Maraviroc

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Disclosures

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Maraviroc

150 mg and 300 mg

Entry Inhibitor

Dosing: twice daily dosing, with or without food
Marviroc: Indications and Dosing

• **Indication**
  - In combination with other antiretroviral agents for adults (and children ≥2 kgs) who have only CCR5-tropic HIV-1
  - Requires HIV Tropism Assay testing before use
  - Not recommended for initial treatment of HIV-1 infection

• **Preparations**
  - Tablets: 25-mg, 75-mg, 150-mg, and 300-mg
  - Oral Solution: 20 mg per mL clear, colorless, strawberry-flavored

• **Dosing**
  - Twice daily dosing, with dose dependent on interactions with other medications
  - Take with or without food

Source: Maraviroc Prescribing Information
## Maraviroc: Recommended Dosage in Adults

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent cytochrome P450 (CYP)3A inhibitors(^a) (+/- potent CYP3A inducer)</td>
<td>150 mg twice a day</td>
</tr>
<tr>
<td>Noninteracting concomitant medications(^b)</td>
<td>300 mg twice a day</td>
</tr>
<tr>
<td>Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor)(^c)</td>
<td>600 mg twice a day</td>
</tr>
</tbody>
</table>

\(^a\) Potent CYP3A inhibitors (+/- potent CYP3A inducer) including: clarithromycin, cobicistat, elvitegravir/ritonavir, itraconazole, ketoconazole, nefazodone, protease inhibitors (except tipranavir/ritonavir), telithromycin.

\(^b\) Noninteracting concomitant medications include all medications that are not potent CYP3A inhibitors or inducers such as: dolutegravir, enfuvirtide, nevirapine, all nucleoside reverse transcriptase inhibitors (NRTIs), raltegravir, and tipranavir/ritonavir.

\(^c\) Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor) including: carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, and rifampin.
## Maraviroc: Dosing Based on Renal Function

### Recommended Maraviroc Dosage in Adults Based on Renal Function

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>Dosage of Maraviroc Based on Renal Function</th>
<th>End-Stage Renal Disease on Regular Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥30 mL/min</td>
<td>CrCl &lt;30 mL/min</td>
<td></td>
</tr>
<tr>
<td><strong>Potent CYP3A inhibitors (with or without a CYP3A inducer)</strong></td>
<td>150 mg twice daily</td>
<td>Contraindicated</td>
</tr>
<tr>
<td><strong>Noninteracting concomitant medications</strong></td>
<td>300 mg twice daily</td>
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<td>600 mg twice daily</td>
<td>Contraindicated</td>
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- **Contraindicated**: Dosing should not be used in these cases.
- **Potent CYP3A inhibitors (with or without a CYP3A inducer)** including: clarithromycin, cobicistat, elvitegravir/ritonavir, itraconazole, ketoconazole, nefazodone, protease inhibitors (except tipranavir/ritonavir), telithromycin.
- **Noninteracting concomitant medications** include all medications that are not potent CYP3A inhibitors or inducers such as: dolutegravir, enfuvirtide, nevirapine, all NRTIs, raltegravir, and tipranavir/ritonavir.
- **Potent and moderate CYP3A inducers** (without a potent CYP3A inhibitor) including: carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, and rifampin.
- **Maraviroc dosing should be decreased to 150 mg twice daily if patients experience symptoms of postural hypotension**

*Source: Maraviroc Prescribing Information*
Maraviroc: Mechanism of Action
Host Cellular Co-Receptors Involved in HIV Entry

**Illustration:** David H. Spach, MD

- **HIV**
- **CD4**
- **Coreceptors:** CCR5, CXCR4
### HIV Tropism

<table>
<thead>
<tr>
<th>R5-Tropic</th>
<th>X4-Tropic</th>
<th>Dual Tropic</th>
<th>Mixed Tropic</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="R5-Tropic Illustration" /></td>
<td><img src="image2" alt="X4-Tropic Illustration" /></td>
<td><img src="image3" alt="Dual Tropic Illustration" /></td>
<td><img src="image4" alt="Mixed Tropic Illustration" /></td>
</tr>
</tbody>
</table>

- **R5-Tropic**: R5
- **X4-Tropic**: X4
- **Dual Tropic**: R5 / X4
- **Mixed Tropic**: R5 / X4

Illustration: David H. Spach, MD
Maraviroc: Mechanism of Action

R5-Tropic HIV (R5)

Intracellular Space
Host Cell

Illustration: David H. Spach, MD
HIV Entry Inhibitor: CCR5 Antagonist

Maraviroc binds to host CCR5 coreceptor, causing conformational changes that prevent binding of HIV gp120 to the CCR5 coreceptor.
Coreceptor Tropism Results: Maraviroc Indication

<table>
<thead>
<tr>
<th>R5</th>
<th>X4</th>
<th>Dual Tropic</th>
<th>Mixed Tropic</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Illustration: David H. Spach, MD

