

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SELZENTRY safely and effectively. See full prescribing information for SELZENTRY.

SELZENTRY (maraviroc) tablets, for oral use  
SELZENTRY (maraviroc) oral solution  
Initial U.S. Approval: 2007

<p><b>WARNING: HEPATOTOXICITY</b>  <i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> <li>• Hepatotoxicity has been reported which may be preceded by severe rash or other features of a systemic allergic reaction (e.g., fever, eosinophilia, or elevated IgE). (5.1)</li> <li>• Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. (5.1)</li> </ul>
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----- **INDICATIONS AND USAGE** -----

SELZENTRY is a CCR5 co-receptor antagonist indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic HIV-1 infection in patients 2 years of age and older weighing at least 10 kg. (1)  
Limitations of Use:

- Not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1. (1)

----- **DOSAGE AND ADMINISTRATION** -----

Prior to initiation of SELZENTRY, test all patients for CCR5 tropism using a highly sensitive tropism assay. (2.1)

SELZENTRY tablets and oral solution are taken twice daily by mouth and may be taken with or without food. SELZENTRY must be given in combination with other antiretroviral medications. (2.2)

Recommended Dosage in Adults: (2.3)

Concomitant Medications	Dosage of SELZENTRY
When given with potent CYP3A inhibitors (with or without potent CYP3A inducers) including PIs (except tipranavir/ritonavir), delavirdine (2.3, 7.1)	150 mg twice daily
With NRTIs, tipranavir/ritonavir, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or CYP3A inducers (2.3, 7.1)	300 mg twice daily
With potent CYP3A inducers including efavirenz (without a potent CYP3A inhibitor) (2.3, 7.1)	600 mg twice daily

A more complete list of coadministered drugs is listed in *Dosage and Administration*. (2)

Pediatric Patients Aged 2 Years and Older and Weighing at Least 10 kg: Administer twice daily. Dosage should be based on body weight (kg) and concomitant medications and should not exceed the recommended adult dose. (2.4)

Patients with Renal Impairment: Dose adjustment may be necessary in patients with renal impairment. (2.5)

----- **DOSAGE FORMS AND STRENGTHS** -----

- Tablets: 25 mg, 75 mg, 150 mg and 300 mg. (3)
- Oral Solution: 20 mg per mL (3)

----- **CONTRAINDICATIONS** -----

- SELZENTRY is contraindicated in patients with severe renal impairment or end-stage renal disease (ESRD) (CrCl less than 30 mL per minute) who are concomitantly taking potent CYP3A inhibitors or inducers. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Hepatotoxicity accompanied by severe rash or systemic allergic reaction, including potentially life-threatening events, has been reported. Hepatic laboratory parameters including ALT, AST, and bilirubin should be obtained prior to starting SELZENTRY and at other time points during treatment as clinically indicated. If rash or symptoms or signs of hepatitis or allergic reaction develop, hepatic laboratory parameters should be monitored and discontinuation of treatment should be considered. When administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with hepatitis B and/or C virus, additional monitoring may be warranted. (5.1)
- Severe and potentially life-threatening skin and hypersensitivity reactions have been reported in patients taking SELZENTRY. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis. Immediately discontinue SELZENTRY and other suspected agents if signs or symptoms of severe skin or hypersensitivity reactions develop and monitor clinical status, including liver aminotransferases, closely. (5.2)
- More cardiovascular events, including myocardial ischemia and/or infarction, were observed in treatment-experienced subjects who received SELZENTRY. Additional monitoring may be warranted. (5.3)
- If patients with severe renal impairment or ESRD receiving SELZENTRY (without concomitant CYP3A inducers or inhibitors) experience postural hypotension, the dose of SELZENTRY should be reduced from 300 mg twice daily to 150 mg twice daily. (5.3)

----- **ADVERSE REACTIONS** -----

- The most common adverse events in treatment-experienced adult subjects (greater than 8% incidence) which occurred at a higher frequency compared with placebo are upper respiratory tract infections, cough, pyrexia, rash, and dizziness. (6.1)
- The most common adverse events in treatment-naive adult subjects (greater than 8% incidence) which occurred at a higher frequency than the comparator arm are upper respiratory tract infections, bronchitis, flatulence, bloating and distention, upper respiratory tract signs and symptoms, and gastrointestinal atonic and hypomotility disorders. (6.1)
- The most common adverse reactions in treatment-experienced pediatric subjects (greater than or equal to 3% incidence) are vomiting, abdominal pain, diarrhea, nausea, and dizziness. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **DRUG INTERACTIONS** -----

- Coadministration with CYP3A inhibitors, including protease inhibitors (except tipranavir/ritonavir) and delavirdine, will increase the concentration of SELZENTRY. (7.1)
- Coadministration with CYP3A inducers, including efavirenz, may decrease the concentration of SELZENTRY. (7.1)
- Coadministration with St. John's wort is not recommended. (7.1)

----- **USE IN SPECIFIC POPULATIONS** -----

- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 07/2018**

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: HEPATOTOXICITY**

3 **Hepatotoxicity has been reported with use of SELZENTRY. Severe rash or evidence of a**  
4 **systemic allergic reaction (e.g., fever, eosinophilia, or elevated IgE) prior to the**  
5 **development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or**  
6 **allergic reaction following use of SELZENTRY should be evaluated immediately [see**  
7 ***Warnings and Precautions (5.1)*].**

8 **1 INDICATIONS AND USAGE**

9 SELZENTRY is indicated in combination with other antiretroviral agents for the treatment of  
10 only CCR5-tropic human immunodeficiency virus type 1 (HIV-1) infection in patients 2 years of  
11 age and older weighing at least 10 kg.

12 Limitations of Use:

- 13 • SELZENTRY is not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1  
14 [*see Microbiology (12.4)*].

15 **2 DOSAGE AND ADMINISTRATION**

16 **2.1 Testing prior to Initiation of SELZENTRY**

17 Prior to initiation of SELZENTRY, test all patients for CCR5 tropism using a highly sensitive  
18 tropism assay. SELZENTRY is recommended for patients with only CCR5-tropic HIV-1  
19 infection. Outgrowth of pre-existing low-level CXCR4- or dual/mixed-tropic HIV-1 not detected  
20 by tropism testing at screening has been associated with virologic failure on SELZENTRY [*see*  
21 *Microbiology (12.4), Clinical Studies (14.1)*].

22 Monitor patients for ALT, AST, and bilirubin prior to initiation of SELZENTRY and at other  
23 time points during treatment as clinically indicated [*see Warnings and Precautions (5.1)*].

24 **2.2 General Dosing Recommendations**

- 25 • SELZENTRY tablets and oral solution are taken twice daily by mouth and may be taken with  
26 or without food.
- 27 • SELZENTRY must be given in combination with other antiretroviral medications.
- 28 • The recommended dosage of SELZENTRY differs based on concomitant medications due to  
29 drug interactions.

30 **2.3 Recommended Dosage in Adults**

31 Table 1 displays oral dosage of SELZENTRY based on different concomitant medications [*see*  
32 *Drug Interactions (7.1)*].

33 **Table 1. Recommended Dosage in Adults**

Concomitant Medications	Dosage of SELZENTRY
Potent CYP3A inhibitors (with or without a potent CYP3A inducer) including: <ul style="list-style-type: none"> <li>• protease inhibitors (except tipranavir/ritonavir)</li> <li>• delavirdine</li> <li>• elvitegravir/ritonavir</li> <li>• ketoconazole, itraconazole, clarithromycin</li> <li>• other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)</li> <li>• boceprevir</li> </ul>	150 mg twice daily
Noninteracting concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all nucleoside reverse transcriptase inhibitors (NRTIs), and enfuvirtide <sup>a</sup>	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: <ul style="list-style-type: none"> <li>• efavirenz</li> <li>• rifampin</li> <li>• etravirine</li> <li>• carbamazepine, phenobarbital, and phenytoin</li> </ul>	600 mg twice daily

34 <sup>a</sup> Noninteracting concomitant medications include all medications that are not potent CYP3A  
35 inhibitors or inducers.

36 **2.4 Recommended Dosage in Pediatric Patients**

37 The recommended dosage of SELZENTRY should be based on body weight (kg) and should not  
38 exceed the recommended adult dose. The recommended dosage also differs based on  
39 concomitant medications due to drug interactions (Table 2 and Table 3) [*see Drug Interactions*  
40 (7.1), *Use in Specific Populations* (8.4)].

41 Before prescribing SELZENTRY tablets, assess children for the ability to swallow tablets. If a  
42 child is unable to reliably swallow SELZENTRY tablets, the oral solution formulation should be  
43 prescribed. Administer the oral solution using the included press-in bottle adapter and oral  
44 dosing syringe.

45 **Table 2. Recommended Dosage in Pediatric Patients Aged 2 Years and Older Weighing**  
46 **at Least 10 kg (Tablets)**

Concomitant Medications	Dosage of SELZENTRY Based on Weight			
	10 kg to <20 kg	20 kg to <30 kg	30 kg to <40 kg	≥40 kg
Potent CYP3A inhibitors (with or without a CYP3A inducer) including:	50 mg twice daily	75 mg twice daily	100 mg twice daily	150 mg twice daily

<ul style="list-style-type: none"> <li>• protease inhibitors (except tipranavir/ritonavir)</li> <li>• delavirdine</li> <li>• elvitegravir/ritonavir</li> <li>• ketoconazole, itraconazole, clarithromycin</li> <li>• other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)</li> <li>• boceprevir</li> </ul>				
Noninteracting concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide <sup>a</sup>	Not recommended	Not recommended	300 mg twice daily	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: <ul style="list-style-type: none"> <li>• efavirenz</li> <li>• rifampin</li> <li>• etravirine</li> <li>• carbamazepine, phenobarbital, and phenytoin</li> </ul>	Not recommended			

47 <sup>a</sup> Noninteracting concomitant medications include all medications that are not potent CYP3A  
 48 inhibitors or inducers.

49 **Table 3. Recommended Dosage in Pediatric Patients Aged 2 Years and Older Weighing**  
 50 **at Least 10 kg (Oral Solution)**

Concomitant Medications	Dosage (Volume of Solution) of SELZENTRY Based on Weight			
	10 kg to <20 kg	20 kg to <30 kg	30 kg to <40 kg	≥40 kg
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: <ul style="list-style-type: none"> <li>• protease inhibitors (except tipranavir/ritonavir)</li> <li>• delavirdine</li> <li>• elvitegravir/ritonavir</li> <li>• ketoconazole, itraconazole,</li> </ul>	50 mg (2.5 mL) twice daily	80 mg (4 mL) twice daily	100 mg (5 mL) twice daily	150 mg (7.5 mL) twice daily

clarithromycin <ul style="list-style-type: none"> <li>• other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)</li> <li>• boceprevir</li> </ul>				
Noninteracting concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide <sup>a</sup>	Not recommended	Not recommended	300 mg (15 mL) twice daily	300 mg (15 mL) twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: <ul style="list-style-type: none"> <li>• efavirenz</li> <li>• rifampin</li> <li>• etravirine</li> <li>• carbamazepine, phenobarbital, and phenytoin</li> </ul>	Not recommended			

51 <sup>a</sup> Noninteracting concomitant medications include all medications that are not potent CYP3A  
 52 inhibitors or inducers.

53 **2.5 Recommended Dosage in Patients with Renal Impairment**

54 Adults

55 Table 4 provides dosing recommendations for patients based on renal function and concomitant  
 56 medications.

57 **Table 4. Recommended Dosage in Adults Based on Renal Function**

Concomitant Medications	Dosage of SELZENTRY Based on Renal Function				
	Normal (CrCl >80 mL/min)	Mild (CrCl >50 and ≤80 mL/min)	Moderate (CrCl ≥30 and ≤50 mL/min)	Severe (CrCl <30 mL/min)	End-Stage Renal Disease on Regular Hemodialysis
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: <ul style="list-style-type: none"> <li>• protease inhibitors (except tipranavir/ritonavir)</li> <li>• delavirdine</li> <li>• elvitegravir/ritonavir</li> </ul>	150 mg twice daily	150 mg twice daily	150 mg twice daily	Contra-indicated	Contra-indicated

<ul style="list-style-type: none"> <li>• ketoconazole, itraconazole, clarithromycin</li> <li>• other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)</li> <li>• boceprevir</li> </ul>					
Noninteracting concomitant medications including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide <sup>a</sup>	300 mg twice daily	300 mg twice daily	300 mg twice daily	300 mg twice daily <sup>b</sup>	300 mg twice daily <sup>b</sup>
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: <ul style="list-style-type: none"> <li>• efavirenz</li> <li>• rifampin</li> <li>• etravirine</li> <li>• carbamazepine, phenobarbital, and phenytoin</li> </ul>	600 mg twice daily	600 mg twice daily	600 mg twice daily	Contra-indicated	Contra-indicated

58 <sup>a</sup> Noninteracting concomitant medications include all medications that are not potent CYP3A  
59 inhibitors or inducers.

60 <sup>b</sup> The dosage of SELZENTRY should be reduced to 150 mg twice daily if there are any  
61 symptoms of postural hypotension [*see Contraindications (4), Warnings and Precautions*  
62 (5.3)].

### 63 Pediatric Patients

64 There are no data to recommend specific doses of SELZENTRY in pediatric patients with mild  
65 or moderate renal impairment [*see Use in Specific Populations (8.6)*]. Additionally,  
66 SELZENTRY is contraindicated for pediatric patients with severe renal impairment or end-stage  
67 renal disease (ESRD) on regular hemodialysis who are receiving potent CYP3A inhibitors [*see*  
68 *Contraindications (4)*].

## 69 **3 DOSAGE FORMS AND STRENGTHS**

70 Tablets:

- 71 • 25-mg blue, oval, film-coated tablets debossed with “MVC 25” on one side and plain on the  
72 other.

- 73 • 75-mg blue, oval, film-coated tablets debossed with “MVC 75” on one side and plain on the  
74 other.
- 75 • 150-mg blue, oval, film-coated tablets debossed with “MVC 150” on one side and plain on  
76 the other.
- 77 • 300-mg blue, oval, film-coated tablets debossed with “MVC 300” on one side and plain on  
78 the other.
- 79 Oral Solution:
- 80 • 20 mg per mL clear, colorless, strawberry-flavored oral solution.

