

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
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning

- 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).
- Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions, Severe Skin and Hypersensitivity Reactions (5.2) 02/2013
Warnings and Precautions, Immune Reconstitution Syndrome (5.4) 08/2012

INDICATIONS AND USAGE

SELZENTRY is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1.

- In treatment-naïve subjects, more subjects treated with SELZENTRY experienced virologic failure and developed lamivudine resistance compared with efavirenz. (12.4,14.3)
- Tropism testing with a highly sensitive tropism assay is required for the appropriate use of SELZENTRY. (1)

DOSAGE AND ADMINISTRATION

When given with potent CYP3A inhibitors (with or without potent CYP3A inducers) including PIs (except tipranavir/ritonavir), delavirdine (2, 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, 7.1)	300 mg twice daily
With potent CYP3A inducers including efavirenz (without a potent CYP3A inhibitor) (2, 7.1)	600 mg twice daily

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

Dose adjustment may be necessary in patients with renal impairment. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 150 mg and 300 mg (3)

CONTRAINDICATIONS

- SELZENTRY should not be used in patients with severe renal impairment or end-stage renal disease (ESRD) (CrCl <30 mL/min) who are 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. Use caution when administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C. (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. Use with caution in patients at increased risk of cardiovascular events. (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 subjects (>8% incidence) which occurred at a higher frequency compared with placebo are upper respiratory tract infections, cough, pyrexia, rash, and dizziness. (6)

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.

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)

USE IN SPECIFIC POPULATIONS

- SELZENTRY should only be used in pregnant women if the potential benefit justifies the potential risk to the fetus. (8.1)
- There are no data available in pediatric patients; therefore, SELZENTRY should not be used in patients younger than 16 years. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised:02/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	
2	DOSAGE AND ADMINISTRATION	
2.1	Dose Recommendations for Patients With Normal Renal Function	
2.2	Dose Recommendations for Patients With Renal Impairment	
3	DOSAGE FORMS AND STRENGTHS	
4	CONTRAINDICATIONS	
5	WARNINGS AND PRECAUTIONS	
5.1	Hepatotoxicity	
5.2	Severe Skin and Hypersensitivity Reactions	
5.3	Cardiovascular Events	
5.4	Immune Reconstitution Syndrome	
5.5	Potential Risk of Infection	
5.6	Potential Risk of Malignancy	
6	ADVERSE REACTIONS	
6.1	Clinical Trials Experience	
6.2	Postmarketing Experience	
7	DRUG INTERACTIONS	
7.1	Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc	
8	USE IN SPECIFIC POPULATIONS	
8.1	Pregnancy	
8.3	Nursing Mothers	
		8.4 Pediatric Use
		8.5 Geriatric Use
		8.6 Renal Impairment
		8.7 Hepatic Impairment
		8.8 Gender
		8.9 Race
10	OVERDOSAGE	
11	DESCRIPTION	
12	CLINICAL PHARMACOLOGY	
12.1	Mechanism of Action	
12.2	Pharmacodynamics	
12.3	Pharmacokinetics	
12.4	Microbiology	
13	NONCLINICAL TOXICOLOGY	
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility	
14	CLINICAL STUDIES	
14.1	Trials in CCR5-Tropic, Treatment-Experienced Subjects	
14.2	Trial in Dual/Mixed-Tropic, Treatment-Experienced Subjects	
14.3	Trial in Treatment-Naïve Subjects	
15	REFERENCES	
16	HOW SUPPLIED/STORAGE AND HANDLING	
17	PATIENT COUNSELING INFORMATION	

*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: HEPATOTOXICITY**

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

8 **1 INDICATIONS AND USAGE**

9 SELZENTRY, in combination with other antiretroviral agents, is indicated for adult
10 patients infected with only CCR5-tropic HIV-1.

11 This indication is based on analyses of plasma HIV-1 RNA levels in 2 controlled trials of
12 SELZENTRY in treatment-experienced subjects and one trial in treatment-naive subjects. Both
13 trials in treatment-experienced subjects were conducted in clinically advanced, 3-class
14 antiretroviral-experienced (nucleoside reverse transcriptase inhibitor [NRTI], non-nucleoside
15 reverse transcriptase inhibitor [NNRTI], protease inhibitor [PI], or enfuvirtide) adults with
16 evidence of HIV-1 replication despite ongoing antiretroviral therapy.

17 The following points should be considered when initiating therapy with SELZENTRY:

- 18 • Adult patients infected with only CCR5-tropic HIV-1 should use SELZENTRY.
- 19 • Tropism testing must be conducted with a highly sensitive tropism assay that has
20 demonstrated the ability to identify patients appropriate for use of SELZENTRY. Outgrowth
21 of pre-existing low-level CXCR4- or dual/mixed-tropic HIV-1 not detected by tropism
22 testing at screening has been associated with virologic failure on SELZENTRY [see
23 *Microbiology (12.4), Clinical Studies (14.3)*].
- 24 • Use of SELZENTRY is not recommended in subjects with dual/mixed- or CXCR4-tropic
25 HIV-1 as efficacy was not demonstrated in a Phase 2 trial of this patient group.
- 26 • The safety and efficacy of SELZENTRY have not been established in pediatric patients.
- 27 • In treatment-naive subjects, more subjects treated with SELZENTRY experienced virologic
28 failure and developed lamivudine resistance compared with efavirenz [see *Microbiology*
29 *(12.4), Clinical Studies (14.3)*].

30 **2 DOSAGE AND ADMINISTRATION**

31 **2.1 Dose Recommendations for Patients With Normal Renal Function**

32 The recommended dose of SELZENTRY differs based on concomitant medications due
33 to drug interactions (see Table 1). SELZENTRY can be taken with or without food.
34 SELZENTRY must be given in combination with other antiretroviral medications.

35 Table 1 gives the recommended dose adjustments [see *Drug Interactions (7.1)*].
36

37 **Table 1. Recommended Dosing Regimen**

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

38

39 **2.2 Dose Recommendations for Patients With Renal Impairment**

40 Table 2 provides dosing recommendations for patients based on renal function and
41 concomitant medications.

42

43 **Table 2. Recommended Dosing Regimens Based on Renal Function**

Concomitant Medications ^a	Dose 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) ^a	150 mg twice daily	150 mg twice daily	150 mg twice daily	NR	NR
Other concomitant medications ^a	300 mg twice daily	300 mg twice daily	300 mg twice daily	300 mg twice daily ^b	300 mg twice daily ^b
Potent CYP3A Inducers (without a potent CYP3A inhibitor) ^a	600 mg twice daily	600 mg twice daily	600 mg twice daily	NR	NR

44 NR = Not recommended.

45 ^a See Table 1 for the list of concomitant medications.

46 ^b The dose of SELZENTRY should be reduced to 150 mg twice daily if there are any
47 symptoms of postural hypotension [*see Warnings and Precautions (5.3)*].

48 **3 DOSAGE FORMS AND STRENGTHS**

- 49 • 150-mg blue, oval, film-coated tablets debossed with “MVC 150” on one side and plain on
50 the other.
- 51 • 300-mg blue, oval, film-coated tablets debossed with “MVC 300” on one side and plain on
52 the other.

53 **4 CONTRAINDICATIONS**

54 SELZENTRY should not be used in patients with severe renal impairment or end-stage
55 renal disease (ESRD) (CrCl <30 mL/min) who are taking potent CYP3A inhibitors or inducers.

56 **5 WARNINGS AND PRECAUTIONS**

57 **5.1 Hepatotoxicity**

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

65 Appropriate laboratory testing including ALT, AST, and bilirubin should be conducted
66 prior to initiating therapy with SELZENTRY and at other timepoints during treatment as
67 clinically indicated. Hepatic laboratory parameters should be obtained in any patient who
68 develops rash, or signs or symptoms of hepatitis, or allergic reaction. Discontinuation of
69 SELZENTRY should be considered in any patient with signs or symptoms of hepatitis, or with
70 increased liver transaminases combined with rash or other systemic symptoms.

