use in patients 16 years of age or younger.[7] [8] Safety and efficacy are not established in treatment-naive HIV infected people or in those with dual- or mixed-tropic or with CXCR4-tropic virus.[9]

In 2006, Pfizer opened a worldwide expanded access program (EAP) to provide maraviroc to patients with HIV who have limited or no treatment options. The multinational EAP will continue to provide maraviroc in countries in which it is not yet available. Patients and health care professionals can visit http://www.maraviroceap.com for more information.[10] [11]

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Maraviroc binds to CCR5, preventing HIV from binding to this receptor. When CCR5 is unavailable, CCR5-tropic HIV cannot engage a CD4 cell to infect the cell. The CCR5-tropic variant of the virus is common in earlier HIV infection, whereas viruses adapted to use the CXCR4 receptor gradually become dominant as HIV infection progresses.[12] Maraviroc did not display efficacy against CXCR4-tropic or mixed- or dual-tropic virus in Phase II efficacy studies.[13]

Peak plasma concentrations (Cmax) of maraviroc are achieved between 0.5 and 4 hours after single oral doses of maraviroc 1,200 mg in healthy volunteers. Maraviroc pharmacokinetics are not dose proportional. The absolute bioavailability of a 100-mg dose is 23% and is predicted to be 33% after a 300-mg dose.[14]

Maraviroc is metabolized by the cytochrome P450 (CYP) liver enzyme system, primarily by CPY3A; metabolites of maraviroc are inactive against HIV-1. The terminal half-life of maraviroc at steady-state is between 14 and 18 hours. Maraviroc, rather than metabolites, was the main component recovered.[15]

Maraviroc is moderately protein bound (approximately 76%) and has a volume of distribution of approximately 194 liters. Renal clearance accounts for approximately 25% of total clearance of maraviroc. Drug concentrations may be increased in patients with renal impairment, although the safety and efficacy of maraviroc have not been studied in this patient population. Dialysis may be useful in reducing maraviroc levels.[16]

Maraviroc is in Pregnancy Category B. No adequate and well-controlled studies have been conducted in pregnant women. However, the incidence of fetal malformations in animal studies, conducted at doses up to 20-fold higher than recommended human doses, was not increased. To monitor maternal-fetal outcomes of pregnant women exposed to maraviroc and other ARV medications, an Antiretroviral Pregnancy Registry has been established. Physicians may register patients online at http://www.APRegistry.com or

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by calling 800-258-4263.[17]

In a small, Phase I study conducted in 2003, 24 HIV infected adults with CCR5-tropic HIV were randomized to receive maraviroc 25 mg once daily, 100 mg twice daily, or placebo. Steady-state drug levels were reached within 7 days, with more favorable drug levels achieved in the fasted state. By Day 14, those receiving 100 mg doses had experienced a viral load decline of more than 20-fold compared with a nearly threefold reduction in the 25-mg group. The drug was well tolerated, and viral load did not rebound immediately upon cessation of the drug, indicating that a proportion of the receptors remain blocked for some time.[18]

Interim Week 24 results of the two Phase IIb/III placebo-controlled studies MOTIVATE-1 and -2 indicate that treatment with maraviroc plus optimized background therapy (OBT) leads to superior viral control compared with OBT alone. These studies are following a total of 1,049 participants, residing in Europe, Australia, Canada, and the United States, who are triple class resistant, had baseline viral loads of more than 5,000 copies/ml, and had baseline CD4 counts of approximately 150 cells/mm3. With maraviroc treatment, these participants had viral load reductions of as much as 99% from baseline at a dosage of maraviroc 300 mg once or twice daily while on OBT. CD4 counts in these participants also increased by 56% to 74% from baseline during this time period.[19] Long-term Week 48 data demonstrate that maraviroc plus OBT significantly increase CD4 count compared with OBT alone. In addition, 3 times as many participants receiving maraviroc plus OBT achieved undetectable viral load levels compared with those receiving OBT alone.[20]

Because the impairment of CCR5 could have a negative impact on regular immune function, safety studies have been performed in both healthy and HIV-1 infected people at doses of up to 1,200 mg of maraviroc daily for 10 to 28 days. These studies showed that maraviroc did not have an effect on immune function, and no increased frequency or severity in infections was seen. However, an increase in CD4 count also was not seen over this time period.[21]