#### 81 **4 CONTRAINDICATIONS**

82 SELZENTRY is contraindicated in patients with severe renal impairment or ESRD (CrCl less  
83 than 30 mL per minute) who are concomitantly taking potent CYP3A inhibitors or inducers [*see*  
84 *Warnings and Precautions (5.3)*].

#### 85 **5 WARNINGS AND PRECAUTIONS**

##### 86 **5.1 Hepatotoxicity**

87 Hepatotoxicity with allergic features including life-threatening events has been reported in  
88 clinical trials and postmarketing. Severe rash or evidence of systemic allergic reaction including  
89 drug-related rash with fever, eosinophilia, elevated IgE, or other systemic symptoms have been  
90 reported in conjunction with hepatotoxicity [*see Warnings and Precautions (5.2)*]. These events  
91 occurred approximately 1 month after starting treatment. Among reported cases of hepatitis,  
92 some were observed in the absence of allergic features or with no pre-existing hepatic disease.

93 Appropriate laboratory testing including ALT, AST, and bilirubin should be conducted prior to  
94 initiating therapy with SELZENTRY and at other time points during treatment as clinically  
95 indicated. Hepatic laboratory parameters should be obtained in any patient who develops rash, or  
96 signs or symptoms of hepatitis, or allergic reaction. Discontinuation of SELZENTRY should be  
97 considered in any patient with signs or symptoms of hepatitis, or with increased liver  
98 transaminases combined with rash or other systemic symptoms.

99 When administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-  
100 infected with hepatitis B and/or C virus, additional monitoring may be warranted. The safety and  
101 efficacy of SELZENTRY have not been specifically studied in patients with significant  
102 underlying liver disorders.

##### 103 **5.2 Severe Skin and Hypersensitivity Reactions**

104 Severe, potentially life-threatening skin and hypersensitivity reactions have been reported in  
105 patients taking SELZENTRY, in most cases concomitantly with other drugs associated with  
106 these reactions. These include cases of Stevens-Johnson syndrome (SJS), toxic epidermal



107 necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) [see  
108 *Adverse Reactions (6.3)*]. The cases were characterized by features including rash, constitutional  
109 findings, and sometimes organ dysfunction, including hepatic failure. Discontinue SELZENTRY  
110 and other suspected agents immediately if signs or symptoms of severe skin or hypersensitivity  
111 reactions develop (including, but not limited to, severe rash or rash accompanied by fever,  
112 malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, lip swelling,  
113 eosinophilia). Delay in stopping treatment with SELZENTRY or other suspect drugs after the  
114 onset of rash may result in a life-threatening reaction. Clinical status, including liver  
115 aminotransferases, should be monitored and appropriate therapy initiated.

### 116 **5.3 Cardiovascular Events**

117 Eleven subjects (1.3%) who received SELZENTRY had cardiovascular events, including  
118 myocardial ischemia and/or infarction, during the Phase 3 trials in treatment-experienced  
119 subjects (total exposure 609 patient-years [300 on SELZENTRY once daily + 309 on  
120 SELZENTRY twice daily]), while no subjects who received placebo had such events (total  
121 exposure 111 patient-years). These subjects generally had cardiac disease or cardiac risk factors  
122 prior to use of SELZENTRY, and the relative contribution of SELZENTRY to these events is  
123 not known.

124 In the Phase 2b/3 trial in treatment-naive adult subjects, 3 subjects (0.8%) who received  
125 SELZENTRY had events related to ischemic heart disease and 5 subjects (1.4%) who received  
126 efavirenz had such events (total exposure 506 and 508 patient-years for SELZENTRY and  
127 efavirenz, respectively).

128 When SELZENTRY was administered to healthy volunteers at doses higher than the  
129 recommended dose, symptomatic postural hypotension was seen at a greater frequency than in  
130 placebo. However, when SELZENTRY was given at the recommended dose in HIV-1–infected  
131 adult subjects in Phase 3 trials, postural hypotension was seen at a rate similar to placebo  
132 (approximately 0.5%).

133 Patients with cardiovascular comorbidities, risk factors for postural hypotension, or receiving  
134 concomitant medication known to lower blood pressure, could be at increased risk of  
135 cardiovascular adverse events triggered by postural hypotension. Additional monitoring may be  
136 warranted.

#### 137 Postural Hypotension in Patients with Renal Impairment

138 An increased risk of postural hypotension may occur in patients with severe renal insufficiency  
139 or in those with ESRD due to increased maraviroc exposure in some patients. SELZENTRY  
140 should be used in patients with severe renal impairment or ESRD only if they are not receiving a  
141 concomitant potent CYP3A inhibitor or inducer. However, the use of SELZENTRY in these  
142 patients should only be considered when no alternative treatment options are available. If adult  
143 patients with severe renal impairment or ESRD experience any symptoms of postural

144 hypotension while taking 300 mg twice daily, the dose should be reduced to 150 mg twice daily  
145 [see Dosage and Administration (2.5)].

#### 146 **5.4 Immune Reconstitution Syndrome**

147 Immune reconstitution syndrome has been reported in patients treated with combination  
148 antiretroviral therapy, including SELZENTRY. During the initial phase of combination  
149 antiretroviral treatment, patients whose immune systems respond may develop an inflammatory  
150 response to indolent or residual opportunistic infections (such as infection with *Mycobacterium*  
151 *avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], tuberculosis, or  
152 reactivation of *Herpes simplex* and *Herpes zoster*), which may necessitate further evaluation and  
153 treatment.

154 Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome)  
155 have also been reported to occur in the setting of immune reconstitution; however, the time to  
156 onset is more variable, and can occur many months after initiation of treatment.

#### 157 **5.5 Potential Risk of Infection**

158 SELZENTRY antagonizes the CCR5 co-receptor located on some immune cells, and therefore  
159 could potentially increase the risk of developing infections. The overall incidence and severity of  
160 infection, as well as AIDS-defining category C infections, were comparable in the treatment  
161 groups during the Phase 3 adult treatment-experienced trials of SELZENTRY. While there was a  
162 higher rate of certain upper respiratory tract infections reported in the treatment arm receiving  
163 SELZENTRY compared with placebo (23% versus 13%), there was a lower rate of pneumonia  
164 (2% versus 5%) reported in subjects receiving SELZENTRY. A higher incidence of Herpes virus  
165 infections (11 per 100 patient-years) was also reported in the treatment arm receiving  
166 SELZENTRY when adjusted for exposure compared with placebo (8 per 100 patient-years).

167 In the Phase 2b/3 trial in treatment-naïve adult subjects, the incidence of AIDS-defining  
168 Category C events when adjusted for exposure was 1.8 for SELZENTRY compared with 2.4 for  
169 efavirenz per 100 patient-years of exposure.

170 Patients should be monitored closely for evidence of infections while receiving SELZENTRY.

#### 171 **5.6 Potential Risk of Malignancy**

172 While no increase in malignancy has been observed with SELZENTRY, due to this drug's  
173 mechanism of action, it could affect immune surveillance and lead to an increased risk of  
174 malignancy.

175 The exposure-adjusted rate for malignancies per 100 patient-years of exposure in adult  
176 treatment-experienced trials was 4.6 for SELZENTRY compared with 9.3 on placebo. In  
177 treatment-naïve adult subjects, the rates were 1.0 and 2.4 per 100 patient-years of exposure for  
178 SELZENTRY and efavirenz, respectively.

179 Long-term follow-up is needed to more fully assess this risk.

180 **6 ADVERSE REACTIONS**

181 The following adverse reactions are discussed in other sections of the labeling:

- 182 • Hepatotoxicity [*see Boxed Warning, Warnings and Precautions (5.1)*]
- 183 • Severe Skin and Hypersensitivity Reactions [*see Warnings and Precautions (5.2)*]
- 184 • Cardiovascular Events [*see Warnings and Precautions (5.3)*]

185 **6.1 Clinical Trials Experience**

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

189 Adverse Reactions in Adult Subjects

190 *Treatment-Experienced Subjects:* The safety profile of SELZENTRY is primarily based on  
191 840 HIV-1–infected subjects who received at least 1 dose of SELZENTRY during two Phase 3  
192 trials. A total of 426 of these subjects received the indicated twice-daily dosing regimen.

193 Assessment of treatment-emergent adverse events is based on the pooled data from 2 trials in  
194 subjects with CCR5-tropic HIV-1 (A4001027 and A4001028). The median duration of therapy  
195 with SELZENTRY for subjects in these trials was 48 weeks, with the total exposure on  
196 SELZENTRY twice daily at 309 patient-years versus 111 patient-years on placebo each  
197 administered with optimized background therapy (OBT). The population was 89% male and  
198 84% white, with mean age of 46 years (range: 17 to 75 years). Subjects received dose  
199 equivalents of 300 mg maraviroc once or twice daily.

200 The most common adverse events reported with twice-daily therapy with SELZENTRY with  
201 frequency rates higher than placebo, regardless of causality, were upper respiratory tract  
202 infections, cough, pyrexia, rash, and dizziness. In these 2 trials, the rate of discontinuation due to  
203 adverse events was 5% for subjects who received SELZENTRY twice daily + OBT as well as  
204 those who received placebo + OBT. Most of the adverse events reported were judged to be mild  
205 to moderate in severity. The data described below occurred with twice-daily dosing of  
206 SELZENTRY.

207 The total numbers of subjects reporting infections were 233 (55%) and 84 (40%) in the group  
208 receiving SELZENTRY twice daily and the placebo group, respectively. Correcting for the  
209 longer duration of exposure on SELZENTRY compared with placebo, the exposure-adjusted  
210 frequency (rate per 100 subject-years) of these events was 133 for both SELZENTRY twice  
211 daily and placebo.

212 Dizziness or postural dizziness occurred in 8% of subjects on either SELZENTRY or placebo,  
213 with 2 subjects (0.5%) on SELZENTRY permanently discontinuing therapy (1 due to syncope, 1  
214 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) permanently discontinuing  
215 therapy due to dizziness.

216 Treatment-emergent adverse events, regardless of causality, from Trials A4001027 and  
 217 A4001028 are summarized in Table 5. Selected events occurring at greater than or equal to 2%  
 218 of subjects and at a numerically higher rate in subjects treated with SELZENTRY are included;  
 219 events that occurred at the same or higher rate on placebo are not displayed.

220 **Table 5. Selected Treatment-Emergent Adverse Events (All Causality)  $\geq$ 2% on**  
 221 **SELZENTRY (and at a Higher Rate Compared with Placebo) in Trials A4001027 and**  
 222 **A4001028 (Pooled Analysis, 48 Weeks)**

Body System/ Adverse Event	SELZENTRY Twice Daily <sup>a</sup>		Placebo	
	(n = 426) %	Exposure- Adjusted Rate (per 100 pt-yrs) PYE = 309 <sup>b</sup>	(n = 209) %	Exposure- Adjusted Rate (per 100 pt-yrs) PYE = 111 <sup>b</sup>
<b>Eye Disorders</b>				
Conjunctivitis	2	3	1	3
Ocular infections, inflammations, and associated manifestations	2	3	1	2
<b>Gastrointestinal Disorders</b>				
Constipation	6	9	3	6
<b>General Disorders and Administration Site Conditions</b>				
Pyrexia	13	20	9	17
Pain and discomfort	4	5	3	5
<b>Infections and Infestations</b>				
Upper respiratory tract infection	23	37	13	27
Herpes infection	8	11	4	8
Sinusitis	7	10	3	6
Bronchitis	7	9	5	9
Folliculitis	4	5	2	4
Anogenital warts	2	3	1	3
Influenza	2	3	0.5	1
Otitis media	2	3	0.5	1
<b>Metabolism and Nutrition Disorders</b>				
Appetite disorders	8	11	7	13
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Joint-related signs and symptoms	7	10	3	5
Muscle pains	3	4	0.5	1

<b>Neoplasms Benign, Malignant, and Unspecified</b>				
Skin neoplasms benign	3	4	1	3
<b>Nervous System Disorders</b>				
Dizziness/postural dizziness	9	13	8	17
Paresthesias and dysesthesias	5	7	3	6
Sensory abnormalities	4	6	1	3
Disturbances in consciousness	4	5	3	6
Peripheral neuropathies	4	5	3	6
<b>Psychiatric Disorders</b>				
Disturbances in initiating and maintaining sleep	8	11	5	10
Depressive disorders	4	6	3	5
Anxiety symptoms	4	5	3	7
<b>Renal and Urinary Disorders</b>				
Bladder and urethral symptoms	5	7	1	3
Urinary tract signs and symptoms	3	4	1	3
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Coughing and associated symptoms	14	21	5	10
Upper respiratory tract signs and symptoms	6	9	3	6
Nasal congestion and inflammations	4	6	3	5
Breathing abnormalities	4	5	2	5
Paranasal sinus disorders	3	4	0.5	1
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	11	16	5	11
Apocrine and eccrine gland disorders	5	7	4	7.5
Pruritus	4	5	2	4
Lipodystrophies	3	5	0.5	1
Erythema	2	3	1	2
<b>Vascular Disorders</b>				
Vascular hypertensive disorders	3	4	2	4

223 <sup>a</sup> 300-mg dose equivalent.

224 <sup>b</sup> PYE = Patient-years of exposure.

225 *Laboratory Abnormalities:* Table 6 shows the treatment-emergent Grade 3-4 laboratory  
 226 abnormalities that occurred in greater than 2% of subjects receiving SELZENTRY.

227 **Table 6. Maximum Shift in Laboratory Test Values (without Regard to Baseline)  $\geq$ 2%**  
 228 **of Grade 3-4 Abnormalities (ACTG Criteria) in Trials A4001027 and A4001028 (Pooled**  
 229 **Analysis, 48 Weeks)**

<b>Laboratory Parameter Preferred Term</b>	<b>Limit</b>	<b>SELZENTRY Twice Daily + OBT (n = 421)<sup>a</sup> %</b>	<b>Placebo + OBT (n = 207)<sup>a</sup> %</b>
Aspartate aminotransferase	>5.0 x ULN	4.8	2.9
Alanine aminotransferase	>5.0 x ULN	2.6	3.4
Total bilirubin	>2.5 x ULN	5.5	5.3
Amylase	>2.0 x ULN	5.7	5.8
Lipase	>2.0 x ULN	4.9	6.3
Absolute neutrophil count	<750/mm <sup>3</sup>	4.3	2.4

230 ULN = Upper limit of normal.

231 <sup>a</sup> Percentages based on total subjects evaluated for each laboratory parameter.