71 Caution should be used when administering SELZENTRY to patients with pre-existing
72 liver dysfunction or who are co-infected with viral hepatitis B or C. The safety and efficacy of
73 SELZENTRY have not been specifically studied in patients with significant underlying liver
74 disorders. In trials of treatment-experienced HIV-1-infected subjects, approximately 6% of
75 subjects were co-infected with hepatitis B and approximately 6% were co-infected with hepatitis
76 C. Due to the small number of co-infected subjects studied, no conclusions can be drawn
77 regarding whether they are at an increased risk for hepatic adverse events with administration of
78 SELZENTRY.

79 **5.2 Severe Skin and Hypersensitivity Reactions**

80 Severe, potentially life-threatening skin and hypersensitivity reactions have been reported
81 in patients taking SELZENTRY, in most cases concomitantly with other drugs associated with
82 these reactions. These include cases of Stevens-Johnson syndrome (SJS), toxic epidermal
83 necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) [*see*

84 *Adverse Reactions (6.2)*. The cases were characterized by features including rash, constitutional
85 findings, and sometimes organ dysfunction, including hepatic failure. Discontinue SELZENTRY
86 and other suspected agents immediately if signs or symptoms of severe skin or hypersensitivity
87 reactions develop (including, but not limited to, severe rash or rash accompanied by fever,
88 malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, lip swelling,
89 eosinophilia). Delay in stopping treatment with SELZENTRY or other suspect drugs after the
90 onset of rash may result in a life-threatening reaction. Clinical status, including liver
91 aminotransferases, should be monitored and appropriate therapy initiated.

92 **5.3 Cardiovascular Events**

93 Use with caution in patients at increased risk for cardiovascular events. Eleven subjects
94 (1.3%) who received SELZENTRY had cardiovascular events, including myocardial ischemia
95 and/or infarction, during the Phase 3 trials in treatment-experienced subjects (total exposure
96 609 patient-years [300 on SELZENTRY once daily + 309 on SELZENTRY twice daily]), while
97 no subjects who received placebo had such events (total exposure 111 patient-years). These
98 subjects generally had cardiac disease or cardiac risk factors prior to use of SELZENTRY, and
99 the relative contribution of SELZENTRY to these events is not known.

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

104 When SELZENTRY was administered to healthy volunteers at doses higher than the
105 recommended dose, symptomatic postural hypotension was seen at a greater frequency than in
106 placebo. However, when SELZENTRY was given at the recommended dose in HIV-1-infected
107 subjects in Phase 3 trials, postural hypotension was seen at a rate similar to placebo
108 (approximately 0.5%). Caution should be used when administering SELZENTRY in patients
109 with a history of postural hypotension or on concomitant medication known to lower blood
110 pressure.

111 Postural Hypotension in Patients With Renal Impairment: Patients with impaired
112 renal function may have cardiovascular co-morbidities and could be at increased risk of
113 cardiovascular adverse events triggered by postural hypotension. An increased risk of postural
114 hypotension may occur in patients with severe renal insufficiency or in those with ESRD due to
115 increased maraviroc exposure in some patients. SELZENTRY should be used in patients with
116 severe renal impairment or ESRD only if they are not receiving a concomitant potent CYP3A
117 inhibitor or inducer. However, the use of SELZENTRY in these patients should only be
118 considered when no alternative treatment options are available. If patients with severe renal
119 impairment or ESRD experience any symptoms of postural hypotension while taking 300 mg
120 twice daily, the dose should be reduced to 150 mg twice daily [*see Dosage and Administration*
121 (2.2)].

122 **5.4 Immune Reconstitution Syndrome**

123 Immune reconstitution syndrome has been reported in patients treated with combination
124 antiretroviral therapy, including SELZENTRY. During the initial phase of combination
125 antiretroviral treatment, patients whose immune system responds may develop an inflammatory
126 response to indolent or residual opportunistic infections (such as infection with *Mycobacterium*
127 *avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis, or
128 reactivation of *Herpes simplex* and *Herpes zoster*), which may necessitate further evaluation and
129 treatment.

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

133 **5.5 Potential Risk of Infection**

134 SELZENTRY antagonizes the CCR5 co-receptor located on some immune cells, and
135 therefore could potentially increase the risk of developing infections. The overall incidence and
136 severity of infection, as well as AIDS-defining category C infections, were comparable in the
137 treatment groups during the Phase 3 treatment-experienced trials of SELZENTRY. While there
138 was a higher rate of certain upper respiratory tract infections reported in the arm receiving
139 SELZENTRY compared with placebo (23% versus 13%), there was a lower rate of pneumonia
140 (2% versus 5%) reported in subjects receiving SELZENTRY. A higher incidence of Herpes virus
141 infections (11 per 100 patient-years) was also reported in the arm receiving SELZENTRY when
142 adjusted for exposure compared with placebo (8 per 100 patient-years).

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

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

148 **5.6 Potential Risk of Malignancy**

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

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

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

157 **6 ADVERSE REACTIONS**

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

- 159 • Hepatotoxicity [*see Boxed Warning, Warnings and Precautions (5.1)*]
- 160 • Severe Skin and Hypersensitivity Reactions [*see Warnings and Precautions (5.2)*]
- 161 • Cardiovascular events [*see Warnings and Precautions (5.3)*]

162 **6.1 Clinical Trials Experience**

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

166 Trials in Treatment-Experienced Subjects: The safety profile of SELZENTRY is
167 primarily based on 840 HIV-1-infected subjects who received at least 1 dose of SELZENTRY
168 during two Phase 3 trials. A total of 426 of these subjects received the indicated twice-daily
169 dosing regimen.

170 Assessment of treatment-emergent adverse events is based on the pooled data from
171 2 trials in subjects with CCR5-tropic HIV-1 (A4001027 and A4001028). The median duration of
172 therapy with SELZENTRY for subjects in these trials was 48 weeks, with the total exposure on
173 SELZENTRY twice daily at 309 patient-years versus 111 patient-years on placebo + optimized
174 background therapy (OBT). The population was 89% male and 84% white, with mean age of
175 46 years (range: 17 to 75 years). Subjects received dose equivalents of 300 mg maraviroc once or
176 twice daily.

177 The most common adverse events reported with twice-daily therapy with SELZENTRY
178 with frequency rates higher than placebo, regardless of causality, were upper respiratory tract
179 infections, cough, pyrexia, rash, and dizziness. Additional adverse events that occurred with
180 once-daily dosing at a higher rate than both placebo and twice-daily dosing were diarrhea,
181 edema, influenza, esophageal candidiasis, sleep disorders, rhinitis, parasomnias, and urinary
182 abnormalities. In these 2 trials, the rate of discontinuation due to adverse events was 5% for
183 subjects who received SELZENTRY twice daily + OBT as well as those who received placebo +
184 OBT. Most of the adverse events reported were judged to be mild to moderate in severity. The
185 data described below occurred with twice-daily dosing of SELZENTRY.

186 The total number of subjects reporting infections were 233 (55%) and 84 (40%) in the
187 group receiving SELZENTRY twice daily and the placebo group, respectively. Correcting for
188 the longer duration of exposure on SELZENTRY compared with placebo, the exposure-adjusted
189 frequency (rate per 100 subject-years) of these events was 133 for both SELZENTRY twice
190 daily and placebo.

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

195 Treatment-emergent adverse events, regardless of causality, from A4001027 and
196 A4001028 are summarized in Table 3. Selected events occurring at $\geq 2\%$ of subjects and at a
197 numerically higher rate in subjects treated with SELZENTRY are included; events that occurred
198 at the same or higher rate on placebo are not displayed.