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</tr>
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Illustration: David H. Spach, MD
Key Clinical Trials
Maraviroc: Summary of Key Studies

• **Trials in Treatment Naïve**
  - ¹MERIT: Maraviroc (QD or BID + ZDV-3TC versus Efavirenz + ZDV-3TC)
    • Maraviroc inferior to efavirenz for virologic suppression

• **Trials In Treatment-Experienced Persons**
  - ²MOTIVATE 1 & MOTIVATE 2: Maraviroc (QD or BID) + OBT
    • Maraviroc + OBT significantly greater virologic suppression than OBT alone

• **Switch Trials**
  - ³ROCnRal (ARNS 157): Switch to 2-drug Maraviroc + Raltegravir
    • In treatment-experienced patients, maraviroc + raltegravir lacked virological robustness

Maraviroc in Patients with Multiclass Antiretroviral Drug Resistance
MOTIVATE 1 and 2: Study Design

- **Background:** Two parallel, randomized, double-blind, placebo-controlled, phase 3 trials comparing 2 doses of maraviroc in treatment-experience persons

- **Inclusion Criteria**
  - Age ≥16 years
  - Treatment experienced
  - Resistance to ≥ 3 ARV classes
  - Only R5-tropic HIV
  - Stable ARV regimen or no regimen for ≥4 weeks with HIV RNA ≥ 5,000 copies/mL

MOTIVATE = Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients

Maraviroc in Patients with Multiclass Antiretroviral Drug Resistance
MOTIVATE 1 and 2: Results

Week 48: Virologic Response (ITT, missing=nonresponse)

Maraviroc in Patients with Multiclass Antiretroviral Drug Resistance

MOTIVATE 1 and 2: Results

Week 48: Change in CD4 Cell Count from Baseline

![Bar chart showing change in CD4 count (cells/mm$^3$) for MVC once daily + OBT, MVC twice daily + OBT, and Placebo + OBT in MOTIVATE 1 and 2 trials.]

Maraviroc in Patients with Multiclass Drug Resistance
MOTIVATE 1 and 2: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Maraviroc QD + OBT (n = 414)</th>
<th>Maraviroc BID + OBT (n = 426)</th>
<th>Placebo (n = 219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>43 (10%)</td>
<td>32 (8%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (3%)</td>
<td>21 (4%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Fever</td>
<td>9 (2%)</td>
<td>24 (6%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (5%)</td>
<td>9 (2%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 (6%)</td>
<td>25 (6%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>16 (4%)</td>
<td>20 (5%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Abbreviations: OBT = optimized background therapy; QD = once daily; BID = twice daily

Adverse Effects
Maraviroc: Potential Severe Drug Reactions

- **Hepatotoxicity** *(Black Box Warning)*
  - Maraviroc can cause severe hepatotoxicity +/- severe skin & hypersensitivity reactions
  - Severe skin rash or systemic allergic reactions may develop prior to hepatotoxicity

- **Skin rash or systemic allergic reactions**
  - Maraviroc may cause severe severe skin and hypersensitivity reactions +/- hepatotoxicity
  - Reactions include fever, eosinophilia, elevated IgE, or other systemic symptoms

- **Timing and Evaluation of Severe Maraviroc-Related Drug Reaction**
  - Timing of severe reactions is approximately 1 month after starting maraviroc
  - Persons taking maraviroc should have immediate evaluation if they develop any of the following: sign or symptoms of hepatitis, a severe skin rash or systemic allergic reaction
Resistance
### Resistance to Maraviroc: Change in Viral Tropism

<table>
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<tr>
<th>R5</th>
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<th>Dual Tropic</th>
<th>Mixed Tropic</th>
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<tbody>
<tr>
<td><strong>Maraviroc Sensitive</strong></td>
<td><strong>Maraviroc Resistant</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **R5**  
  - Maraviroc Sensitive: CCR5
  - Maraviroc Resistant: CCR5

- **X4**  
  - Maraviroc Sensitive: CXCR4
  - Maraviroc Resistant: CXCR4

- **Dual Tropic**  
  - Maraviroc Sensitive: CCR5/CXCR4
  - Maraviroc Resistant: CCR5/CXCR4

- **Mixed Tropic**  
  - Maraviroc Sensitive: CCR5
  - Maraviroc Resistant: CXCR4

*Illustration: David H. Spach, MD*
Resistance to Maraviroc: HIV Binds to CCR5 in Presence of Maraviroc
Maraviroc: Summary

- Oral, twice-daily HIV entry inhibitor that selectively binds to human C-C chemokine receptor 5 (CCR5)
- Need to perform HIV tropism assay prior to use
- Typically used as part of salvage antiretroviral therapy for heavily-treatment experienced individuals
- Can be combined with other entry inhibitors (ibalizumab, enfuvirtide, fostemsavir), and other salvage antiretroviral medications
- Generally well tolerated with few long-term adverse effects or drug interactions, though rarely
- Rarely may cause hepatotoxicity and/or severe skin and allergic reactions
Acknowledgments

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