232 *Treatment-Naive Subjects: Treatment-Emergent Adverse Events:* Treatment-emergent adverse  
 233 events, regardless of causality, from Trial A4001026, a double-blind, comparative, controlled  
 234 trial in which 721 treatment-naive subjects received SELZENTRY 300 mg twice daily (n = 360)  
 235 or efavirenz 600 mg once daily (n = 361) in combination with lamivudine/zidovudine  
 236 (COMBIVIR) for 96 weeks, are summarized in Table 7. Selected events occurring in greater  
 237 than or equal to 2% of subjects and at a numerically higher rate in subjects treated with  
 238 SELZENTRY are included; events that occurred at the same or higher rate on efavirenz are not  
 239 displayed.

240 **Table 7. Selected Treatment-Emergent Adverse Events (All Causality)  $\geq$ 2% on**  
 241 **SELZENTRY (and at a Higher Rate Compared with Efavirenz) in Trial A4001026 (96**  
 242 **Weeks)**

<b>Body System/ Adverse Event</b>	<b>SELZENTRY 300 mg Twice Daily + Lamivudine/Zidovudine (n = 360) %</b>	<b>Efavirenz 600 mg Once Daily + Lamivudine/Zidovudine (n = 361) %</b>
<b>Blood and Lymphatic System Disorders</b>		
Anemias NEC	8	5
Neutropenias	4	3
<b>Ear and Labyrinth Disorders</b>		

Ear disorders NEC	3	2
<b>Gastrointestinal Disorders</b>		
Flatulence, bloating, and distention	10	7
Gastrointestinal atonic and hypomotility disorders NEC	9	5
Gastrointestinal signs and symptoms NEC	3	2
<b>General Disorders and Administration Site Conditions</b>		
Body temperature perception	3	1
<b>Infections and Infestations</b>		
Upper respiratory tract infection	32	30
Bronchitis	13	9
Herpes infection	7	6
Bacterial infections NEC	6	3
<i>Herpes zoster/varicella</i>	5	4
Tinea infections	4	3
Lower respiratory tract and lung infections	3	2
<i>Neisseria</i> infections	3	0
Viral infections NEC	3	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Joint-related signs and symptoms	6	5
<b>Nervous System Disorders</b>		
Paresthesias and dysesthesias	4	3
Memory loss (excluding dementia)	3	1
<b>Renal and Urinary Disorders</b>		
Bladder and urethral symptoms	4	3
<b>Reproductive System and Breast Disorders</b>		
Erection and ejaculation conditions and disorders	3	2
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Upper respiratory tract signs and symptoms	9	5
<b>Skin and Subcutaneous Disorders</b>		
Nail and nail bed conditions	6	2

(excluding infections and infestations)		
Lipodystrophies	4	3
Acnes	3	2
Alopecias	2	1

243 *Laboratory Abnormalities:*

244 **Table 8. Maximum Shift in Laboratory Test Values (without Regard to Baseline)  $\geq 2\%$**   
 245 **of Grade 3-4 Abnormalities (ACTG Criteria) in Trial A4001026 (96 Weeks)**

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

246 ULN = Upper limit of normal.

247 <sup>a</sup> n = Total number of subjects evaluable for laboratory abnormalities.

248 Percentages based on total subjects evaluated for each laboratory parameter. If the same subject  
 249 in a given treatment group had greater than 1 occurrence of the same abnormality, only the  
 250 most severe is counted.

251 *Less Common Adverse Events in Clinical Trials:* The following adverse events occurred in less  
 252 than 2% of subjects treated with SELZENTRY or at a rate similar to the comparator. These  
 253 events have been included because of their seriousness and either increased frequency on  
 254 SELZENTRY or are potential risks due to the mechanism of action. Events attributed to the  
 255 subjects' underlying HIV-1 infection are not listed.

256 *Blood and Lymphatic System:* Marrow depression and hypoplastic anemia.

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

259 *Hepatobiliary Disorders:* Hepatic cirrhosis, hepatic failure, cholestatic jaundice, portal  
 260 vein thrombosis, jaundice.



261 *Infections and Infestations:* Endocarditis, infective myositis, viral meningitis, pneumonia,  
262 treponema infections, septic shock, *Clostridium difficile* colitis, meningitis.

263 *Musculoskeletal and Connective Tissue Disorders:* Myositis, osteonecrosis,  
264 rhabdomyolysis, blood CK increased.

265 *Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps):*  
266 Abdominal neoplasm, anal cancer, basal cell carcinoma, Bowen's disease, cholangiocarcinoma,  
267 diffuse large B-cell lymphoma, lymphoma, metastases to liver, esophageal carcinoma,  
268 nasopharyngeal carcinoma, squamous cell carcinoma, squamous cell carcinoma of skin, tongue  
269 neoplasm (malignant stage unspecified), anaplastic large cell lymphomas T- and null-cell types,  
270 bile duct neoplasms malignant, endocrine neoplasms malignant and unspecified.

271 *Nervous System Disorders:* Cerebrovascular accident, convulsions and epilepsy, tremor  
272 (excluding congenital), facial palsy, hemianopia, loss of consciousness, visual field defect.

### 273 Clinical Trials Experience in Pediatric Subjects

274 Trial A4001031 is an open-label trial in which 103 treatment-experienced, CCR5-tropic, HIV-1–  
275 infected pediatric subjects aged 2 to less than 18 years weighing at least 10 kg received  
276 SELZENTRY twice daily in combination with OBT. The dose of SELZENTRY was based on  
277 body surface area (BSA) and on whether the subject was receiving potent CYP3A inhibitors  
278 and/or inducers. The median duration of therapy with SELZENTRY was 131 weeks with 72% of  
279 subjects receiving study treatment for greater than 48 weeks and 62% of subjects receiving study  
280 treatment for 96 weeks.

281 In these 103 children and adolescents, the safety profile through 96 weeks was similar to that for  
282 adults. Most of the adverse reactions reported were mild to moderate; severe (Grade 3 and 4)  
283 adverse reactions occurred in 2% of subjects. The most common adverse reactions (all grades)  
284 reported with twice-daily therapy with SELZENTRY were vomiting (12%), abdominal pain  
285 (4%), diarrhea (4%), nausea (4%), and dizziness (3%). Three subjects (3%) discontinued due to  
286 adverse events.

287 Maraviroc-related gastrointestinal adverse events through 48 weeks (nausea, vomiting, diarrhea,  
288 constipation, and abdominal pain/cramps) were observed more commonly in subjects who  
289 received the SELZENTRY oral solution (21%) compared with those who received  
290 SELZENTRY tablets (16%). Subjects were permitted to change formulations after Week 48.

### 291 **6.2 Postmarketing Experience**

292 The following adverse events have been identified during post-approval use of SELZENTRY.  
293 Because these reactions are reported voluntarily from a population of uncertain size, it is not  
294 always possible to reliably estimate their frequency or establish a causal relationship to drug  
295 exposure.

### 296 Skin and Subcutaneous Tissue Disorders

297 Stevens-Johnson syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS),  
298 toxic epidermal necrolysis (TEN).

## 299 **7 DRUG INTERACTIONS**

### 300 **7.1 Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc**

301 Maraviroc is metabolized by CYP3A, and is also a substrate for P-glycoprotein (P-gp), organic  
302 anion-transporting polypeptide (OATP)1B1, and multidrug resistance-associated protein  
303 (MRP)2. The pharmacokinetics of maraviroc are likely to be modulated by inhibitors and  
304 inducers of CYP3A and P-gp, and may be modulated by inhibitors of OATP1B1 and MRP2.  
305 Therefore, a dosage adjustment may be required when maraviroc is coadministered with those  
306 drugs [see *Dosage and Administration (2.3, 2.4)*].

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

311 Additional drug interaction information is available [see *Clinical Pharmacology (12.3)*].

## 312 **8 USE IN SPECIFIC POPULATIONS**

### 313 **8.1 Pregnancy**

#### 314 Pregnancy Exposure Registry

315 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to  
316 SELZENTRY during pregnancy. Physicians are encouraged to register patients by calling the  
317 Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

#### 318 Risk Summary

319 Limited data on the use of SELZENTRY during pregnancy from the APR and case reports are  
320 not sufficient to inform a drug-associated risk of birth defects and miscarriage. In animal  
321 reproduction studies, no evidence of adverse developmental outcomes was observed with  
322 maraviroc. During organogenesis in the rat and rabbit, systemic exposures (AUC) to maraviroc  
323 were approximately 20 times (rats) and 5 times (rabbits) the exposure in humans at the  
324 recommended 300-mg twice-daily dose. In the rat pre- and post-natal development study,  
325 maternal systemic exposure (AUC) to maraviroc was approximately 14 times the exposure in  
326 humans at the recommended 300-mg twice-daily dose (*see Data*).

327 The estimated background risk of major birth defects and miscarriage for the indicated  
328 population is unknown. All pregnancies have a background risk of birth defect, loss, or other  
329 adverse outcomes. In the U.S. general population, the estimated background risk of major birth  
330 defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%,  
331 respectively.

332 Data

333 *Animal Data:* Maraviroc was administered orally to pregnant rats (up to 1,000 mg per kg per  
334 day) and rabbits (up to 75 mg per kg per day) on gestation Days 6 to 17 and 7 to 19, respectively.  
335 No adverse effects on embryo-fetal development were observed at these dose levels, resulting in  
336 exposures (AUC) approximately 20 times (rats) and 5 times (rabbits) higher than human  
337 exposures at the recommended daily dose. In the rat pre- and post-natal development study,  
338 maraviroc was administered orally at up to 1,000 mg per kg per day on gestation Day 6 to  
339 lactation/post-partum Day 20, with development of the offspring (including fertility and  
340 reproductive performance) unaffected by maternal administration of maraviroc at an exposure  
341 (AUC) approximately 14 times higher than human exposure at the recommended daily dose.

342 **8.2 Lactation**

343 Risk Summary

344 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the  
345 United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1  
346 infection.

347 There are no data on the presence of maraviroc in human milk, the effects on the breastfed  
348 infant, or the effects on milk production. When administered to lactating rats, maraviroc was  
349 present in milk (*see Data*). Because of the potential for (1) HIV transmission (in HIV-negative  
350 infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse  
351 reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if  
352 they are receiving SELZENTRY.

353 Data

354 Maraviroc (and related metabolites) was excreted into the milk of lactating rats following a  
355 single oral dose of maraviroc (100 mg per kg) on lactation Day 12, with a maximal milk  
356 concentration achieved one hour post-administration at a milk concentration approximately 2.5  
357 times that of maternal plasma concentrations.

358 **8.4 Pediatric Use**

359 The safety, pharmacokinetic (PK) profile, and antiviral activity of SELZENTRY were evaluated  
360 in treatment-experienced, CCR5-tropic, HIV-1-infected pediatric subjects aged 2 to less than 18  
361 years weighing at least 10 kg in an open-label, multicenter clinical trial, A4001031 [*see Adverse*  
362 *Reactions (6.1), Clinical Studies (14.2)*]. Pharmacokinetics were evaluated in a total of 98  
363 pediatric subjects: 85 subjects received SELZENTRY and concomitant medications that included  
364 potent CYP3A inhibitors with or without potent CYP3A inducers, 10 subjects received  
365 SELZENTRY and noninteracting medications (not containing potent CYP3A inhibitors or potent  
366 CYP3A inducers), and three subjects received SELZENTRY and medications that included  
367 potent CYP3A inducers without potent CYP3A inhibitors [*see Clinical Pharmacology (12.3)*].

368 See *Dosage and Administration* (2.4, 2.5) for dosing recommendations for pediatric patients  
369 aged 2 years and older and weighing at least 10 kg. The pharmacokinetics, safety, and efficacy of  
370 maraviroc in patients younger than 2 years have not been established. Therefore, SELZENTRY  
371 is not recommended in this patient population. Additionally, there are insufficient data to make  
372 dosing recommendations for use of SELZENTRY in pediatric patients concomitantly receiving  
373 noninteracting medications and weighing less than 30 kg or in pediatric patients concomitantly  
374 receiving potent CYP3A inducers without a potent CYP3A inhibitor [*see Dosage and*  
375 *Administration* (2.4, 2.5)].

## 376 **8.5 Geriatric Use**

377 There were insufficient numbers of subjects aged 65 and over in the clinical trials to determine  
378 whether they respond differently from younger subjects. In general, caution should be exercised  
379 when administering SELZENTRY in elderly patients, also reflecting the greater frequency of  
380 decreased hepatic and renal function, of concomitant disease and other drug therapy.

## 381 **8.6 Renal Impairment**

382 Recommended doses of SELZENTRY for adult patients with impaired renal function (CrCl less  
383 than or equal to 80 mL per minute) are based on the results of a pharmacokinetic trial conducted  
384 in healthy adult subjects with various degrees of renal impairment. Maraviroc has not been  
385 studied in pediatric patients with renal impairment. There are no data to recommend specific  
386 doses of SELZENTRY in pediatric patients with mild to moderate renal impairment [*see Use in*  
387 *Specific Populations* (8.4)]. SELZENTRY is contraindicated in pediatric patients with severe  
388 renal impairment or ESRD on regular hemodialysis who are receiving potent CYP3A inhibitors  
389 [*see Contraindications* (4)].

390 The pharmacokinetics of maraviroc in adult subjects with mild and moderate renal impairment  
391 was similar to that in subjects with normal renal function [*see Clinical Pharmacology* (12.3)]. A  
392 limited number of adult subjects with mild and moderate renal impairment in the Phase 3 clinical  
393 trials (n = 131 and n = 12, respectively) received the same dose of SELZENTRY as that  
394 administered to subjects with normal renal function. In these subjects, there was no apparent  
395 difference in the adverse event profile for maraviroc compared with subjects with normal renal  
396 function.

397 If adult patients with severe renal impairment or ESRD not receiving a concomitant potent  
398 CYP3A inhibitor or inducer experience any symptoms of postural hypotension while taking  
399 SELZENTRY 300 mg twice daily, the dose should be reduced to 150 mg twice daily. No trials  
400 have been performed in subjects with severe renal impairment or ESRD co-treated with potent  
401 CYP3A inhibitors or inducers. Hence, no dose of SELZENTRY can be recommended, and  
402 SELZENTRY is contraindicated for these patients [*see Dosage and Administration* (2.3),  
403 *Contraindications* (4), *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.3)].