199

200 **Table 3. Percentage of Subjects With Selected Treatment-Emergent Adverse Events (All**
 201 **Causality) $\geq 2\%$ on SELZENTRY (and at a higher rate compared with placebo)**
 202 **Trials A4001027 and A4001028 (Pooled Analysis, 48 Weeks)**

Body System/ Adverse Event	SELZENTRY Twice Daily ^a		Placebo	
	N = 426 (%)	Exposure- adjusted rate (per 100 pt-yrs) PYE = 309 ^b	N = 209 (%)	Exposure- adjusted rate (per 100 pt-yrs) PYE = 111 ^b
Eye Disorders				
Conjunctivitis	2	3	1	3
Ocular infections, inflammations, and associated manifestations	2	3	1	2
Gastrointestinal Disorders				
Constipation	6	9	3	6
General Disorders and Administration Site Conditions				
Pyrexia	13	20	9	17
Pain and discomfort	4	5	3	5
Infections and Infestations				
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
Pneumonia	2	3	5	10
Anogenital warts	2	3	1	3
Influenza	2	3	0.5	1
Otitis media	2	3	0.5	1
Metabolism and Nutrition Disorders				
Appetite disorders	8	11	7	13
Musculoskeletal and Connective Tissue Disorders				
Joint-related signs and symptoms	7	10	3	5
Muscle pains	3	4	0.5	1
Neoplasms Benign, Malignant, and Unspecified				
Skin neoplasms benign	3	4	1	3
Nervous System Disorders				
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
Psychiatric Disorders				
Disturbances in initiating and maintaining sleep	8	11	5	10
Depressive disorders	4	6	3	5
Anxiety symptoms	4	5	3	7
Renal and Urinary Disorders				
Bladder and urethral symptoms	5	7	1	3
Urinary tract signs and symptoms	3	4	1	3
Respiratory, Thoracic, and Mediastinal Disorders				
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
Skin and Subcutaneous Tissue Disorders				
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
Erythemas	2	3	1	2
Vascular Disorders				
Vascular hypertensive disorders	3	4	2	4

203 ^a300-mg dose equivalent.

204 ^bPYE = Patient-years of exposure.

205

206 Laboratory Abnormalities: Table 4 shows the treatment-emergent Grade 3-4 laboratory
207 abnormalities that occurred in >2% of subjects receiving SELZENTRY.

208

209 **Table 4. Maximum Shift in Laboratory Test Values (Without Regard to Baseline)**
 210 **Incidence $\geq 2\%$ of Grade 3-4 Abnormalities (ACTG Criteria) Trials A4001027 and**
 211 **A4001028 (Pooled Analysis, 48 Weeks)**

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

212 ^aPercentages based on total subjects evaluated for each laboratory parameter.

213 ULN=upper limit of normal.

214

215 Trial in Treatment-Naive Subjects: Treatment-Emergent Adverse Events:

216 Treatment-emergent adverse events, regardless of causality, from Trial A4001026, a
 217 double-blind, comparative, controlled trial in which 721 treatment-naive subjects received
 218 SELZENTRY 300 mg twice daily (N = 360) or efavirenz (N = 361) in combination with
 219 zidovudine/lamivudine for 96 weeks, are summarized in Table 5. Selected events occurring in
 220 $\geq 2\%$ of subjects and at a numerically higher rate in subjects treated with SELZENTRY are
 221 included; events that occurred at the same or higher rate on efavirenz are not displayed.

222

223 **Table 5. Percentage of Subjects With Selected Treatment-Emergent Adverse Events (All**
 224 **Causality) ($\geq 2\%$ on SELZENTRY and at a higher rate compared with efavirenz)**
 225 **Trial A4001026 (96 Weeks)**

Body System/ Adverse Event	SELZENTRY 300 mg Twice Daily + Zidovudine/Lamivudine (N = 360) %	Efavirenz 600 mg Once Daily + Zidovudine/Lamivudine (N = 361) %
Blood and Lymphatic System Disorders		
Anemias NEC	8	5
Neutropenias	4	3
Ear and Labyrinth Disorders		
Ear disorders NEC	3	2
Gastrointestinal Disorders		
Flatulence, bloating, and distention	10	7

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

infections and infestations)

Laboratory Abnormalities:

Table 6. Maximum Shift in Laboratory Test Values (Without Regard to Baseline) Incidence $\geq 2\%$ of Grade 3-4 Abnormalities (ACTG Criteria) Trial A4001026 (96 Weeks)

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

^a N = Total number of subjects evaluable for laboratory abnormalities.

ULN=upper limit of normal.

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

Less Common Adverse Events in Clinical Trials: The following adverse events

occurred in <2% of subjects treated with SELZENTRY. These events have been included because of their seriousness and either increased frequency on SELZENTRY or are potential risks due to the mechanism of action. Events attributed to the patient's underlying HIV-1 infection are not listed.

Blood and Lymphatic System: Marrow depression and hypoplastic anemia.

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

Hepatobiliary Disorders: Hepatic cirrhosis, hepatic failure, cholestatic jaundice, portal vein thrombosis, hypertransaminasemia, jaundice.

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

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

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

Abdominal neoplasm, anal cancer, basal cell carcinoma, Bowen's disease, cholangiocarcinoma,

253 diffuse large B-cell lymphoma, lymphoma, metastases to liver, esophageal carcinoma,
254 nasopharyngeal carcinoma, squamous cell carcinoma, squamous cell carcinoma of skin, tongue
255 neoplasm (malignant stage unspecified), anaplastic large cell lymphomas T- and null-cell types,
256 bile duct neoplasms malignant, endocrine neoplasms malignant and unspecified.

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

260 **6.2 Postmarketing Experience**

261 The following events have been identified during post-approval use of SELZENTRY and
262 are not listed above. Because these reactions are reported voluntarily from a population of
263 unknown size, it is not possible to estimate their frequency or establish a causal relationship to
264 exposure to SELZENTRY.

265 Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome (SJS), drug
266 rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN).

267 **7 DRUG INTERACTIONS**

268 **7.1 Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc**

269 Maraviroc is a substrate of CYP3A and P-glycoprotein (P-gp) and hence its
270 pharmacokinetics are likely to be modulated by inhibitors and inducers of these
271 enzymes/transporters. Therefore, a dose adjustment may be required when maraviroc is
272 coadministered with those drugs [*see Dosage and Administration (2)*].

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

277 For additional drug interaction information, see *Clinical Pharmacology (12.3)*.

278 **8 USE IN SPECIFIC POPULATIONS**

279 **8.1 Pregnancy**

280 Pregnancy Category B: The incidence of fetal variations and malformations was not
281 increased in embryofetal toxicity studies performed with maraviroc in rats at exposures (AUC)
282 approximately 20-fold higher and in rabbits at approximately 5-fold higher than human
283 exposures at the recommended daily dose (up to 1,000 mg/kg/day in rats and 75 mg/kg/day in
284 rabbits). During the pre- and postnatal development studies in the offspring, development of the
285 offspring, including fertility and reproductive performance, was not affected by the maternal
286 administration of maraviroc.

287 However, there are no adequate and well-controlled studies in pregnant women. Because
288 animal reproduction studies are not always predictive of human response, SELZENTRY should
289 be used during pregnancy only if clearly needed.

290 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant
291 women exposed to SELZENTRY and other antiretroviral agents, an Antiretroviral Pregnancy

292 Registry has been established. Physicians are encouraged to register patients by calling 1-800-
293 258-4263.

294 **8.3 Nursing Mothers**

295 **The Centers for Disease Control and Prevention recommend that HIV-infected**
296 **mothers not breastfeed their infants to avoid risking postnatal transmission of HIV**
297 **infection.** Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. It
298 is not known whether maraviroc is secreted into human milk. Because of the potential for both
299 HIV transmission and serious adverse reactions in nursing infants, mothers should be instructed
300 not to breastfeed if they are receiving SELZENTRY.

301 **8.4 Pediatric Use**

302 The pharmacokinetics, safety and efficacy of maraviroc in patients younger than 16 years
303 have not been established. Therefore, maraviroc should not be used in this patient population.