In an evaluation of 973 treatment-experienced patients in two ongoing Phase III trials, important predictors of virologic success (viral load less than 400 copies/ml at 24 weeks) included the mean predicted trough concentration of maraviroc, the baseline viral load, and the baseline CD4 count.[22]

In the Phase III MERIT study, maraviroc 300 mg twice daily was compared with efavirenz 600 mg once daily, both in combination with zidovudine/lamivudine. A total of 721 treatment-naïve, HIV-infected patients with CCR5-tropic virus and without evidence of HIV resistance were selected to participate. Rates of virologic suppression to less than 400 copies/mL and less than 50 copies/mL were greater in the efavirenz-treated arm and did not reach criteria for noninferiority of maraviroc.[23] [24]

However, a 2008 reanalysis of the MERIT data that used a newer, more sensitive tropism assay identified 104 of the original 721 patients who actually harbored CXCR4-tropic virus. After their exclusion, analysis of only patients with CCR5-tropic virus resulted in Week 48 virologic suppression rates of 68.5% and 68.3% for maraviroc- and efavirenz-treated arms, respectively, which met criteria for maraviroc noninferiority.[25]

HIV-1 variants with reduced susceptibility to maraviroc have been selected in cell cultures. In an in vitro study using six primary CCR5 HIV-1 isolates, those able to replicate in the presence of high maraviroc concentrations emerged gradually after multiple passages of all isolates. Two isolates resistant to maraviroc continued to use the CCR5 receptor and one isolate developed the ability to use the CXCR4 receptor. In the viruses that remained R5 tropic, two different sets of mutations developed in the gp120 V3 loop region; this and other data suggest that changes in viral tropism are independent of maraviroc.[26] [27] All CCR5 antagonists bind to CCR5 in a pocket formed by transmembrane helices and extracellular loop 2 (ECL2); it appears that subtle differences in occupation of the binding pocket may block replication of some HIV strains. As a result, scientists are optimistic that resistance to an HIV

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coreceptor antagonist will not necessarily lead to drug class resistance.[28]

Clinical resistance to maraviroc has not yet been fully defined. Virologic failure has been associated with viral tropism switches that occur over time. In an examination of 5 participants who had CCR5-tropic virus at the time of treatment failure while on maraviroc, all 5 had mutations at position 13 or 26 of the V3 loop of CCR5. In an examination of 20 participants who had CXCR4-tropic virus at the time of treatment failure while on maraviroc, 14 participants experienced outgrowth of CXCR4-tropic virus that was undetectable at study entry, whereas 6 experienced a tropism switch.[29] Of the 1,043 patients with R5 virus at screening for the 2 ongoing Phase III trials, 7.6% displayed dual- or mixed-tropism at baseline measurements taken approximately 5 weeks later. In subsequent interim analysis, CXCR4-tropic virus was identified in approximately 60% of patients who failed treatment on maraviroc compared with 6% of patients who experienced treatment failure while on placebo.[30]

Adverse Events/Toxicity

In the two Phase II/III MOTIVATE-1 and -2 studies, adverse effects at Week 24 interim analysis were similar to those that occurred with optimized background therapy (OBT) alone. In these studies, 5% or fewer study participants in both placebo and treatment groups discontinued treatment because of adverse events.[31]

These two studies showed no increase in mortality or malignancy and no clear evidence of hepatotoxicity. However, an increase in Candida, herpes, and influenza infections were observed in these studies.[32]

In 24-week analysis of these two clinical studies, the most common maraviroc-related adverse effects (occurring in more than 8% of patients and more often than in the placebo group) were cough, fever, upper respiratory infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness. Additional adverse effects noted with greater incidence in the once-daily treatment arm included diarrhea, edema, sleep disorders, rhinitis, and urinary abnormalities. Serious adverse events occurred in less than 2% of maraviroc-treated patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis. Grade 3 to 4 treatment-emergent laboratory abnormalities occurring in at least 2% of patients included increased bilirubin, amylase, lipase, AST, and ALT levels.[33] At Week 48 analysis of the same studies, the most commonly observed adverse events in the maraviroc plus OBT arm were diarrhea, nausea, fatigue, and headache, all of which occurred with similar incidence in the OBT-only arm.[34]