## 404 **8.7 Hepatic Impairment**

405 Maraviroc is principally metabolized by the liver; therefore, when administering this drug to  
406 patients with hepatic impairment, maraviroc concentrations may be increased. Maraviroc  
407 concentrations are higher when SELZENTRY 150 mg is administered with a potent CYP3A  
408 inhibitor compared with following administration of 300 mg without a CYP3A inhibitor, so  
409 patients with moderate hepatic impairment who receive SELZENTRY 150 mg with a potent  
410 CYP3A inhibitor should be monitored closely for maraviroc-associated adverse events.  
411 Maraviroc has not been studied in subjects with severe hepatic impairment or in pediatric  
412 patients with any degree of hepatic impairment [*see Warnings and Precautions (5.1), Clinical*  
413 *Pharmacology (12.3)*].

## 414 **10 OVERDOSAGE**

415 The highest single dose administered in clinical trials was 1,200 mg. The dose-limiting adverse  
416 event was postural hypotension, which was observed at 600 mg. While the recommended dose  
417 for SELZENTRY in patients receiving a CYP3A inducer without a CYP3A inhibitor is 600 mg  
418 twice daily, this dose is appropriate due to enhanced metabolism.

419 Prolongation of the QT interval was seen in dogs and monkeys at plasma concentrations 6 and  
420 12 times, respectively, those expected in humans at the intended exposure of 300-mg equivalents  
421 twice daily. However, no significant QT prolongation was seen in the trials in treatment-  
422 experienced subjects with HIV using the recommended doses of maraviroc, or in a specific  
423 pharmacokinetic trial to evaluate the potential of maraviroc to prolong the QT interval [*see*  
424 *Clinical Pharmacology (12.2)*].

425 There is no specific antidote for overdose with maraviroc. Treatment of overdose should consist  
426 of general supportive measures including keeping the patient in a supine position, careful  
427 assessment of patient vital signs, blood pressure, and ECG.

428 Administration of activated charcoal may also be used to aid in removal of unabsorbed drug.  
429 Hemodialysis had a minimal effect on maraviroc clearance and exposure in a trial in subjects  
430 with ESRD [*see Clinical Pharmacology (12.3)*].

## 431 **11 DESCRIPTION**

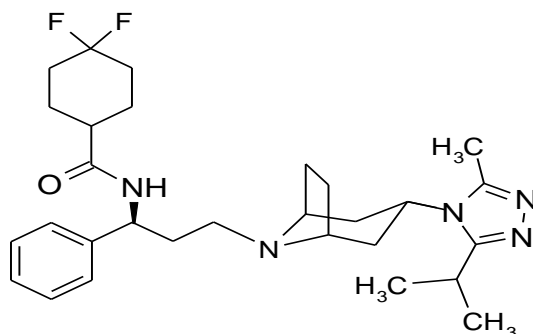
432 SELZENTRY (maraviroc) is a selective, slowly reversible, small molecule antagonist of the  
433 interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents  
434 CCR5-tropic HIV-1 entry into cells.

435 SELZENTRY film-coated tablets for oral administration contain 25, 75, 150, or 300 mg of  
436 maraviroc and the following inactive ingredients: dibasic calcium phosphate (anhydrous),  
437 magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film coat  
438 (Opadry II Blue [85G20583]) contains FD&C blue #2 aluminum lake, soya lecithin,  
439 polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide.

440 SELZENTRY oral solution contains 20 mg per mL of maraviroc and the following inactive  
441 ingredients: citric acid (anhydrous), purified water, sodium benzoate, sodium citrate dihydrate,  
442 strawberry flavoring (501440T), and sucralose.

443 Maraviroc is chemically described as 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-  
444 1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl} cyclohexanecarboxamide.

445 The molecular formula is C<sub>29</sub>H<sub>41</sub>F<sub>2</sub>N<sub>5</sub>O and the structural formula is:



446  
447 Maraviroc is a white to pale-colored powder with a molecular weight of 513.67. It is highly  
448 soluble across the physiological pH range (pH 1.0 to 7.5).

## 449 12 CLINICAL PHARMACOLOGY

### 450 12.1 Mechanism of Action

451 Maraviroc is an HIV-1 antiviral drug [*see Microbiology (12.4)*].

### 452 12.2 Pharmacodynamics

#### 453 Exposure-Response Relationship in Treatment-Experienced Adult Subjects

454 The relationship between maraviroc, modeled plasma trough concentration (C<sub>min</sub>) (1 to 9 samples  
455 per subject taken on up to 7 visits), and virologic response was evaluated in  
456 973 treatment-experienced HIV-1-infected subjects with varied optimized background  
457 antiretroviral regimens in Trials A4001027 and A4001028. The C<sub>min</sub>, baseline viral load, baseline  
458 CD4+ cell count, and overall sensitivity score (OSS) were found to be important predictors of  
459 virologic success (defined as viral load less than 400 copies per mL at 24 weeks). Table 9  
460 illustrates the proportions of subjects with virologic success (%) within each C<sub>min</sub> quartile for  
461 150-mg twice-daily and 300-mg twice-daily groups.

462 **Table 9. Treatment-Experienced Subjects with Virologic Success by C<sub>min</sub> Quartile (Q1-**  
 463 **Q4)**

	150 mg Twice Daily (with CYP3A Inhibitors)			300 mg Twice Daily (without CYP3A Inhibitors)		
	n	Median C <sub>min</sub>	% Subjects with Virologic Success	n	Median C <sub>min</sub>	% 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

464 Exposure-Response Relationship in Treatment-Naive Adult Subjects

465 The relationship between maraviroc, modeled plasma trough concentration (C<sub>min</sub>) (1 to  
 466 12 samples per subject taken on up to 8 visits), and virologic response was evaluated in  
 467 294 treatment-naive HIV-1–infected subjects receiving maraviroc 300 mg twice daily in  
 468 combination with lamivudine/zidovudine in Trial A4001026. Table 10 illustrates the proportion  
 469 (%) of subjects with virologic success less than 50 copies per mL at 48 weeks within each C<sub>min</sub>  
 470 quartile for the 300-mg twice-daily dose.

471 **Table 10. Treatment-Naive Subjects with Virologic Success by C<sub>min</sub> Quartile (Q1-Q4)**

	300 mg Twice Daily		
	n	Median C <sub>min</sub>	% Subjects with Virologic Success
Q1	75	23	57.3
Q2	72	39	72.2
Q3	73	56	74.0
Q4	74	81	83.8

472 Eighteen of 75 (24%) subjects in Q1 had no measurable maraviroc concentration on at least one  
 473 occasion versus 1 of 73 and 1 of 74 in Q3 and Q4, respectively.

474 Effects on Electrocardiogram

475 A placebo-controlled, randomized, crossover trial to evaluate the effect on the QT interval of  
 476 healthy male and female volunteers was conducted with 3 single oral doses of maraviroc and  
 477 moxifloxacin. The placebo-adjusted mean maximum (upper 1-sided 95% CI) increases in QTc  
 478 from baseline after 100, 300, and 900 mg of maraviroc were -2 (0), -1 (1), and 1 (3) msec,  
 479 respectively, and 13 (15) msec for moxifloxacin 400 mg. No subject in any group had an  
 480 increase in QTc of greater than or equal to 60 msec from baseline. No subject experienced an  
 481 interval exceeding the potentially clinically relevant threshold of 500 msec.

482 **12.3 Pharmacokinetics**

483 **Table 11. Mean Maraviroc Pharmacokinetic Parameters in Adults**

Patient Population	Maraviroc Dose	n	AUC <sub>12</sub> (ng.h/mL)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)
Healthy volunteers (Phase 1)	300 mg twice daily	64	2,908	888	43.1
Asymptomatic HIV subjects (Phase 2a)	300 mg twice daily	8	2,550	618	33.6
Treatment-experienced HIV subjects (Phase 3) <sup>a</sup>	300 mg twice daily	94	1,513	266	37.2
	150 mg twice daily (+ CYP3A inhibitor)	375	2,463	332	101
Treatment-naive HIV subjects (Phase 2b/3) <sup>a</sup>	300 mg twice daily	344	1,865	287	60

484 <sup>a</sup> The estimated exposure is lower compared with other trials possibly due to sparse sampling,  
485 food effect, compliance, and concomitant medications.

486 Absorption

487 Peak maraviroc plasma concentrations are attained 0.5 to 4 hours following single oral doses of 1  
488 to 1,200 mg administered to uninfected volunteers. The pharmacokinetics of oral maraviroc are  
489 not dose proportional over the dose range.

490 The absolute bioavailability of a 100-mg dose is 23% and is predicted to be 33% at 300 mg.  
491 Maraviroc is a substrate for the efflux transporter P-gp.

492 *Effect of Food on Oral Absorption:* Coadministration of a 300-mg tablet with a high-fat breakfast  
493 reduced maraviroc C<sub>max</sub> and AUC by 33% and coadministration of 75 mg of oral solution with a  
494 high-fat breakfast reduced maraviroc AUC by 73% in healthy adult volunteers. Studies with the  
495 tablet formulation demonstrated a reduced food effect at higher doses.

496 There were no food restrictions in the adult trials (using the tablet formulation) or in the pediatric  
497 trial (using both tablet and oral solution formulations) that demonstrated the efficacy/antiviral  
498 activity and safety of maraviroc [*see Clinical Studies (14.1, 14.2)*].

499 Distribution

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

503 Elimination

504 *Metabolism:* Trials in humans and in vitro studies using human liver microsomes and expressed  
505 enzymes have demonstrated that maraviroc is principally metabolized by the cytochrome P450  
506 system to metabolites that are essentially inactive against HIV-1. In vitro studies indicate that  
507 CYP3A is the major enzyme responsible for maraviroc metabolism. In vitro studies also indicate



508 that polymorphic enzymes CYP2C9, CYP2D6, and CYP2C19 do not contribute significantly to  
509 the metabolism of maraviroc.

510 Maraviroc is the major circulating component (~42% drug-related radioactivity) following a  
511 single oral dose of 300 mg [<sup>14</sup>C]-maraviroc. The most significant circulating metabolite in  
512 humans is a secondary amine (~22% radioactivity) formed by N-dealkylation. This polar  
513 metabolite has no significant pharmacological activity. Other metabolites are products of  
514 mono-oxidation and are only minor components of plasma drug-related radioactivity.

515 *Excretion:* The terminal half-life of maraviroc following oral dosing to steady state in healthy  
516 subjects was 14 to 18 hours. A mass balance/excretion trial was conducted using a single 300-mg  
517 dose of <sup>14</sup>C-labeled maraviroc. Approximately 20% of the radiolabel was recovered in the urine  
518 and 76% was recovered in the feces over 168 hours. Maraviroc was the major component present  
519 in urine (mean of 8% dose) and feces (mean of 25% dose). The remainder was excreted as  
520 metabolites.

#### 521 Specific Populations

522 *Patients with Hepatic Impairment:* Maraviroc is primarily metabolized and eliminated by the  
523 liver. A trial compared the pharmacokinetics of a single 300-mg dose of SELZENTRY in  
524 subjects with mild (Child-Pugh Class A, n = 8) and moderate (Child-Pugh Class B, n = 8)  
525 hepatic impairment with pharmacokinetics in healthy subjects (n = 8). The mean C<sub>max</sub> and AUC  
526 were 11% and 25% higher, respectively, for subjects with mild hepatic impairment, and 32% and  
527 46% higher, respectively, for subjects with moderate hepatic impairment compared with subjects  
528 with normal hepatic function. These changes do not warrant a dose adjustment. Maraviroc  
529 concentrations are higher when SELZENTRY 150 mg is administered with a potent CYP3A  
530 inhibitor compared with following administration of 300 mg without a CYP3A inhibitor, so  
531 patients with moderate hepatic impairment who receive SELZENTRY 150 mg with a potent  
532 CYP3A inhibitor should be monitored closely for maraviroc-associated adverse events. The  
533 pharmacokinetics of maraviroc have not been studied in subjects with severe hepatic impairment  
534 [*see Warnings and Precautions (5.1)*].

535 *Patients with Renal Impairment:* A trial compared the pharmacokinetics of a single 300-mg dose  
536 of SELZENTRY in adult subjects with severe renal impairment (CrCl less than 30 mL per  
537 minute, n = 6) and ESRD (n = 6) with healthy volunteers (n = 6). Geometric mean ratios for  
538 maraviroc C<sub>max</sub> and AUC<sub>inf</sub> were 2.4-fold and 3.2-fold higher, respectively, for subjects with  
539 severe renal impairment, and 1.7-fold and 2.0-fold higher, respectively, for subjects with ESRD  
540 as compared with subjects with normal renal function in this trial. Hemodialysis had a minimal  
541 effect on maraviroc clearance and exposure in subjects with ESRD. Exposures observed in  
542 subjects with severe renal impairment and ESRD were within the range observed in previous  
543 300-mg single-dose trials of SELZENTRY in healthy volunteers with normal renal function.  
544 However, maraviroc exposures in the subjects with normal renal function in this trial were 50%  
545 lower than those observed in previous trials. Based on the results of this trial, no dose adjustment

546 is recommended for patients with renal impairment receiving SELZENTRY without a potent  
547 CYP3A inhibitor or inducer. However, if patients with severe renal impairment or ESRD  
548 experience any symptoms of postural hypotension while taking SELZENTRY 300 mg twice  
549 daily, their dose should be reduced to 150 mg twice daily [see *Dosage and Administration (2.3)*,  
550 *Warnings and Precautions (5.3)*].