304 **8.5 Geriatric Use**

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

310 **8.6 Renal Impairment**

311 Recommended doses of SELZENTRY for patients with impaired renal function
312 ($\text{CrCl} \leq 80 \text{ mL/min}$) are based on the results of a pharmacokinetic trial conducted in healthy
313 subjects with various degrees of renal impairment. The pharmacokinetics of maraviroc in
314 subjects with mild and moderate renal impairment was similar to that in subjects with normal
315 renal function [see *Clinical Pharmacology (12.3)*]. A limited number of subjects with mild and
316 moderate renal impairment in the Phase 3 clinical trials ($n = 131$ and $n = 12$, respectively)
317 received the same dose of SELZENTRY as that administered to subjects with normal renal
318 function. In these subjects there was no apparent difference in the adverse event profile for
319 maraviroc compared with subjects with normal renal function.

320 If patients with severe renal impairment or ESRD not receiving a concomitant potent
321 CYP3A inhibitor or inducer experience any symptoms of postural hypotension while taking
322 SELZENTRY 300 mg twice daily, the dose should be reduced to 150 mg twice daily. No trials
323 have been performed in subjects with severe renal impairment or ESRD co-treated with potent
324 CYP3A inhibitors or inducers. Hence, no dose of SELZENTRY can be recommended, and
325 SELZENTRY is contraindicated for these patients [see *Dosage and Administration (2.2)*,
326 *Contraindications (4)*, *Warnings and Precautions (5.2)*, *Clinical Pharmacology (12.3)*].

327 **8.7 Hepatic Impairment**

328 Maraviroc is principally metabolized by the liver; therefore, caution should be exercised
329 when administering this drug to patients with hepatic impairment, because maraviroc
330 concentrations may be increased. Maraviroc concentrations are higher when SELZENTRY
331 150 mg is administered with a potent CYP3A inhibitor compared with following administration

332 of 300 mg without a CYP3A inhibitor, so patients with moderate hepatic impairment who
333 receive SELZENTRY 150 mg with a potent CYP3A inhibitor should be monitored closely for
334 maraviroc-associated adverse events. Maraviroc has not been studied in subjects with severe
335 hepatic impairment [*see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)*].

336 **8.8 Gender**

337 Population pharmacokinetic analysis of pooled Phase 1/2a data indicated gender (female:
338 n = 96, 23.2% of the total population) does not affect maraviroc concentrations. Dosage
339 adjustment based on gender is not necessary.

340 **8.9 Race**

341 Population pharmacokinetic analysis of pooled Phase 1/2a data indicated exposure was
342 26.5% higher in Asians (N = 95) as compared with non-Asians (n = 318). However, a trial
343 designed to evaluate pharmacokinetic differences between Caucasians (n = 12) and Singaporeans
344 (n = 12) showed no difference between these 2 populations. No dose adjustment based on race is
345 needed.

346 **10 OVERDOSAGE**

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

351 Prolongation of the QT interval was seen in dogs and monkeys at plasma concentrations
352 6 and 12 times, respectively, those expected in humans at the intended exposure of 300 mg
353 equivalents twice daily. However, no significant QT prolongation was seen in the trials in
354 treatment-experienced subjects with HIV using the recommended doses of maraviroc or in a
355 specific pharmacokinetic trial to evaluate the potential of maraviroc to prolong the QT interval
356 [*see Clinical Pharmacology (12.3)*].

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

360 If indicated, elimination of unabsorbed active maraviroc should be achieved by emesis.
361 Administration of activated charcoal may also be used to aid in removal of unabsorbed drug.
362 Since maraviroc is moderately protein-bound, dialysis may be beneficial in removal of this
363 medicine.

364 **11 DESCRIPTION**

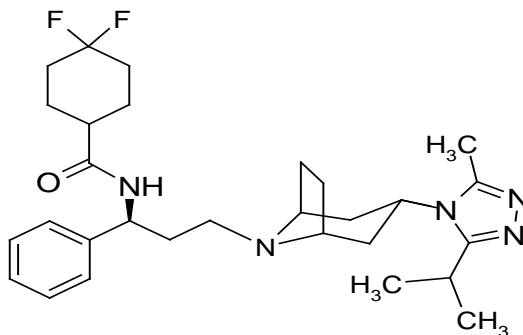
365 SELZENTRY (maraviroc) is a selective, slowly reversible, small molecule antagonist of
366 the interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents
367 CCR5-tropic HIV-1 entry into cells.

368 SELZENTRY is available as film-coated tablets for oral administration containing either
369 150 or 300 mg of maraviroc and the following inactive ingredients: dibasic calcium phosphate
370 (anhydrous), magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The

371 film coat (Opadry[®] II Blue [85G20583]) contains FD&C blue #2 aluminum lake, soya lecithin,
372 polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide.

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

376 The molecular formula is C₂₉H₄₁F₂N₅O and the structural formula is:
377



378
379

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

382 **12 CLINICAL PHARMACOLOGY**

383 **12.1 Mechanism of Action**

384 Maraviroc is an antiviral drug [see *Clinical Pharmacology* (12.4)].

385 **12.2 Pharmacodynamics**

386 Exposure-Response Relationship in Treatment-Experienced Subjects: The
387 relationship between maraviroc, modeled plasma trough concentration (C_{min}) (1 to 9 samples
388 per patient taken on up to 7 visits), and virologic response was evaluated in
389 973 treatment-experienced HIV-1-infected subjects with varied optimized background
390 antiretroviral regimens in Trials A4001027 and A4001028. The C_{min}, baseline viral load,
391 baseline CD4+ cell count, and overall sensitivity score (OSS) were found to be important
392 predictors of virologic success (defined as viral load <400 copies/mL at 24 weeks). Table 7
393 illustrates the proportions of subjects with virologic success (%) within each C_{min} quartile for
394 150-mg twice-daily and 300-mg twice-daily groups.
395

396 **Table 7. Treatment-Experienced Subjects With Virologic Success by C_{min} Quartile (Q1-Q4)**

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

397

398 **Exposure-Response Relationship in Treatment-Naive Subjects:** The relationship
399 between maraviroc, modeled plasma trough concentration (C_{min}) (1 to 12 samples per patient
400 taken on up to 8 visits), and virologic response was evaluated in 294 treatment-naive HIV-1-
401 infected subjects receiving maraviroc 300 mg twice daily in combination with
402 zidovudine/lamivudine in Trial A4001026. Table 8 illustrates the proportion (%) of subjects with
403 virologic success <50 copies/mL at 48 weeks within each C_{min} quartile for the 300-mg
404 twice-daily dose.

405

406 **Table 8. Treatment-Naive Subjects With Virologic Success by C_{min} Quartile (Q1-Q4)**

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

407

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

410 **Effects on Electrocardiogram:** A placebo-controlled, randomized, crossover trial to
411 evaluate the effect on the QT interval of healthy male and female volunteers was conducted with
412 3 single oral doses of maraviroc and moxifloxacin. The placebo-adjusted mean maximum (upper
413 1-sided 95% CI) increases in QTc from baseline after 100, 300, and 900 mg of maraviroc were
414 -2 (0), -1 (1), and 1 (3) msec, respectively, and 13 (15) msec for moxifloxacin 400 mg. No
415 subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced
416 an interval exceeding the potentially clinically relevant threshold of 500 msec.

417 **12.3 Pharmacokinetics**

418

419 **Table 9. Mean Maraviroc Pharmacokinetic Parameters**

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

420 ^a The estimated exposure is lower compared with other trials possibly due to sparse sampling,
421 food effect, compliance, and concomitant medications.

422

423 **Absorption:** Peak maraviroc plasma concentrations are attained 0.5 to 4 hours following
424 single oral doses of 1 to 1,200 mg administered to uninfected volunteers. The pharmacokinetics
425 of oral maraviroc are not dose proportional over the dose range.

426 The absolute bioavailability of a 100-mg dose is 23% and is predicted to be 33% at
427 300 mg. Maraviroc is a substrate for the efflux transporter P-gp.

428 **Effect of Food on Oral Absorption:** Coadministration of a 300-mg tablet with a
429 high-fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers. There were
430 no food restrictions in the trials that demonstrated the efficacy and safety of maraviroc [*see*
431 *Clinical Studies (14)*]. Therefore, maraviroc can be taken with or without food at the
432 recommended dose [*see Dosage and Administration (2)*].