One case of possible drug-associated hepatotoxicity with allergy has been reported in a study of healthy volunteers. Systemic allergic reaction prior to the onset of hepatotoxicity may involve pruritic rash, eosinophilia, or increased IgE levels. Although no statistically significant increases in Grade 3 to 4 liver function tests have been reported, an increased rate of hepatic adverse events has been observed in treatment-experienced patients. Immediate evaluation and possible discontinuation of maraviroc are warranted in patients exhibiting signs or symptoms of hepatotoxicity, including systemic rash reactions or abnormal liver function tests.[35] To date, only 6% of patients in clinical studies have been coinfected with hepatitis B or C virus; large-scale clinical trials with coinfected individuals are needed to determine the risk of hepatic adverse events in these patients. Maraviroc should be prescribed to patients with HIV and hepatitis coinfections with caution.[36] [37]

Immune reconstitution syndrome has also been reported. In addition, patients taking maraviroc should be monitored for risk of infection because of CCR5-antagonism effects on some immune cells.[38]

Cardiovascular events, including myocardial ischemia or infarction, have been observed at higher rates in maraviroc-treated patients than in placebo. QT prolongation has been observed in animal studies at up to 12 times the recommended human dosage, but no prolongation has been noted

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Adverse Events/Toxicity (cont.)

in treatment-experienced patients taking recommended dosages. When given to HIV infected patients in Phase III studies at recommended dosages, no greater rates of postural hypotension were observed. However, the dose-limiting adverse effect in clinical studies, observed at daily doses of maraviroc 600 mg, is postural hypotension.[39]

Drug and Food Interactions

Coadministration of a 300-mg tablet and a high-fat meal has resulted in reduced Cmax and AUC by 33% each in healthy volunteers. However, because no food restrictions were enacted during clinical trials, maraviroc may be taken with or without food.[40]

Maraviroc is a cytochrome P450 (CYP) 3A and p-glycoprotein (Pgp) substrate and may require dosage adjustments when administered with CYP- or Pgp-modulating medications. CYP3A/Pgp inhibitors such as ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir, and atazanavir increase maraviroc Cmax and AUC; CYP3A/Pgp inducers such as carbamazepine, phenytoin, phenobarbital, rifampin, and efavirenz decrease maraviroc Cmax and AUC. Tipranavir/ritonavir, a CPY3A inhibitor but a Pgp inducer, does not affect maraviroc pharmacokinetics.[41]

Clinical Trials

For information on clinical trials that involve Maraviroc, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Maraviroc AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[42]

Dosage Form: Maraviroc is available as 150- and 300-mg film-coated tablets. The recommended dose of maraviroc differs when administered with concomitant medications because of potential drug interactions.[43]

Maraviroc must be given in combination with other antiretroviral medications. Safety and efficacy have not been established in patients 16 years of age or younger. Dosage adjustments are required when maraviroc is administered in combination with CYP inhibitors or inducers; specific adjustments according to the coadministered medication can be found in the manufacturer prescribing information.[44]

Storage: Film-coated tablets should be stored at 25 C (77 F), with excursions permitted between 15 C and 30 C (59 F and 86 F). Maraviroc tablet shelf-life is 24 months.[45]

Chemistry

CAS Name: Cyclohexanecarboxamide, 4,4-difluoro-N-((1S)-3-((3-exo)-3-(3-methyl-5-(1-methylethyl)-4H -1,2,4-triazol-4-yl)-8-azabicyclo(3.2.1) oct-8-yl)-1-phenylpropyl)-[46]

CAS Number: 376348-65-1[47]

Molecular formula: C29-H41-F2-N5-O[48]

C67.81%, H8.04%, F7.40%, N13.63%, 03.11%[49]

Molecular weight: 513.67[50]

Physical Description: White to pale-colored powder.[51]

Solubility: Highly soluble across the pH range of 1 to 7.5.[52]

Other Names

UK-427,857[53]

Celsentri[54]

MVC[55]

Further Reading

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Manufacturer Information

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Pfizer Inc
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New York, NY 10017-5755
(800) 438-1985

Selzentry
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(800) 438-1985

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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