551 In addition, the trial compared the pharmacokinetics of multiple-dose SELZENTRY in  
552 combination with saquinavir/ritonavir 1,000/100 mg twice daily (a potent CYP3A inhibitor  
553 combination) for 7 days in subjects with mild renal impairment (CrCl greater than 50 and less  
554 than or equal to 80 mL per minute, n = 6) and moderate renal impairment (CrCl greater than or  
555 equal to 30 and less than or equal to 50 mL per minute, n = 6) with healthy volunteers with  
556 normal renal function (n = 6). Subjects received 150 mg of SELZENTRY at different dose  
557 frequencies (healthy volunteers – every 12 hours; mild renal impairment – every 24 hours;  
558 moderate renal impairment – every 48 hours). Compared with healthy volunteers (dosed every  
559 12 hours), geometric mean ratios for maraviroc AUC<sub>tau</sub>, C<sub>max</sub>, and C<sub>min</sub> were 50% higher, 20%  
560 higher, and 43% lower, respectively, for subjects with mild renal impairment (dosed every  
561 24 hours). Geometric mean ratios for maraviroc AUC<sub>tau</sub>, C<sub>max</sub>, and C<sub>min</sub> were 16% higher, 29%  
562 lower, and 85% lower, respectively, for subjects with moderate renal impairment (dosed every  
563 48 hours) compared with healthy volunteers (dosed every 12 hours). Based on the data from this  
564 trial, no adjustment in dose is recommended for patients with mild or moderate renal impairment  
565 [see *Dosage and Administration (2.3)*].

566 *Pediatric Patients:* The pharmacokinetics of maraviroc were evaluated in CCR5-tropic, HIV-1–  
567 infected, treatment-experienced pediatric subjects aged 2 to less than 18 years. In the dose-  
568 finding stage of Trial A4001031, doses were administered with food on intensive PK evaluation  
569 days and optimized to achieve an average concentration over the dosing interval (C<sub>avg</sub>) of  
570 greater than 100 ng per mL. Throughout the trial, on non-intensive PK evaluation days maraviroc  
571 was taken with or without food. The initial dose of maraviroc was based on BSA and  
572 concomitant medication category (i.e., presence of CYP3A inhibitors and/or inducers). The  
573 conversion of dosing to a weight (kg)-band basis in children provides comparable exposures with  
574 those observed in the trial at the corresponding BSA.

575 Maraviroc pharmacokinetic parameters in pediatric subjects receiving potent CYP3A inhibitors  
576 with or without a potent CYP3A inducer (Table 12) and in subjects weighing greater than or  
577 equal to 30 kg and receiving noninteracting concomitant medications (Table 13) were similar to  
578 those observed in adults. Insufficient pharmacokinetic data are available to make a comparison  
579 between adults and pediatric subjects weighing less than 30 kg and receiving noninteracting  
580 concomitant medications or between adult and pediatric subjects receiving concomitant  
581 medications consisting of a potent CYP3A inducer without CYP3A inhibitor.

582 **Table 12. Maraviroc Pharmacokinetic Parameters in Treatment-Experienced Pediatric**  
 583 **Patients Receiving SELZENTRY with Potent CYP3A Inhibitors (with or without a**  
 584 **Potent CYP3A Inducer)**

Weight	Dose of SELZENTRY	Maraviroc Pharmacokinetic Parameter <sup>a</sup> Geometric Mean			
		AUC <sub>12</sub> (ng.h/mL)	C <sub>avg</sub> (ng/mL)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)
10 kg to <20 kg	50 mg twice daily	2,349	196	324	78
20 kg to <30 kg	75 mg twice daily	3,020	252	394	118
30 kg to <40 kg	100 mg twice daily	3,229	269	430	126
≥40 kg	150 mg twice daily	4,044	337	563	152

585 <sup>a</sup> The covariate distribution of the study population of 85 subjects on CYP3A-inhibitor-  
 586 containing regimens was randomly sampled with replacement to obtain 1,000 subjects. Shown  
 587 in the table are model-predicted steady-state PK parameters for the 1,000 subjects in the  
 588 simulation dataset.

589 **Table 13. Maraviroc Pharmacokinetic Parameters in Treatment-Experienced Pediatric**  
 590 **Patients Receiving SELZENTRY with Noninteracting Concomitant Medications<sup>a</sup>**

Weight (n)	Dose of SELZENTRY	Maraviroc Pharmacokinetic Parameter Geometric Mean			
		AUC <sub>12</sub> (ng.h/mL)	C <sub>avg</sub> (ng/mL)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)
<30 kg		Insufficient data			
≥30 kg (n = 5) <sup>b</sup>	300 mg twice daily	1,998	167	413	50.6

591 <sup>a</sup> Noninteracting concomitant medications include all medications that are not potent CYP3A  
 592 inhibitors or inducers.

593 <sup>b</sup> Nine observations from 5 subjects.

594 *Geriatric Patients:* Pharmacokinetics of maraviroc have not been fully evaluated in the elderly  
 595 (aged 65 years and older). Based on population pharmacokinetic analyses, age did not have a  
 596 clinically relevant effect on maraviroc exposure in subjects up to age 65 years [see *Use in*  
 597 *Specific Populations (8.5)*].

598 *Race and Gender:* Based on population pharmacokinetics and 2 clinical CYP3A5 genotype  
 599 analyses for race, no dosage adjustment is recommended based on race or gender.

600 Drug Interaction Studies

601 *Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc:* Maraviroc is a substrate of  
 602 CYP3A and P-gp and hence its pharmacokinetics are likely to be modulated by inhibitors and

603 inducers of these enzymes/transporters. The CYP3A/P-gp inhibitors ketoconazole, boceprevir,  
 604 lopinavir/ritonavir, ritonavir, darunavir/ritonavir, saquinavir/ritonavir, and atazanavir ± ritonavir  
 605 all increased the C<sub>max</sub> and AUC of maraviroc (Table 14). The CYP3A and/or P-gp inducers  
 606 rifampin, etravirine, and efavirenz decreased the C<sub>max</sub> and AUC of maraviroc (Table 14). While  
 607 not studied, potent CYP3A and/or P-gp inducers carbamazepine, phenobarbital, and phenytoin  
 608 are expected to decrease maraviroc concentrations. Based on in vitro study results, maraviroc is  
 609 also a substrate of OATP1B1 and MRP2; its pharmacokinetics may be modulated by inhibitors of  
 610 these transporters.

611 Tipranavir/ritonavir (net CYP3A inhibitor/P-gp inducer) did not affect the steady-state  
 612 pharmacokinetics of maraviroc (Table 14). Cotrimoxazole and tenofovir did not affect the  
 613 pharmacokinetics of maraviroc.

614 **Table 14. Effect of Coadministered Agents on the Pharmacokinetics of Maraviroc**

Coadministered Drug and Dose	n	Dose of SELZENTRY	Ratio (90% CI) of Maraviroc Pharmacokinetic Parameters with/without Coadministered Drug (No Effect = 1.00)		
			C <sub>min</sub>	AUC <sub>tau</sub>	C <sub>max</sub>
<b>CYP3A and/or P-gp Inhibitors</b>					
Ketoconazole 400 mg q.d.	12	100 mg b.i.d.	3.75 (3.01, 4.69)	5.00 (3.98, 6.29)	3.38 (2.38, 4.78)
Ritonavir 100 mg b.i.d.	8	100 mg b.i.d.	4.55 (3.37, 6.13)	2.61 (1.92, 3.56)	1.28 (0.79, 2.09)
Saquinavir (soft gel capsules) /ritonavir 1,000 mg/100 mg b.i.d.	11	100 mg b.i.d.	11.3 (8.96, 14.1)	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
Lopinavir/ritonavir 400 mg/100 mg b.i.d.	11	300 mg b.i.d.	9.24 (7.98, 10.7)	3.95 (3.43, 4.56)	1.97 (1.66, 2.34)
Atazanavir 400 mg q.d.	12	300 mg b.i.d.	4.19 (3.65, 4.80)	3.57 (3.30, 3.87)	2.09 (1.72, 2.55)
Atazanavir/ritonavir 300 mg/100 mg q.d.	12	300 mg b.i.d.	6.67 (5.78, 7.70)	4.88 (4.40, 5.41)	2.67 (2.32, 3.08)
Darunavir/ritonavir 600 mg/100 mg b.i.d.	12	150 mg b.i.d.	8.00 (6.35, 10.1)	4.05 (2.94, 5.59)	2.29 (1.46, 3.59)
Boceprevir 800 mg t.i.d.	14	150 mg b.i.d.	2.78 (2.40, 3.23)	3.02 (2.53, 3.59)	3.33 (2.54, 4.36)
Elvitegravir/ritonavir 150 mg/100 mg q.d.	11	150 mg b.i.d.	4.23 (3.47, 5.16)	2.86 (2.33, 3.51)	2.15 (1.71, 2.69)
<b>CYP3A and/or P-gp Inducers</b>					
Efavirenz 600 mg q.d.	12	100 mg b.i.d.	0.55 (0.43, 0.72)	0.55 (0.49, 0.62)	0.49 (0.38, 0.63)
Efavirenz 600 mg q.d.	12	200 mg b.i.d. (+ efavirenz): 100 mg b.i.d. (alone)	1.09 (0.89, 1.35)	1.15 (0.98, 1.35)	1.16 (0.87, 1.55)
Rifampicin 600 mg q.d.	12	100 mg b.i.d.	0.22 (0.17, 0.28)	0.37 (0.33, 0.41)	0.34 (0.26, 0.43)

Rifampicin 600 mg q.d.	12	200 mg b.i.d. (+ rifampicin): 100 mg b.i.d. (alone)	0.66 (0.54, 0.82)	1.04 (0.89, 1.22)	0.97 (0.72, 1.29)
Etravirine 200 mg b.i.d.	14	300 mg b.i.d.	0.61 (0.53, 0.71)	0.47 (0.38, 0.58)	0.40 (0.28, 0.57)
Nevirapine <sup>a</sup> 200 mg b.i.d. (+ lamivudine 150 mg b.i.d., tenofovir 300 mg q.d.)	8	300 mg single dose	–	1.01 (0.65, 1.55)	1.54 (0.94, 2.51)
<b>CYP3A and/or P-gp Inhibitors and Inducers</b>					
Lopinavir/ritonavir + efavirenz 400 mg/100 mg b.i.d. + 600 mg q.d.	11	300 mg b.i.d.	6.29 (4.72, 8.39)	2.53 (2.24, 2.87)	1.25 (1.01, 1.55)
Saquinavir(soft gel capsules) /ritonavir + efavirenz 1,000 mg/100 mg b.i.d. + 600 mg q.d.	11	100 mg b.i.d.	8.42 (6.46, 10.97)	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)
Darunavir/ritonavir + etravirine 600 mg/100 mg b.i.d. + 200 mg b.i.d.	10	150 mg b.i.d.	5.27 (4.51, 6.15)	3.10 (2.57, 3.74)	1.77 (1.20, 2.60)
Fosamprenavir/ritonavir 700 mg/100 mg b.i.d.	14	300 mg b.i.d.	4.74 (4.03, 5.57)	2.49 (2.19, 2.82)	1.52 (1.27, 1.82)
Fosamprenavir/ritonavir 1,400 mg/100 mg q.d.	14	300 mg q.d.	1.80 (1.53, 2.13)	2.26 (1.99, 2.58)	1.45 (1.20, 1.74)
Tipranavir/ritonavir 500 mg/200 mg b.i.d.	12	150 mg b.i.d.	1.80 (1.55, 2.09)	1.02 (0.85, 1.23)	0.86 (0.61, 1.21)
<b>Other</b>					
Raltegravir 400 mg b.i.d.	17	300 mg b.i.d.	0.90 (0.85, 0.96)	0.86 (0.80, 0.92)	0.79 (0.67, 0.94)

615 <sup>a</sup> Compared with historical data.

616 *Effect of Maraviroc on the Pharmacokinetics of Concomitant Drugs:* Maraviroc is unlikely to  
617 inhibit the metabolism of coadministered drugs metabolized by the following cytochrome P  
618 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A) or to inhibit the  
619 uptake of OATP1B1 or the export of MRP2 because maraviroc did not inhibit activity of those  
620 enzymes or transporters at clinically relevant concentrations in vitro. Maraviroc does not induce  
621 CYP1A2 in vitro. Additionally, in vitro studies have shown that maraviroc is not a substrate for,  
622 and does not inhibit, any of the major renal uptake inhibitors (organic anion transporter [OAT]1,  
623 OAT3, organic cation transporter [OCT]2, novel organic cation transporter [OCTN]1, and  
624 OCTN2) at clinically relevant concentrations.

625 In vitro results suggest that maraviroc could inhibit P-gp in the gut. However, maraviroc did not  
626 significantly affect the pharmacokinetics of digoxin in vivo, indicating maraviroc may not  
627 significantly inhibit or induce P-gp clinically.

628 Drug interaction trials were performed with maraviroc and other drugs likely to be  
629 coadministered or commonly used as probes for pharmacokinetic interactions (Table 14).

630 Coadministration of fosamprenavir 700 mg/ritonavir 100 mg twice daily and maraviroc 300 mg  
631 twice daily decreased the  $C_{min}$  and AUC of amprenavir by 36% and 35%, respectively.

632 Coadministration of fosamprenavir 1,400 mg/ritonavir 100 mg once daily and maraviroc 300 mg  
633 once daily decreased the  $C_{min}$  and AUC by 15% and 30%, respectively. No dosage adjustment is  
634 necessary when SELZENTRY is dosed 150 mg twice daily in combination with  
635 fosamprenavir/ritonavir dosed once or twice daily. Fosamprenavir should be given with ritonavir  
636 when coadministered with SELZENTRY.

637 Maraviroc had no significant effect on the pharmacokinetics of elvitegravir, boceprevir,  
638 zidovudine, or lamivudine. Maraviroc decreased the  $C_{min}$  and AUC of raltegravir by 27% and  
639 37%, respectively, which is not clinically significant. Maraviroc had no clinically relevant effect  
640 on the pharmacokinetics of midazolam, the oral contraceptives ethinylestradiol and  
641 levonorgestrel, no effect on the urinary 6 $\beta$ -hydroxycortisol/cortisol ratio, suggesting no induction  
642 of CYP3A in vivo. Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg  
643 twice daily or less in vivo and did not cause inhibition of CYP2D6 in vitro until concentrations  
644 greater than 100 microM. However, there was 234% increase in debrisoquine MR on treatment  
645 compared with baseline at 600 mg once daily, suggesting potential inhibition of CYP2D6 at  
646 higher doses.

## 647 **12.4 Microbiology**

### 648 Mechanism of Action

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

### 653 Antiviral Activity in Cell Culture

654 Maraviroc inhibits the replication of CCR5-tropic laboratory strains and primary isolates of  
655 HIV-1 in models of acute peripheral blood leukocyte infection. The mean  $EC_{50}$  value (50%  
656 effective concentration) for maraviroc against HIV-1 group M isolates (subtypes A to J and  
657 circulating recombinant form AE) and group O isolates ranged from 0.1 to 4.5 nM (0.05 to  
658 2.3 ng per mL) in cell culture.