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

436 **Metabolism:** Trials in humans and in vitro studies using human liver microsomes and
437 expressed enzymes have demonstrated that maraviroc is principally metabolized by the
438 cytochrome P450 system to metabolites that are essentially inactive against HIV-1. In vitro
439 studies indicate that CYP3A is the major enzyme responsible for maraviroc metabolism. In vitro
440 studies also indicate that polymorphic enzymes CYP2C9, CYP2D6, and CYP2C19 do not
441 contribute significantly to the metabolism of maraviroc.

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

447 **Excretion:** The terminal half-life of maraviroc following oral dosing to steady state in
448 healthy subjects was 14 to 18 hours. A mass balance/excretion trial was conducted using a single
449 300-mg dose of ¹⁴C-labeled maraviroc. Approximately 20% of the radiolabel was recovered in

450 the urine and 76% was recovered in the feces over 168 hours. Maraviroc was the major
451 component present in urine (mean of 8% dose) and feces (mean of 25% dose). The remainder
452 was excreted as metabolites.

453 **Hepatic Impairment:** Maraviroc is primarily metabolized and eliminated by the liver. A
454 trial compared the pharmacokinetics of a single 300-mg dose of SELZENTRY in subjects with
455 mild (Child-Pugh Class A, n = 8), and moderate (Child-Pugh Class B, n = 8) hepatic impairment
456 to pharmacokinetics in healthy subjects (n = 8). The mean C_{max} and AUC were 11% and 25%
457 higher, respectively, for subjects with mild hepatic impairment, and 32% and 46% higher,
458 respectively, for subjects with moderate hepatic impairment compared with subjects with normal
459 hepatic function. These changes do not warrant a dose adjustment. Maraviroc concentrations are
460 higher when SELZENTRY 150 mg is administered with a potent CYP3A inhibitor compared
461 with following administration of 300 mg without a CYP3A inhibitor, so patients with moderate
462 hepatic impairment who receive SELZENTRY 150 mg with a potent CYP3A inhibitor should be
463 monitored closely for maraviroc-associated adverse events. The pharmacokinetics of maraviroc
464 have not been studied in subjects with severe hepatic impairment [*see Warnings and Precautions*
465 (5.1)].

466 **Renal Impairment:** A trial compared the pharmacokinetics of a single 300-mg dose of
467 SELZENTRY in subjects with severe renal impairment ($CL_{cr} < 30$ mL/min, n = 6) and ESRD
468 (n = 6) to healthy volunteers (n = 6). Geometric mean ratios for maraviroc C_{max} and AUC_{inf} were
469 2.4-fold and 3.2-fold higher, respectively, for subjects with severe renal impairment, and 1.7-fold
470 and 2.0-fold higher, respectively, for subjects with ESRD as compared with subjects with normal
471 renal function in this trial. Hemodialysis had a minimal effect on maraviroc clearance and
472 exposure in subjects with ESRD. Exposures observed in subjects with severe renal impairment
473 and ESRD were within the range observed in previous 300-mg single-dose trials of
474 SELZENTRY in healthy volunteers with normal renal function. However, maraviroc exposures
475 in the subjects with normal renal function in this trial were 50% lower than that observed in
476 previous trials. Based on the results of this trial, no dose adjustment is recommended for patients
477 with renal impairment receiving SELZENTRY without a potent CYP3A inhibitor or inducer.
478 However, if patients with severe renal impairment or ESRD experience any symptoms of
479 postural hypotension while taking SELZENTRY 300 mg twice daily, their dose should be
480 reduced to 150 mg twice daily [*see Dosage and Administration (2.2); Warnings and Precautions*
481 (5.2)].

482 In addition, the trial compared the pharmacokinetics of multiple-dose SELZENTRY in
483 combination with saquinavir/ritonavir 1,000/100 mg twice daily (a potent CYP3A inhibitor
484 combination) for 7 days in subjects with mild renal impairment ($CL_{cr} > 50$ and ≤ 80 mL/min,
485 n = 6) and moderate renal impairment ($CL_{cr} \geq 30$ and ≤ 50 mL/min, n = 6) to healthy volunteers
486 with normal renal function (n = 6). Subjects received 150 mg of SELZENTRY at different dose
487 frequencies (healthy volunteers – every 12 hours; mild renal impairment – every 24 hours;
488 moderate renal impairment – every 48 hours). Compared with healthy volunteers (dosed every
489 12 hours), geometric mean ratios for maraviroc AUC_{tau} , C_{max} , and C_{min} were 50% higher, 20%

490 higher, and 43% lower, respectively, for subjects with mild renal impairment (dosed every
491 24 hours). Geometric mean ratios for maraviroc AUC_{tau}, C_{max}, and C_{min} were 16% higher, 29%
492 lower, and 85% lower, respectively, for subjects with moderate renal impairment (dosed every
493 48 hours) compared with healthy volunteers (dosed every 12 hours). Based on the data from this
494 trial, no adjustment in dose is recommended for patients with mild or moderate renal impairment
495 [see *Dosage and Administration (2.2)*].

496 **Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc:** Maraviroc is a
497 substrate of CYP3A and P-gp and hence its pharmacokinetics are likely to be modulated by
498 inhibitors and inducers of these enzymes/transporters. The CYP3A/P-gp inhibitors ketoconazole,
499 lopinavir/ritonavir, ritonavir, darunavir/ritonavir, saquinavir/ritonavir, and atazanavir ± ritonavir
500 all increased the C_{max} and AUC of maraviroc (see Table 10). The CYP3A inducers rifampin,
501 etravirine, and efavirenz decreased the C_{max} and AUC of maraviroc (see Table 10).

502 Tipranavir/ritonavir (net CYP3A inhibitor/P-gp inducer) did not affect the steady-state
503 pharmacokinetics of maraviroc (see Table 10). Cotrimoxazole and tenofovir did not affect the
504 pharmacokinetics of maraviroc.

505

506

Table 10. 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 _{min}	AUC _{tau}	C _{max}
CYP3A and/or P-gp Inhibitors					
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)
CYP3A and/or P-gp Inducers					
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 (0.377, 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 ^a 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)
CYP3A and/or P-gp Inhibitors and Inducers					
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 (0.850, 1.23)	0.86 (0.61, 1.21)
Other					
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)

507 ^aCompared with historical data.

508

509 Effect of Maraviroc on the Pharmacokinetics of Concomitant Drugs: Maraviroc is
510 unlikely to inhibit the metabolism of coadministered drugs metabolized by the following
511 cytochrome P enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A)
512 because maraviroc did not inhibit activity of those enzymes at clinically relevant concentrations
513 in vitro. Maraviroc does not induce CYP1A2 in vitro.

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

517 Drug interaction trials were performed with maraviroc and other drugs likely to be
518 coadministered or commonly used as probes for pharmacokinetic interactions (see Table 10).

519 Coadministration of fosamprenavir 700 mg/ritonavir 100 mg twice daily and maraviroc
520 300 mg twice daily decreased the C_{min} and AUC of amprenavir by 36% and 35%, respectively.
521 Coadministration of fosamprenavir 1,400 mg/ritonavir 100 mg once daily and maraviroc 300 mg
522 once daily decreased the C_{min} and AUC by 15% and 30%, respectively. No dosage adjustment is
523 necessary when SELZENTRY is dosed 150 mg twice daily in combination with
524 fosamprenavir/ritonavir dosed once or twice daily. Fosamprenavir should be given with ritonavir
525 when coadministered with SELZENTRY.

526 Maraviroc had no effect on the pharmacokinetics of zidovudine or lamivudine. Maraviroc
527 decreased the C_{min} and AUC of raltegravir by 27% and 37%, respectively, which is not
528 clinically significant. Maraviroc had no clinically relevant effect on the pharmacokinetics of
529 midazolam, the oral contraceptives ethinylestradiol and levonorgestrel, no effect on the urinary
530 6β -hydroxycortisol/cortisol ratio, suggesting no induction of CYP3A in vivo. Maraviroc had no
531 effect on the debrisoquine metabolic ratio (MR) at 300 mg twice daily or less in vivo and did not
532 cause inhibition of CYP2D6 in vitro until concentrations $>100 \mu\text{M}$. However, there was 234%
533 increase in debrisoquine MR on treatment compared with baseline at 600 mg once daily,
534 suggesting potential inhibition of CYP2D6 at higher dose.

535 **12.4 Microbiology**

536 Mechanism of Action: Maraviroc is a member of a therapeutic class called CCR5 co-
537 receptor antagonists. Maraviroc selectively binds to the human chemokine receptor CCR5
538 present on the cell membrane, preventing the interaction of HIV-1 gp120 and CCR5 necessary
539 for CCR5-tropic HIV-1 to enter cells. CXCR4-tropic and dual-tropic HIV-1 entry is not inhibited
540 by maraviroc.

541 Antiviral Activity in Cell Culture: Maraviroc inhibits the replication of CCR5-tropic
542 laboratory strains and primary isolates of HIV-1 in models of acute peripheral blood leukocyte
543 infection. The mean EC_{50} value (50% effective concentration) for maraviroc against HIV-1
544 group M isolates (subtypes A to J and circulating recombinant form AE) and group O isolates
545 ranged from 0.1 to 4.5 nM (0.05 to 2.3 ng/mL) in cell culture.

546 When used with other antiretroviral agents in cell culture, the combination of maraviroc
547 was not antagonistic with NNRTIs (delavirdine, efavirenz, and nevirapine), NRTIs (abacavir,
548 didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), or
549 protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir,
550 saquinavir, and tipranavir). Maraviroc was additive/synergistic with the HIV fusion inhibitor
551 enfuvirtide. Maraviroc was not active against CXCR4-tropic and dual-tropic viruses (EC_{50} value
552 $>10 \mu\text{M}$). The antiviral activity of maraviroc against HIV-2 has not been evaluated.

553 *Resistance in Cell Culture:* HIV-1 variants with reduced susceptibility to maraviroc
554 have been selected in cell culture, following serial passage of 2 CCR5-tropic viruses (CCI/85 and
555 RU570). The maraviroc-resistant viruses remained CCR5-tropic with no evidence of a change
556 from a CCR5-tropic virus to a CXCR4-using virus. Two amino acid residue substitutions in the
557 V3-loop region of the HIV-1 envelope glycoprotein (gp160), A316T, and I323V (HXB2
558 numbering), were shown to be necessary for the maraviroc-resistant phenotype in the HIV-1
559 isolate CCI/85. In the RU570 isolate a 3-amino acid residue deletion in the V3 loop, ΔQAI
560 (HXB2 positions 315 to 317), was associated with maraviroc resistance. The relevance of the
561 specific gp120 mutations observed in maraviroc-resistant isolates selected in cell culture to
562 clinical maraviroc resistance is not known. Maraviroc-resistant viruses were characterized
563 phenotypically by concentration-response curves that did not reach 100% inhibition in
564 phenotypic drug assays, rather than increases in EC₅₀ values.

565 *Cross-Resistance in Cell Culture:* Maraviroc had antiviral activity against HIV-1
566 clinical isolates resistant to NNRTIs, NRTIs, PIs, and the fusion inhibitor enfuvirtide in cell
567 culture (EC₅₀ values ranged from 0.7 to 8.9 nM (0.36 to 4.57 ng/mL). Maraviroc-resistant viruses
568 that emerged in cell culture remained susceptible to the enfuvirtide and the protease inhibitor
569 saquinavir.

570 *Clinical Resistance:* Virologic failure on maraviroc can result from genotypic and
571 phenotypic resistance to maraviroc, through outgrowth of undetected CXCR4-using virus present
572 before maraviroc treatment (see *Tropism* below), through resistance to background therapy drugs
573 (Table 11), or due to low exposure to maraviroc [see *Clinical Pharmacology (12.2)*].

574 *Antiretroviral Treatment-Experienced Subjects (Trials A4001027 and*
575 *A4001028):* Week 48 data from treatment-experienced subjects failing maraviroc-containing
576 regimens with CCR5-tropic virus (n = 58) have identified 22 viruses that had decreased
577 susceptibility to maraviroc characterized in phenotypic drug assays by concentration-response
578 curves that did not reach 100% inhibition. Additionally, CCR5-tropic virus from 2 of these
579 treatment-failure subjects had ≥3-fold shifts in EC₅₀ values for maraviroc at the time of failure.

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

585 *Antiretroviral Treatment-Naive Subjects (Trial A4001026):* Treatment-naive
586 subjects receiving SELZENTRY had more virologic failures and more treatment-emergent
587 resistance to the background regimen drugs compared with those receiving efavirenz (Table 11).

588

589 **Table 11. Development of Resistance to Maraviroc or Efavirenz and Background Drugs in**
590 **Antiretroviral Treatment-Naive Trial A4001026 for Patients with CCR5-Tropic Virus at**
591 **Screening Using Enhanced Sensitivity TROFILE[®] Assay**

	Maraviroc	Efavirenz
--	-----------	-----------

Total N in dataset (as-treated)	273	241
Total virologic failures (as-treated)	85(31%)	56 (23%)
Evaluable virologic failures with post baseline genotypic and phenotypic data	73	43
• Lamivudine resistance	39 (53%)	13 (30%)
• Zidovudine resistance	2 (3%)	0
• Efavirenz resistance	--	23 (53%)
• Phenotypic resistance to maraviroc ^a	19 (26 %)	

592 ^a Includes subjects failing with CXCR4- or dual/mixed-tropism because these viruses are not
593 intrinsically susceptible to maraviroc.

594

595 In an as-treated analysis of treatment-naive subjects at 96 weeks, 32 subjects failed a
596 maraviroc-containing regimen with CCR5-tropic virus and had a tropism result at failure; 7 of
597 these subjects had evidence of maraviroc phenotypic resistance defined as
598 concentration-response curves that did not reach 95% inhibition. One additional subject had a
599 ≥ 3 -fold shift in the EC₅₀ value for maraviroc at the time of failure. A clonal analysis of the V3
600 loop amino acid envelope sequences was performed from 6 of the 7 subjects. Changes in V3
601 loop amino acid sequence differed between each of these different subjects, even for those
602 infected with the same virus clade suggesting that there are multiple diverse pathways to
603 maraviroc resistance. The subjects who failed with CCR5-tropic virus and without a detectable
604 maraviroc shift in susceptibility were not evaluated for genotypic resistance.

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

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

611 **Antiretroviral Treatment-Experienced Subjects:** In the majority of cases, treatment
612 failure on maraviroc was associated with detection of CXCR4-using virus (i.e., CXCR4- or
613 dual/mixed-tropic) which was not detected by the tropism assay prior to treatment.
614 CXCR4-using virus was detected at failure in approximately 55% of subjects who failed
615 treatment on maraviroc by Week 48, as compared with 9% of subjects who experienced
616 treatment failure in the placebo arm. To investigate the likely origin of the on-treatment
617 CXCR4-using virus, a detailed clonal analysis was conducted on virus from 20 representative
618 subjects (16 subjects from the maraviroc arms and 4 subjects from the placebo arm) in whom
619 CXCR4-using virus was detected at treatment failure. From analysis of amino acid sequence
620 differences and phylogenetic data, it was determined that CXCR4-using virus in these subjects
621 emerged from a low level of pre-existing CXCR4-using virus not detected by the tropism assay
622 (which is population-based) prior to treatment rather than from a coreceptor switch from
623 CCR5-tropic virus to CXCR4-using virus resulting from mutation in the virus.

624 Detection of CXCR4-using virus prior to initiation of therapy has been associated with a
625 reduced virological response to maraviroc. Furthermore, subjects failing maraviroc twice daily at
626 Week 48 with CXCR4-using virus had a lower median increase in CD4+ cell counts from
627 baseline (+41 cells/mm³) than those subjects failing with CCR5-tropic virus (+162 cells/mm³).
628 The median increase in CD4+ cell count in subjects failing in the placebo arm was +7 cells/mm³.