659 When used with other antiretroviral agents in cell culture, the combination of maraviroc was not  
660 antagonistic with non-nucleoside reverse transcriptase inhibitors (NNRTIs: delavirdine,  
661 efavirenz, and nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine,

662 tenofovir, zalcitabine, and zidovudine), or protease inhibitors (PIs: amprenavir, atazanavir,  
663 darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir). Maraviroc was  
664 not antagonistic with the HIV-1 gp41 fusion inhibitor enfuvirtide. Maraviroc was not active  
665 against CXCR4-tropic and dual-tropic viruses ( $EC_{50}$  value greater than 10  $\mu$ M). The  
666 antiviral activity of maraviroc against HIV-2 has not been evaluated.

667 *Resistance in Cell Culture:* HIV-1 variants with reduced susceptibility to maraviroc have been  
668 selected in cell culture following serial passage of 2 CCR5-tropic viruses (CCI/85 and RU570).  
669 The maraviroc-resistant viruses remained CCR5-tropic with no evidence of a change from a  
670 CCR5-tropic virus to a CXCR4-using virus. Two amino acid residue substitutions in the V3-loop  
671 region of the HIV-1 envelope glycoprotein (gp160), A316T, and I323V (HXB2 numbering),  
672 were shown to be necessary for the maraviroc-resistant phenotype in the HIV-1 isolate CCI/85.  
673 In the RU570 isolate a 3-amino acid residue deletion in the V3 loop,  $\Delta$ QAI (HXB2 positions 315  
674 to 317), was associated with maraviroc resistance. The relevance of the specific gp120  
675 substitutions observed in maraviroc-resistant isolates selected in cell culture to clinical maraviroc  
676 resistance is not known. Maraviroc-resistant viruses were characterized phenotypically by  
677 concentration-response curves that did not reach 100% inhibition in phenotypic drug assays,  
678 rather than increases in  $EC_{50}$  values.

679 *Cross-Resistance in Cell Culture:* Maraviroc had antiviral activity against HIV-1 clinical isolates  
680 resistant to NNRTIs, NRTIs, PIs, and the gp41 fusion inhibitor enfuvirtide in cell culture ( $EC_{50}$   
681 values ranged from 0.7 to 8.9 nM [0.36 to 4.57 ng per mL]). Maraviroc-resistant viruses that  
682 emerged in cell culture remained susceptible to enfuvirtide and the protease inhibitor saquinavir.

683 *Clinical Resistance:* Virologic failure on maraviroc can result from genotypic and phenotypic  
684 resistance to maraviroc, through outgrowth of undetected CXCR4-using virus present before  
685 maraviroc treatment (see *Tropism* below), through resistance to background therapy drugs (Table  
686 15), or due to low exposure to maraviroc [*see Clinical Pharmacology (12.2)*].

687 *Antiretroviral Treatment-Experienced Adult Subjects (Trials A4001027 and A4001028):* Week  
688 48 data from treatment-experienced subjects failing maraviroc-containing regimens with  
689 CCR5-tropic virus (n = 58) have identified 22 viruses that had decreased susceptibility to  
690 maraviroc characterized in phenotypic drug assays by concentration-response curves that did not  
691 reach 100% inhibition. Additionally, CCR5-tropic virus from 2 of these treatment-failure  
692 subjects had greater than or equal to 3-fold shifts in  $EC_{50}$  values for maraviroc at the time of  
693 failure.

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

699 *Antiretroviral Treatment-Naive Adult Subjects (Trial A4001026)*: Treatment-naive subjects  
 700 receiving SELZENTRY had more virologic failures and more treatment-emergent resistance to  
 701 the background regimen drugs compared with those receiving efavirenz (Table 15).

702 **Table 15. Development of Resistance to Maraviroc or Efavirenz and Background Drugs**  
 703 **in Antiretroviral Treatment-Naive Trial A4001026 for Patients with Only CCR5-Tropic**  
 704 **Virus at Screening Using Enhanced Sensitivity TROFILE Assay**

	<b>Maraviroc</b>	<b>Efavirenz</b>
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 <sup>a</sup>	19 (26%)	–

705 <sup>a</sup> Includes subjects failing with CXCR4- or dual/mixed-tropism because these viruses are not  
 706 intrinsically susceptible to maraviroc.

707 In an as-treated analysis of treatment-naive subjects at 96 weeks, 32 subjects failed a  
 708 maraviroc-containing regimen with CCR5-tropic virus and had a tropism result at failure; 7 of  
 709 these subjects had evidence of maraviroc phenotypic resistance defined as  
 710 concentration-response curves that did not reach 95% inhibition. One additional subject had a  
 711 greater than or equal to 3-fold shift in the EC<sub>50</sub> value for maraviroc at the time of failure. A  
 712 clonal analysis of the V3 loop amino acid envelope sequences was performed from 6 of the  
 713 7 subjects. Changes in V3 loop amino acid sequence differed between each of these different  
 714 subjects, even for those infected with the same virus clade, suggesting that there are multiple  
 715 diverse pathways to maraviroc resistance. The subjects who failed with CCR5-tropic virus and  
 716 without a detectable maraviroc shift in susceptibility were not evaluated for genotypic resistance.

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

720 *Tropism*: In both treatment-experienced and treatment-naive subjects, detection of CXCR4-using  
 721 virus prior to initiation of therapy has been associated with a reduced virologic response to  
 722 maraviroc.

723 *Antiretroviral Treatment-Experienced Subjects (Trials A4001027 and A4001028)*: In the  
 724 majority of cases, treatment failure on maraviroc was associated with detection of CXCR4-using  
 725 virus (i.e., CXCR4- or dual/mixed-tropic) which was not detected by the tropism assay prior to  
 726 treatment. CXCR4-using virus was detected at failure in approximately 55% of subjects who



727 failed treatment on maraviroc by Week 48, as compared with 9% of subjects who experienced  
728 treatment failure in the placebo arm. To investigate the likely origin of the on-treatment  
729 CXCR4-using virus, a detailed clonal analysis was conducted on virus from 20 representative  
730 subjects (16 subjects from the maraviroc arms and 4 subjects from the placebo arm) in whom  
731 CXCR4-using virus was detected at treatment failure. From analysis of amino acid sequence  
732 differences and phylogenetic data, it was determined that CXCR4-using virus in these subjects  
733 emerged from a low level of pre-existing CXCR4-using virus not detected by the tropism assay  
734 (which is population-based) prior to treatment rather than from a co-receptor switch from  
735 CCR5-tropic virus to CXCR4-using virus resulting from mutation in the virus.

736 Detection of CXCR4-using virus prior to initiation of therapy has been associated with a reduced  
737 virological response to maraviroc. Furthermore, subjects failing twice-daily maraviroc at Week  
738 48 with CXCR4-using virus had a lower median increase in CD4+ cell counts from baseline  
739 (+41 cells per mm<sup>3</sup>) than those subjects failing with CCR5-tropic virus (+162 cells per mm<sup>3</sup>).  
740 The median increase in CD4+ cell count in subjects failing in the placebo arm was +7 cells per  
741 mm<sup>3</sup>.

742 *Antiretroviral Treatment-Naive Subjects (Trial A4001026)*: In a 96-week trial of antiretroviral  
743 treatment-naive subjects, 14% (12 of 85) who had only CCR5-tropic virus at screening with an  
744 enhanced sensitivity tropism assay (TROFILE) and failed therapy on maraviroc had  
745 CXCR4-using virus at the time of treatment failure. A detailed clonal analysis was conducted in  
746 2 previously antiretroviral treatment-naive subjects enrolled in a Phase 2a monotherapy trial who  
747 had CXCR4-using virus detected after 10 days' treatment with maraviroc. Consistent with the  
748 detailed clonal analysis conducted in treatment-experienced subjects, the CXCR4-using variants  
749 appear to emerge from outgrowth of a pre-existing undetected CXCR4-using virus. Screening  
750 with an enhanced sensitivity tropism assay reduced the number of maraviroc virologic failures  
751 with CXCR4- or dual/mixed-tropic virus at failure to 12 compared with 24 when screening with  
752 the original tropism assay. All but one (11 of 12; 92%) of the maraviroc failures failing with  
753 CXCR4- or dual/mixed-tropic virus also had genotypic and phenotypic resistance to the  
754 background drug lamivudine at failure and 33% (4 of 12) developed zidovudine-associated  
755 resistance substitutions.

756 Subjects who had only CCR5-tropic virus at baseline and failed maraviroc therapy with  
757 CXCR4-using virus had a median increase in CD4+ cell counts from baseline of +113 cells per  
758 mm<sup>3</sup> while those subjects failing with CCR5-tropic virus had an increase of +135 cells per mm<sup>3</sup>.  
759 The median increase in CD4+ cell count in subjects failing in the efavirenz arm was +95 cells  
760 per mm<sup>3</sup>.

761 *Antiretroviral Treatment-Experienced Pediatric Subjects (Trial A4001031)*: In the Week 48  
762 analysis of Trial A4001031 (n = 103), the mechanisms of resistance to maraviroc observed in the  
763 treatment-experienced pediatric population were similar to those observed in adult populations:  
764 reasons for virologic failure included failing with CXCR4- or dual/mixed-tropic virus, evidence

765 of reduced maraviroc susceptibility as measured by a decrease in maximal percentage inhibition  
766 (MPI), and emergence of resistance to background drug in the regimen.

## 767 **13 NONCLINICAL TOXICOLOGY**

### 768 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### 769 Carcinogenesis

770 Long-term oral carcinogenicity studies of maraviroc were carried out in rasH2 transgenic mice  
771 (6 months) and in rats for up to 96 weeks (females) and 104 weeks (males). No drug-related  
772 increases in tumor incidence were found in mice at 1,500 mg per kg per day and in male and  
773 female rats at 900 mg per kg per day. The highest exposures in rats were approximately 11 times  
774 those observed in humans at the therapeutic dose of 300 mg twice daily for the treatment of  
775 HIV-1 infection.

#### 776 Mutagenesis

777 Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames test in Salmonella and  
778 E. coli), a chromosome aberration test in human lymphocytes, and mouse bone marrow  
779 micronucleus test.

#### 780 Impairment of Fertility

781 Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of  
782 treated male rats at approximately 20-fold higher exposures (AUC) than in humans given the  
783 recommended 300-mg twice-daily dose.

## 784 **14 CLINICAL STUDIES**

### 785 **14.1 Clinical Studies in Adult Subjects**

786 The clinical efficacy and safety of SELZENTRY are derived from analyses of data from 3 trials  
787 in adult subjects infected with CCR5-tropic HIV-1: Trials A4001027 and A4001028 in  
788 antiretroviral treatment-experienced adult subjects and Trial A4001026 in treatment-naive  
789 subjects. These trials were supported by a 48-week trial in antiretroviral treatment-experienced  
790 adult subjects infected with dual/mixed-tropic HIV-1, Trial A4001029.

#### 791 Trials in CCR5-Tropic, Treatment-Experienced Subjects

792 Trials A4001027 and A4001028 were double-blind, randomized, placebo-controlled, multicenter  
793 trials in subjects infected with CCR5-tropic HIV-1. Subjects were required to have an HIV-1  
794 RNA greater than 5,000 copies per mL despite at least 6 months of prior therapy with at least  
795 1 agent from 3 of the 4 antiretroviral drug classes (greater than or equal to 1 NRTI, greater than  
796 or equal to 1 NNRTI, greater than or equal to 2 PIs, and/or enfuvirtide) or documented resistance  
797 to at least 1 member of each class. All subjects received an optimized background regimen  
798 consisting of 3 to 6 antiretroviral agents (excluding low-dose ritonavir) selected on the basis of

799 the subject's prior treatment history and baseline genotypic and phenotypic viral resistance  
800 measurements. In addition to the optimized background regimen, subjects were then randomized  
801 in a 2:2:1 ratio to SELZENTRY 300 mg once daily, SELZENTRY 300 mg twice daily, or  
802 placebo. Doses were adjusted based on background therapy as described in *Dosage and*  
803 *Administration* (2), Table 1.

804 In the pooled analysis for Trials A4001027 and A4001028, the demographics and baseline  
805 characteristics of the treatment groups were comparable (Table 16). Of the 1,043 subjects with a  
806 CCR5-tropism result at screening, 7.6% had a dual/mixed-tropism result at the baseline visit 4 to  
807 6 weeks later. This illustrates the background change from CCR5- to dual/mixed-tropism result  
808 over time in this treatment-experienced population, prior to a change in antiretroviral regimen or  
809 administration of a CCR5 co-receptor antagonist.

810 **Table 16. Demographic and Baseline Characteristics of Subjects in Trials A4001027**  
811 **and A4001028**

	<b>SELZENTRY Twice Daily (n = 426)</b>	<b>Placebo (n = 209)</b>
Age (years)		
Mean (range)	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%)
Region:		
U.S.	276 (64.8%)	135 (64.6%)
Non-U.S.	150 (35.2%)	74 (35.4%)
Subjects with previous enfuvirtide use	142 (33.3%)	62 (29.7%)
Subjects with enfuvirtide as part of OBT	182 (42.7%)	91 (43.5%)
Baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)		
Mean (range)	4.85 (2.96-6.88)	4.86 (3.46-7.07)
Subjects with screening viral load ≥100,000 copies/mL	179 (42.0%)	84 (40.2%)
Baseline CD4+ cell count (cells/mm <sup>3</sup> )		
Median (range)	167 (2-820)	171 (1-675)
Subjects with baseline CD4+ cell count ≤200 cells/mm <sup>3</sup> )	250 (58.7%)	118 (56.5%)
Subjects with Overall Susceptibility Score (OSS): <sup>a</sup>		
0	57 (13.4%)	35 (16.7%)
1	136 (31.9%)	44 (21.1%)

2	104 (24.4%)	59 (28.2%)
≥3	125 (29.3%)	66 (31.6%)
Subjects with enfuvirtide resistance substitutions	90 (21.2%)	45 (21.5%)
Median number of resistance-associated: <sup>b</sup>		
PI substitutions	10	10
NNRTI substitutions	1	1
NRTI substitutions	6	6

812 <sup>a</sup> OSS - Sum of active drugs in OBT based on combined information from genotypic and  
813 phenotypic testing.