629 *Antiretroviral Treatment-Naive Subjects:* In a 96-week trial of antiretroviral
630 treatment-naive subjects, 14% (12/85) who had CCR5-tropic virus at screening with an enhanced
631 sensitivity tropism assay (TROFILE) and failed therapy on maraviroc had CXCR4-using virus at
632 the time of treatment failure. A detailed clonal analysis was conducted in 2 previously
633 antiretroviral treatment-naive subjects enrolled in a Phase 2a monotherapy trial who had
634 CXCR4-using virus detected after 10 days treatment with maraviroc. Consistent with the detailed
635 clonal analysis conducted in treatment-experienced subjects, the CXCR4-using variants appear
636 to emerge from outgrowth of a pre-existing undetected CXCR4-using virus. Screening with an
637 enhanced sensitivity tropism assay reduced the number of maraviroc virologic failures with
638 CXCR4- or dual/mixed-tropic virus at failure to 12 compared with 24 when screening with the
639 original tropism assay. All but one (11/12; 92%) of the maraviroc failures failing with CXCR4-
640 or dual/mixed-tropic virus also had genotypic and phenotypic resistance to the background drug
641 lamivudine at failure and 33% (4/12) developed zidovudine-associated resistance substitutions.

642 Subjects who had CCR5-tropic virus at baseline and failed maraviroc therapy with
643 CXCR4-using virus had a median increase in CD4+ cell counts from baseline of +113 cells/mm³
644 while those subjects failing with CCR5-tropic virus had an increase of +135 cells/mm³. The
645 median increase in CD4+ cell count in subjects failing in the efavirenz arm was +95 cells/mm³.

646 **13 NONCLINICAL TOXICOLOGY**

647 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

648 Carcinogenesis: Long-term oral carcinogenicity studies of maraviroc were carried out
649 in rasH2 transgenic mice (6 months) and in rats for up to 96 weeks (females) and 104 weeks
650 (males). No drug-related increases in tumor incidence were found in mice at 1,500 mg/kg/day
651 and in male and female rats at 900 mg/kg/day. The highest exposures in rats were approximately
652 11 times those observed in humans at the therapeutic dose of 300 mg twice daily for the
653 treatment of HIV-1 infection.

654 Mutagenesis: Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames
655 test in *Salmonella* and *E. coli*), a chromosome aberration test in human lymphocytes, and rat
656 bone marrow micronucleus test.

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

660 **14 CLINICAL STUDIES**

661 The clinical efficacy and safety of SELZENTRY are derived from analyses of data from
662 3 trials in adult subjects infected with CCR5-tropic HIV-1: A4001027 and A4001028 in

663 antiretroviral treatment-experienced adult subjects and A4001026 in treatment-naive subjects.
664 These trials were supported by a 48-week trial in antiretroviral treatment-experienced adult
665 subjects infected with dual/mixed-tropic HIV-1, A4001029.

666 **14.1 Trials in CCR5-Tropic, Treatment-Experienced Subjects**

667 Trials A4001027 and A4001028 were double-blind, randomized, placebo-controlled,
668 multicenter trials in subjects infected with CCR5-tropic HIV-1. Subjects were required to have
669 an HIV-1 RNA of greater than 5,000 copies/mL despite at least 6 months of prior therapy with at
670 least 1 agent from 3 of the 4 antiretroviral drug classes (≥ 1 NRTI, ≥ 1 NNRTI, ≥ 2 PIs, and/or
671 enfuvirtide) or documented resistance to at least 1 member of each class. All subjects received an
672 optimized background regimen consisting of 3 to 6 antiretroviral agents (excluding low-dose
673 ritonavir) selected on the basis of the subject's prior treatment history and baseline genotypic and
674 phenotypic viral resistance measurements. In addition to the optimized background regimen,
675 subjects were then randomized in a 2:2:1 ratio to SELZENTRY 300 mg once daily,
676 SELZENTRY 300 mg twice daily, or placebo. Doses were adjusted based on background
677 therapy as described in *Dosing and Administration*, Table 1.

678 In the pooled analysis for A4001027 and A4001028, the demographics and baseline
679 characteristics of the treatment groups were comparable (Table 12). Of the 1,043 subjects with a
680 CCR5-tropism result at screening, 7.6% had a dual/mixed-tropism result at the baseline visit 4 to
681 6 weeks later. This illustrates the background change from CCR5- to dual/mixed-tropism result
682 over time in this treatment-experienced population, prior to a change in antiretroviral regimen or
683 administration of a CCR5 co-receptor antagonist.
684

685 **Table 12. Demographic and Baseline Characteristics of Subjects in Trials A4001027 and**
686 **A4001028**

	SELZENTRY Twice Daily (N = 426)	Placebo (N = 209)
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 ₁₀ 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 ³)		
Median (range)	167 (2-820)	171 (1-675)
Subjects with baseline CD4+ cell count ≤200 cells/mm ³	250 (58.7%)	118 (56.5%)
Subjects with Overall Susceptibility Score (OSS): ^a		
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 mutations	90 (21.2%)	45 (21.5%)
Median number of resistance-associated: ^b		
PI mutations	10	10
NNRTI mutations	1	1
NRTI mutations	6	6

687 ^a OSS - Sum of active drugs in OBT based on combined information from genotypic and
688 phenotypic testing.

689 ^b Resistance mutations based on IAS guidelines.¹

690

691 The Week 48 results for the pooled Trials A4001027 and A4001028 are shown in
692 Table 13.

693

694 **Table 13. Outcomes of Randomized Treatment at Week 48**

695 **Trials A4001027 and A4001028**

Outcome	SELZENTRY Twice Daily (N = 426)	Placebo (N = 209)	Mean Difference
Mean change from Baseline to Week 48 in HIV-1 RNA (log ₁₀ 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%) ^a	1 (0.5%)	

696 ^a One additional subject died while receiving open-label therapy with SELZENTRY subsequent
697 to discontinuing double-blind placebo due to insufficient response.

698

699 After 48 weeks of therapy, the proportions of subjects with HIV-1 RNA <400 copies/mL
700 receiving SELZENTRY compared with placebo were 56% and 22%, respectively. The mean
701 changes in plasma HIV-1 RNA from baseline to Week 48 were -1.84 log₁₀ copies/mL for
702 subjects receiving SELZENTRY + OBT compared with -0.78 log₁₀ copies/mL for subjects
703 receiving OBT only. The mean increase in CD4+ cell count was higher on SELZENTRY twice
704 daily + OBT (124 cells/mm³) than on placebo + OBT (60 cells/mm³).

705 **14.2 Trial in Dual/Mixed-Tropic, Treatment-Experienced Subjects**

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

714 **14.3 Trial in Treatment-Naive Subjects**

715 Trial A4001026 is an ongoing, randomized, double-blind, multicenter trial in subjects
716 infected with CCR5-tropic HIV-1 classified by the original TROFILE tropism assay. Subjects
717 were required to have plasma HIV-1 RNA $\geq 2,000$ copies/mL and could not have: 1) previously
718 received any antiretroviral therapy for >14 days, 2) an active or recent opportunistic infection or
719 a suspected primary HIV-1 infection, or 3) phenotypic or genotypic resistance to zidovudine,
720 lamivudine, or efavirenz. Subjects were randomized in a 1:1:1 ratio to SELZENTRY 300 mg
721 once daily, SELZENTRY 300 mg twice daily, or efavirenz 600 mg once daily, each in
722 combination with zidovudine/lamivudine. The efficacy and safety of SELZENTRY are based on
723 the comparison of SELZENTRY twice daily versus efavirenz. In a pre-planned interim analysis
724 at 16 weeks, SELZENTRY 300 mg once daily failed to meet the pre-specified criteria for
725 demonstrating non-inferiority and was discontinued.