814 <sup>b</sup> Resistance substitutions based on IAS guidelines.<sup>1</sup>

815 The Week 48 results for the pooled Trials A4001027 and A4001028 are shown in Table 17.

816 **Table 17. Outcomes of Randomized Treatment at Week 48 in Trials A4001027 and**  
817 **A4001028**

<b>Outcome</b>	<b>SELZENTRY Twice Daily (n = 426)</b>	<b>Placebo (n = 209)</b>	<b>Mean Difference</b>
Mean change from Baseline to Week 48 in HIV-1 RNA (log <sub>10</sub> copies/mL)	-1.84	-0.78	-1.05
<400 copies/mL at Week 48	239 (56%)	47 (22%)	34%
<50 copies/mL at Week 48	194 (46%)	35 (17%)	29%
Discontinuations:			
Insufficient clinical response	97 (23%)	113 (54%)	–
Adverse events	19 (4%)	11 (5%)	–
Other	27 (6%)	18 (9%)	–
Subjects with treatment-emergent CDC Category C events	22 (5%)	16 (8%)	–
Deaths (during trial or within 28 days of last dose)	9 (2%) <sup>a</sup>	1 (0.5%)	–

818 <sup>a</sup> One additional subject died while receiving open-label therapy with SELZENTRY subsequent  
819 to discontinuing double-blind placebo due to insufficient response.

820 After 48 weeks of therapy, the proportions of subjects with HIV-1 RNA less than 400 copies per  
821 mL receiving SELZENTRY compared with placebo were 56% and 22%, respectively. The mean  
822 changes in plasma HIV-1 RNA from baseline to Week 48 were –1.84 log<sub>10</sub> copies per mL for  
823 subjects receiving SELZENTRY + OBT compared with –0.78 log<sub>10</sub> copies per mL for subjects  
824 receiving OBT only. The mean increase in CD4+ cell count was higher on SELZENTRY twice  
825 daily + OBT (124 cells per mm<sup>3</sup>) than on placebo + OBT (60 cells per mm<sup>3</sup>).

826 Trial in Dual/Mixed-Tropic, Treatment-Experienced Subjects

827 Trial A4001029 was an exploratory, randomized, double-blind, multicenter trial to determine the  
 828 safety and efficacy of SELZENTRY in subjects infected with dual/mixed co-receptor tropic  
 829 HIV-1. The inclusion/exclusion criteria were similar to those for Trials A4001027 and  
 830 A4001028 above and the subjects were randomized in a 1:1:1 ratio to SELZENTRY once daily,  
 831 SELZENTRY twice daily, or placebo. No increased risk of infection or HIV-1 disease  
 832 progression was observed in the subjects who received SELZENTRY. Use of SELZENTRY was  
 833 not associated with a significant decrease in HIV-1 RNA compared with placebo in these  
 834 subjects and no adverse effect on CD4+ cell count was noted.

835 Trial in Treatment-Naive Subjects

836 Trial A4001026 was a randomized, double-blind, multicenter trial in subjects infected with  
 837 CCR5-tropic HIV-1 classified by the original TROFILE tropism assay. Subjects were required to  
 838 have plasma HIV-1 RNA greater than or equal to 2,000 copies per mL and could not have: 1)  
 839 previously received any antiretroviral therapy for greater than 14 days, 2) an active or recent  
 840 opportunistic infection or a suspected primary HIV-1 infection, or 3) phenotypic or genotypic  
 841 resistance to zidovudine, lamivudine, or efavirenz. Subjects were randomized in a 1:1:1 ratio to  
 842 SELZENTRY 300 mg once daily, SELZENTRY 300 mg twice daily, or efavirenz 600 mg once  
 843 daily, each in combination with lamivudine/zidovudine. The efficacy and safety of  
 844 SELZENTRY are based on the comparison of SELZENTRY twice daily versus efavirenz. In a  
 845 pre-planned interim analysis at 16 weeks, SELZENTRY 300 mg once daily failed to meet the  
 846 pre-specified criteria for demonstrating non-inferiority and was discontinued.

847 The demographic and baseline characteristics of the maraviroc and efavirenz treatment groups  
 848 were comparable (Table 18). Subjects were stratified by screening HIV-1 RNA levels and by  
 849 geographic region. The median CD4+ cell counts and mean HIV-1 RNA at baseline were similar  
 850 for both treatment groups.

851 **Table 18. Demographic and Baseline Characteristics of Subjects in Trial A4001026**

	<b>SELZENTRY 300 mg Twice Daily + Lamivudine/Zidovudine (n = 360)</b>	<b>Efavirenz 600 mg Once Daily + Lamivudine/Zidovudine (n = 361)</b>
Age (years):		
Mean	36.7	37.4
Range	20-69	18-77
Female, n%	104 (29)	102 (28)
Race, n%:		
White	204 (57)	198 (55)
Black	123 (34)	133 (37)
Asian	6 (2)	5 (1)
Other	27 (8)	25 (7)

Median (range) CD4+ cell count (cells/microL)	241 (5-1,422)	254 (8-1,053)
Median (range) HIV-1 RNA (log <sub>10</sub> copies/mL)	4.9 (3-7)	4.9 (3-7)

852 The treatment outcomes at 96 weeks for Trial A4001026 are shown in Table 19. Treatment  
853 outcomes are based on reanalysis of the screening samples using a more sensitive tropism assay,  
854 enhanced sensitivity TROFILE HIV tropism assay, which became available after the Week 48  
855 analysis; approximately 15% of the subjects identified as CCR5-tropic in the original analysis  
856 had dual/mixed- or CXCR4-tropic virus. Screening with enhanced sensitivity version of the  
857 TROFILE tropism assay reduced the number of maraviroc virologic failures with CXCR4- or  
858 dual/mixed-tropic virus at failure to 12 compared with 24 when screening with the original  
859 TROFILE HIV tropism assay.

860 **Table 19. Trial Outcome (Snapshot) at Week 96 Using Enhanced Sensitivity Assay<sup>a</sup>**

<b>Outcome at Week 96<sup>b</sup></b>	<b>SELZENTRY 300 mg Twice Daily + Lamivudine/Zidovudine (n = 311) n (%)</b>	<b>Efavirenz 600 mg Once Daily + Lamivudine/Zidovudine (n = 303) n (%)</b>
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 <sup>c</sup>	43 (14)	36 (12)

861 <sup>a</sup> The total number of subjects (311, 303) in Table 19 represents the subjects who had a  
862 CCR5-tropic virus in the reanalysis of screening samples using the more sensitive tropism  
863 assay. This reanalysis reclassified approximately 15% of subjects shown in Table 18 as having  
864 dual/mixed- or CXCR4-tropic virus. These numbers are different than those presented in Table  
865 18 because the numbers in Table 18 reflect the subjects with CCR5-tropic virus according to

866 the original tropism assay.

867 <sup>b</sup> Week 48 results: Virologic responders (less than 400): 228 of 311 (73%) in SELZENTRY, 219  
868 of 303 (72%) in efavirenz;

869 Virologic responders (less than 50): 213 of 311 (69%) in SELZENTRY, 207 of 303 (68%) in  
870 efavirenz.

871 <sup>c</sup> Other reasons for discontinuation include lost to follow-up, withdrawn, protocol violation, and  
872 other.

873 The median increase from baseline in CD4+ cell counts at Week 96 was 184 cells per mm<sup>3</sup> for  
874 the arm receiving SELZENTRY compared with 155 cells per mm<sup>3</sup> for the efavirenz arm.

## 875 **14.2 Clinical Studies in Pediatric Subjects**

### 876 Trial in CCR5-Tropic, Treatment-Experienced Subjects

877 Trial A4001031 is an open-label, multicenter trial in pediatric subjects aged 2 to less than  
878 18 years infected with only CCR5-tropic HIV-1. Subjects were required to have HIV-1 RNA  
879 greater than 1,000 copies per mL at screening. All subjects (n = 103) received SELZENTRY  
880 twice daily and OBT. Dosing of SELZENTRY was based on BSA and doses were adjusted  
881 based on whether the subject was receiving potent CYP3A inhibitors and/or inducers.

882 The population was 52% female and 69% black, with mean age of 10 years (range: 2 to  
883 17 years). At baseline, mean plasma HIV-1 RNA was 4.4 log<sub>10</sub> copies per mL (range: 2.4 to  
884 6.2 log<sub>10</sub> copies per mL), mean CD4+ cell count was 551 cells per mm<sup>3</sup> (range: 1 to  
885 1,654 cells per mm<sup>3</sup>), and mean CD4+ percent was 21% (range: 0% to 42%).

886 At 48 weeks, 48% of subjects treated with SELZENTRY and OBT achieved plasma HIV-1 RNA  
887 less than 48 copies per mL and 65% of subjects achieved plasma HIV-1 RNA less than  
888 400 copies per mL. The mean CD4+ cell count (percent) increase from baseline to Week 48 was  
889 247 cells per mm<sup>3</sup> (5%).

## 890 **15 REFERENCES**

891 1. IAS-USA Drug Resistance Mutations Figures.  
892 <http://www.iasusa.org/pub/topics/2006/issue3/125.pdf>

## 893 **16 HOW SUPPLIED/STORAGE AND HANDLING**

894 SELZENTRY film-coated tablets are available as follows:

895 25-mg, 75-mg, 150-mg, and 300-mg tablets are blue, biconvex, oval, film-coated tablets  
896 debossed with “MVC 25”, “MVC 75”, “MVC 150”, or “MVC 300”, respectively, on one side  
897 and plain on the other.

898 25-mg tablets: Bottle of 120 tablets (NDC 49702-233-08).

899 75-mg tablets: Bottle of 120 tablets (NDC 49702-235-08).

900 150-mg tablets: Bottle of 60 tablets (NDC 49702-223-18).

901 300-mg tablets: Bottle of 60 tablets (NDC 49702-224-18).

902 SELZENTRY film-coated tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions  
903 permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

904 SELZENTRY oral solution is a clear, colorless, strawberry-flavored liquid. Each mL of the  
905 solution contains 20 mg of maraviroc. It is packaged in plastic bottles as follows:

906 Bottle of 230 mL (NDC 49702-237-55). Each bottle is packaged with one press-in bottle adapter  
907 and one 10-mL oral dosing syringe with 0.5-mL gradations. The press-in bottle adapter and oral  
908 dosing syringe are not made with natural rubber latex. This product does not require  
909 reconstitution.

910 SELZENTRY oral solution should be stored at 20°C to 25°C (68°F to 77°F); excursions  
911 permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

912 Discard any unused oral solution 60 days after first opening the bottle.

## 913 **17 PATIENT COUNSELING INFORMATION**

914 Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions  
915 for Use).

### 916 Hepatotoxicity

917 Inform patients that hepatotoxicity, including life-threatening cases, has been reported with  
918 SELZENTRY; therefore, it is important to inform the healthcare professional if patients have  
919 underlying hepatitis B or C or elevations in liver-associated tests prior to treatment. Inform  
920 patients to stop SELZENTRY and seek medical evaluation immediately if they develop signs or  
921 symptoms of hepatitis or allergic reaction following use of SELZENTRY. Advise patients that  
922 laboratory tests for liver enzymes and bilirubin will be ordered prior to starting SELZENTRY, at  
923 other times during treatment, and if they develop severe rash or signs and symptoms of hepatitis  
924 or an allergic reaction on treatment [see *Dosage and Administration (2.1), Warnings and*  
925 *Precautions (5.1, 5.2)*].

### 926 Cardiovascular Events

927 When administering SELZENTRY in patients with cardiovascular comorbidities, a history of  
928 postural hypotension or receiving concomitant medication known to lower blood pressure, advise  
929 patients that they may be at increased risk for cardiovascular events. Advise patients to avoid  
930 driving or operating machinery if they experience dizziness while taking SELZENTRY [see  
931 *Warnings and Precautions (5.3)*].

### 932 Drug Interactions

933 Advise patients to inform their healthcare provider of concomitant HIV medications as dosage of  
934 SELZENTRY may be modified depending on other HIV medications taken with SELZENTRY.



935 Advise patients that coadministration of SELZENTRY with St. John’s wort is not recommended  
936 as it can lead to loss of virologic response and possible resistance to SELZENTRY [*see Dosage*  
937 *and Administration (2.2), Drug Interactions (7.1)*].

938 Missed Dosage

939 Inform patients that it is important to take SELZENTRY in combination with other antiretroviral  
940 medications on a regular dosing schedule with or without food. Advise patients to avoid missing  
941 doses as it can result in development of resistance. Instruct patients that if they miss a dose, to  
942 take it as soon as they remember. Advise patients not to double their next dose or take more than  
943 the prescribed dose [*see Dosage and Administration (2.2)*].

944 Pregnancy

945 Inform patients that there is insufficient data on the safety of SELZENTRY in pregnancy. Inform  
946 patients that there is an antiretroviral pregnancy registry that monitors pregnancy outcomes in  
947 women exposed to SELZENTRY during pregnancy [*see Use in Specific Populations (8.1)*].

948 Lactation

949 Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby  
950 in breast milk [*see Use in Specific Populations (8.2)*].

951

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962 Research Triangle Park, NC 27709

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965 SEL:13PI

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967  
968

PHARMACIST-DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT

<b>MEDICATION GUIDE</b>	
<b>SELZENTRY (sell-ZEN-tree) (maraviroc) tablets</b>	<b>SELZENTRY (sell-ZEN-tree) (maraviroc) oral solution</b>
<p><b>What is the most important information I should know about SELZENTRY?</b> <b>SELZENTRY can cause serious side effects including serious liver problems (liver toxicity).</b> An allergic reaction may happen before liver problems occur. <b>Stop taking SELZENTRY and call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:</b></p> <ul style="list-style-type: none"><li>• an itchy rash on your body (allergic reaction)</li><li>• your skin or the white part of your eyes turns yellow (jaundice)</li><li>• dark or “tea-colored” urine</li><li>• vomiting</li><li>• pain, aching, or tenderness on the right side of your stomach area</li></ul> <p>Your healthcare provider will do blood tests to check your liver before you begin treatment with SELZENTRY and as needed during treatment, and if you get a severe rash, signs and symptoms of liver problems, or an allergic reaction during treatment with SELZENTRY.</p>	
<p><b>What is SELZENTRY?</b> SELZENTRY is a prescription HIV-1 (Human Immunodeficiency Virus type 1) medicine used with other antiretroviral medicines to treat CCR5-tropic HIV-1 infection in people 2 years of age and older weighing at least 22 lb (10 kg). HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Use of SELZENTRY is not recommended in people with dual/mixed or CXCR4-tropic HIV-1. The safety and effectiveness of SELZENTRY has not been established in children younger than 2 years of age.</p>	
<p><b>Who should not take SELZENTRY?</b> <b>Do not take SELZENTRY if you:</b></p> <ul style="list-style-type: none"><li>• have severe kidney problems or are on hemodialysis and are also taking certain other medications.</li></ul>	
<p><b>What should I tell my healthcare provider before taking SELZENTRY?</b> <b>Before you take SELZENTRY, tell your healthcare provider about all of your medical conditions, including if you:</b></p> <ul style="list-style-type: none"><li>• have or have had liver problems including hepatitis B or C virus infection.</li><li>• have heart problems.</li><li>• have kidney problems.</li><li>• have low blood pressure or take medicines to lower blood pressure.</li><li>• are pregnant or plan to become pregnant. It is not known if SELZENTRY may harm your unborn baby. <b>Pregnancy Registry.</b> There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby.</li></ul>	

Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take SELZENTRY.** You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Talk to your healthcare provider about the best way to feed your baby.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with SELZENTRY. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with SELZENTRY.

**Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take SELZENTRY with other medicines. Your healthcare provider may need to change your dose of SELZENTRY when you take it with certain medicines.

- **You should not take SELZENTRY if you also take St. John's wort (*Hypericum perforatum*).**

#### **How should I take SELZENTRY?**

- **Take SELZENTRY exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking SELZENTRY without first talking with your healthcare provider.
- If you miss a dose of SELZENTRY, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Stay under the care of a healthcare provider while taking SELZENTRY.
- Swallow SELZENTRY tablets whole. Do not chew the tablets.
- SELZENTRY may be taken with or without food.
- For children aged 2 years and older and weighing at least 22 lb (10 kg), your healthcare provider will prescribe a dose of SELZENTRY based on your child's body weight and other medicines they are taking.
- Tell your healthcare provider if your child has trouble swallowing tablets. SELZENTRY comes as tablets or as a liquid (oral solution).
- SELZENTRY oral solution should be given with the supplied press-in bottle adapter and oral dosing syringe. See the Instructions for Use that comes with SELZENTRY oral solution for information about the right way to take a dose.
- Do not run out of SELZENTRY. The virus in your blood may increase and the virus in your blood may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much SELZENTRY, call your healthcare provider or go to the nearest hospital emergency room right away.

#### **What are the possible side effects of SELZENTRY?**

- **SELZENTRY can cause serious side effects including:**
- **See "What is the most important information I should know about SELZENTRY?"**
- **Serious skin rash and allergic reactions.** Severe and potentially life-threatening skin reactions and allergic reactions have been reported in some patients taking SELZENTRY. If you develop a rash with

any of the following symptoms, stop using SELZENTRY and contact your doctor right away:

- fever
  - generally ill feeling
  - muscle aches
  - blisters or sores in your mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the mouth or face or lips
  - problems breathing
  - yellowing of the skin or whites of your eyes
  - dark or tea-colored urine
  - pain, aching, or tenderness on the right side below the ribs
  - loss of appetite
  - nausea/vomiting
- **Heart problems** including heart attack.
  - **Low blood pressure when standing up (postural hypotension)** can cause dizziness or fainting. You should avoid driving or operating heavy machinery if you have dizziness while taking SELZENTRY.
  - **Changes in your immune system (Immune Reconstitution 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. Tell your healthcare provider right away if you develop new symptoms after you start taking SELZENTRY.
  - **Possible chance of infection or cancer.** SELZENTRY affects other immune system cells and therefore may possibly increase your chance for getting other infections or cancer.

**The most common side effects of SELZENTRY in adults include** colds and cold-like symptoms, cough, fever, rash, bloating and gas, indigestion, constipation, and dizziness.

**The most common side effects of SELZENTRY in children include** vomiting, abdominal pain, diarrhea, nausea, and dizziness.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SELZENTRY. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store SELZENTRY?**

- Store SELZENTRY tablets and oral solution at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away any unused oral solution 60 days after first opening the bottle.

**Keep SELZENTRY and all medicines out of the reach of children.**

#### **General information about SELZENTRY**

Medicines are sometimes prescribed for purposes other than those mentioned in a Medication Guide. Do not use SELZENTRY for a condition for which it was not prescribed. Do not give SELZENTRY to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information about SELZENTRY that is written for health professionals.

For more information go to [www.selzentry.com](http://www.selzentry.com).

#### **What are the ingredients in SELZENTRY?**

Active ingredient: maraviroc

Inactive ingredients:

Tablets: Dibasic calcium phosphate (anhydrous), magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. Tablet film-coating contains: FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide.

Oral Solution: Citric acid, purified water, sodium benzoate, sodium citrate dihydrate, strawberry flavoring (501440T), and sucralose.

Manufactured for:



ViiV Healthcare

Research Triangle Park, NC 27709

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SEL:8MG

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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**INSTRUCTIONS FOR USE**  
**SELZENTRY (sell-ZEN-tree)**  
**(maraviroc)**  
**oral solution**

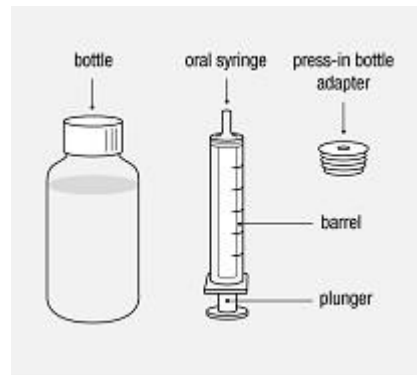
Read this Instructions for Use before you start taking SELZENTRY oral solution and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.



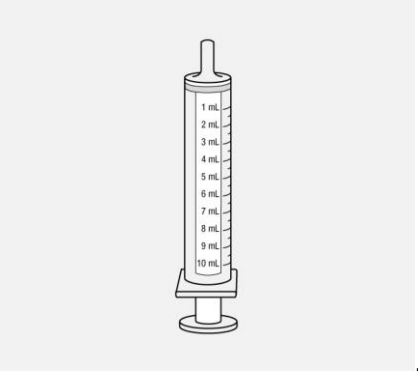
**Important information about measuring SELZENTRY oral solution:**

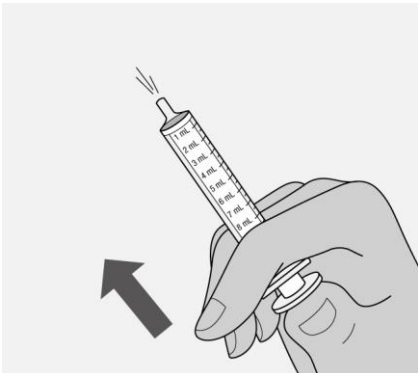


Always use the oral syringe that comes with your SELZENTRY oral solution to measure your prescribed dose. Ask your healthcare provider or pharmacist to show you how to measure your prescribed dose if you are not sure.


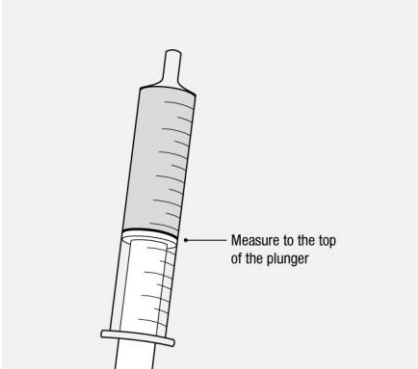

**Each carton of SELZENTRY oral solution contains:**

- 1 oral dosing syringe
- 1 press-in bottle adapter
- 1 bottle of SELZENTRY oral solution


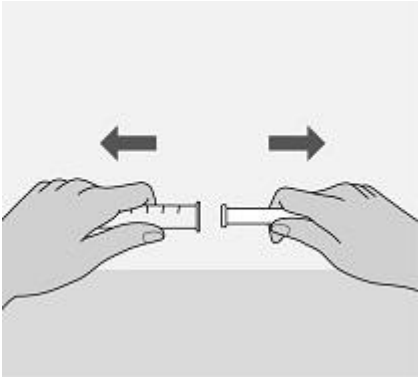
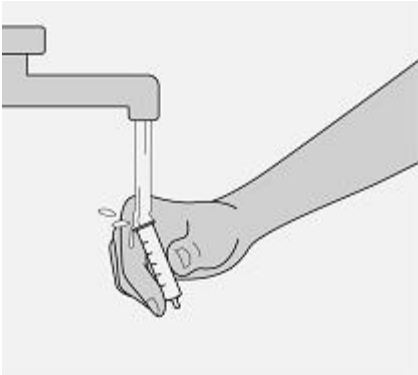


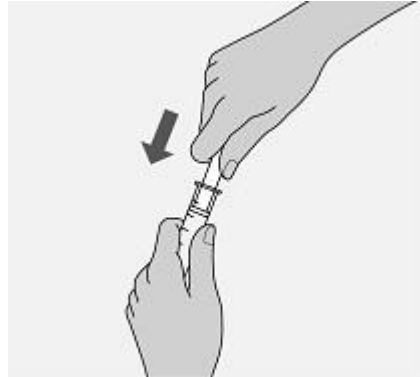
<p><b>Before each use: Wash your hands with soap and water and place the items from the carton on a clean flat surface.</b></p> <p><b>Step 1. Open the bottle of SELZENTRY oral solution.</b></p> <p>Open the bottle by pushing down firmly on the child-resistant cap and turning it counter-clockwise. <b>See Figure A.</b></p> <p><b>Do not throw away the child-resistant cap.</b></p>	<p><b>Figure A. Opening the bottle</b></p> 
<p><b>Step 2. First time use only: Insert the press-in bottle adapter.</b></p> <p>Remove the press-in bottle adapter and oral syringe from the plastic overwrap. With the bottle on a flat surface, push the ribbed end of the press-in bottle adapter all the way into the neck of the bottle while holding the bottle firmly. <b>See Figure B.</b></p> <p><b>Note: Do not remove the press-in bottle adapter from the bottle after it is inserted.</b></p>	<p><b>Figure B. Inserting the press-in bottle adapter</b></p> 
<p><b>Step 3. Find your prescribed dose on the oral syringe.</b></p> <p>Check the dose in milliliters (mL) as prescribed by your healthcare provider. Find this marking on the oral syringe. <b>See Figure C.</b></p>	<p><b>Figure C. Find your prescribed dose</b></p> 
<p><b>Step 4. Remove air from oral syringe.</b></p> <p>Push the oral syringe plunger to the bottom of the barrel of the syringe (toward its tip) to remove excess air. <b>See Figure D.</b></p>	<p><b>Figure D. Removing air from oral syringe.</b></p>

	
<p><b>Step 5. Insert the oral syringe.</b></p> <p>Insert the oral syringe into the upright bottle through the opening of the press-in bottle adapter until it is firmly in place. <b>See Figure E.</b></p>	<p><b>Figure E. Inserting the oral syringe</b></p> 
<p><b>Step 6. Withdraw the prescribed dose of SELZENTRY from the bottle.</b></p> <p>With the oral syringe in place, turn the bottle upside down. Pull back the plunger of the oral syringe until the top of the plunger is even with the markings on the oral syringe for your prescribed dose. <b>See Figure F.</b></p> <p>If you see air bubbles in the oral syringe, fully push the plunger in to empty the oral solution back into the bottle. Then withdraw your prescribed dose of oral solution.</p>	<p><b>Figure F. Withdrawing the oral solution</b></p> 
<p><b>Step 7. Removing the oral syringe.</b></p> <p>Turn the bottle upright and place the bottle on a flat surface. Remove the oral syringe from the bottle adapter and bottle by pulling straight up on the oral syringe. <b>See Figure G.</b></p>	<p><b>Figure G. Removing the oral syringe</b></p>

	
<p><b>Step 8. Check the dose withdrawn.</b></p> <p>Check that the correct dose was drawn up into the oral syringe. <b>See Figure H.</b></p> <p>If the dose is not correct, insert the oral syringe tip firmly into the bottle adapter. Fully push in the plunger so that the oral solution flows back into the bottle. Repeat Steps 6 and 7.</p>	<p><b>Figure H. Checking the dose withdrawn.</b></p> 
<p><b>Step 9. Take the dose of SELZENTRY. See Figure I.</b></p> <p>Place the tip of the oral syringe into the inside of the child's cheek.</p> <p>Slowly push the plunger all the way down to give all the medicine in the oral syringe. Make sure the child has time to swallow the medicine.</p> <p><b>Note:</b> If the prescribed dose is more than 10 mL, you will need to divide the dose. Follow the instructions given to you by your healthcare provider or pharmacist about how to divide the dose and repeat Steps 5 through 9.</p>	<p><b>Figure I. Taking the dose of SELZENTRY</b></p> 
<p><b>Step 10. Close the bottle.</b></p> <p>Close the bottle tightly by turning the child-resistant cap clockwise, leaving the press-in bottle adapter in place. <b>See Figure J.</b></p>	<p><b>Figure J. Closing the bottle</b></p>



	
<p><b>Step 11. Clean the oral syringe.</b></p> <p>Rinse the oral syringe with tap water after each use.</p> <p>Remove the plunger from the barrel by pulling the plunger and the barrel away from each other. <b>See Figure K.</b></p> <p>Rinse both with water. <b>See Figure L.</b></p> <p>Allow to air dry.</p>	<p><b>Figure K. Removing the plunger from the barrel</b></p>  <p><b>Figure L. Rinsing the plunger and barrel</b></p> 
<p><b>Step 12. Put the oral syringe back together.</b></p> <p>When the barrel and plunger are dry, put the oral syringe back together by inserting the plunger into the barrel. <b>See Figure M.</b> Store the oral syringe with the SELZENTRY oral solution.</p> <p><b>Do not throw away the oral syringe.</b></p>	<p><b>Figure M. Putting the oral syringe back together</b></p>



**How should I store SELZENTRY?**

Store SELZENTRY oral solution at room temperature between 68°F to 77°F (20°C to 25°C). Throw away any unused oral solution 60 days after first opening the bottle.

**Keep SELZENTRY and all medicines out of the reach of children.**

Manufactured for:



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