726 The demographic and baseline characteristics of the maraviroc and efavirenz treatment
727 groups were comparable (Table 14). Subjects were stratified by screening HIV-1 RNA levels and
728 by geographic region. The median CD4+ cell counts and mean HIV-1 RNA at baseline were
729 similar for both treatment groups.

730

731 **Table 14. Demographic and Baseline Characteristics of Subjects in Trial A4001026**

	SELZENTRY 300 mg Twice Daily + Zidovudine/Lamivudine (N = 360)	Efavirenz 600 mg Once Daily + Zidovudine/Lamivudine (N = 361)
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/ μ L)	241 (5-1,422)	254 (8-1,053)
Median (range) HIV-1 RNA (log ₁₀ copies/mL)	4.9 (3-7)	4.9 (3-7)

732

733 The treatment outcomes at 96 weeks for Trial A4001026 are shown in Table 15.
734 Treatment outcomes are based on reanalysis of the screening samples using a more sensitive
735 tropism assay, Enhanced sensitivity TROFILE HIV tropism assay, which became available after
736 the Week 48 analysis, approximately 15% of the subjects identified as CCR5-tropic in the
737 original analysis had dual/mixed- or CXCR4-tropic virus. Screening with enhanced sensitivity
738 version of the TROFILE tropism assay reduced the number of maraviroc virologic failures with
739 CXCR4- or dual/mixed-tropic virus at failure to 12 compared with 24 when screening with the
740 original TROFILE HIV tropism assay.

741

742 **Table 15: Trial Outcome (Snapshot) at Week 96 Using Enhanced Sensitivity Assay^a**

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

743 ^a The total number of subjects (Ns) in Table 15 represents the subjects who had a CCR5-tropic
744 virus in the reanalysis of screening samples using the more sensitive tropism assay. This
745 reanalysis reclassified approximately 15% of subjects shown in Table 14 as having dual/mixed-
746 or CXCR4-tropic virus. These numbers are different than those presented in Table 14 because
747 the numbers in Table 14 reflect the subjects with CCR5-tropic virus according to the original
748 tropism assay.

749 ^b Week 48 results: Virologic responders (<400): 228/311 (73%) in SELZENTRY, 219/303
750 (72%) in efavirenz;

751 Virologic responders (<50): 213/311 (69 %) in SELZENTRY, 207/303 (68%) in efavirenz.

752 ^c Other reasons for discontinuation include lost to follow-up, withdrawn, protocol violation, and
753 other.

754

755 The median increase from baseline in CD4+ cell counts at Week 96 was 184 cells/mm³
756 for the arm receiving SELZENTRY compared with 155 cells/mm³ for the efavirenz arm.

757 **15 REFERENCES**

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

760 **16 HOW SUPPLIED/STORAGE AND HANDLING**

761 SELZENTRY film-coated tablets are available as follows:

762 150- and 300-mg tablets are blue, biconvex, oval, film-coated tablets debossed with “MVC 150”
763 or “MVC 300” on one side and plain on the other.

764 Bottle packs 150-mg tablets: 60 tablets (NDC 49702-223-18).

765 Bottle packs 300-mg tablets: 60 tablets (NDC 49702-224-18).

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

768 **17 PATIENT COUNSELING INFORMATION**

769 *See FDA-approved patient labeling (Medication Guide)*

770 Patients should be informed that liver problems including life-threatening cases have
771 been reported with SELZENTRY. Patients should be informed that if they develop signs or
772 symptoms of hepatitis or allergic reaction following use of SELZENTRY (rash, skin or eyes look
773 yellow, dark urine, vomiting, abdominal pain), they should stop SELZENTRY and seek medical
774 evaluation immediately. Patients should understand that laboratory tests for liver enzymes and
775 bilirubin will be ordered prior to starting SELZENTRY, at other times during treatment, and if
776 they develop severe rash or signs and symptoms of hepatitis or an allergic reaction on treatment
777 [see *Warnings and Precautions (5.1), (5.2)*].

778 Patients should be informed that SELZENTRY is not a cure for HIV-1 infection and
779 patients may continue to experience illnesses associated with HIV-1 infection, including
780 opportunistic infections.

781 Patients should remain under the care of a physician when using SELZENTRY.

782 Patients should be advised to avoid doing things that can spread HIV-1 infection to
783 others.

- 784 • **Do not share needles or other injection equipment.**
785 • **Do not share personal items that can have blood or body fluids on them, like**
786 **toothbrushes and razor blades.**
787 • **Do not have any kind of sex without protection.** Always practice safe sex by using a latex
788 or polyurethane condom to lower the chance of sexual contact with semen, vaginal
789 secretions, or blood.
790 • **Do not breastfeed.** We do not know if SELZENTRY can be passed to your baby in your
791 breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not
792 breastfeed because HIV-1 can be passed to the baby in the breast milk.

793 Patients should be advised that it is important to take all their anti-HIV medicines as
794 prescribed and at the same time(s) each day. SELZENTRY must always be used in combination
795 with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without

796 consulting their physician. If a dose is missed, patients should take the next dose of
797 SELZENTRY as soon as possible and then take their next scheduled dose at its regular time. If it
798 is less than 6 hours before their next scheduled dose, they should not take the missed dose and
799 should instead wait and take the next dose at the regular time.

800 Patients should be advised that when their supply of SELZENTRY starts to run low, they
801 should ask their doctor or pharmacist for a refill.

802 Caution should be used when administering SELZENTRY in patients with a history of
803 postural hypotension or on concomitant medication known to lower blood pressure. Patients
804 should be advised that if they experience dizziness while taking SELZENTRY, they should
805 avoid driving or operating machinery.

806

807 TROFILE[®] is a registered trademark of Monogram Biosciences, Inc.

808

809 Manufactured for:



810

811 ViiV Healthcare

812 Research Triangle Park, NC 27709

813

814 by:

815 Pfizer Manufacturing Deutschland GmbH

816 Freiburg, Germany

817

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819

820

821 SEL: PI

822

823 PHARMACIST-DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT

824 -----

825

MEDICATION GUIDE

826

SELZENTRY[®] (sell-ZEN-tree) Tablets

827

(maraviroc)

828

829 Read the Medication Guide that comes with SELZENTRY before you start taking it
830 and each time you get a refill. There may be new information. This information
831 does not take the place of talking with your healthcare provider about your medical
832 condition or treatment.

833

834 **What is the most important information I should know about SELZENTRY?**

835

836 **Serious side effects have occurred with SELZENTRY, including liver**
837 **problems (liver toxicity).** An allergic reaction may happen before liver problems
838 occur. Stop taking SELZENTRY and call your healthcare provider right away if you
839 get any of the following symptoms:

- 840 • an itchy rash on your body (allergic reaction)
- 841 • yellowing of your skin or whites of your eyes (jaundice)
- 842 • dark (tea-colored) urine
- 843 • vomiting
- 844 • upper right stomach area (abdominal) pain

845

846 **What is SELZENTRY?**

847 SELZENTRY is an anti-HIV medicine called a CCR5 antagonist. HIV-1 (Human
848 Immunodeficiency Virus) is the virus that causes AIDS (Acquired Immune
849 Deficiency Syndrome).

850

851 SELZENTRY is used with other anti-HIV medicines in adults with CCR5-tropic HIV-1
852 infection.

853

854 Use of SELZENTRY is not recommended in people with dual/mixed or CXCR4-tropic
855 HIV-1.

856

- 857 • SELZENTRY will not cure HIV-1 infection.
- 858 • People taking SELZENTRY may still develop infections, including opportunistic
859 infections or other conditions that happen with HIV-1 infection.
- 860 • It is very important that you stay under the care of your healthcare provider
861 during treatment with SELZENTRY.
- 862 • The long-term effects of SELZENTRY are not known at this time.

863

864 SELZENTRY has not been studied in children less than 16 years of age.

865

866 **General information about SELZENTRY**

867 SELZENTRY does not cure HIV-1 infection and you may continue to experience
868 illnesses associated with HIV-1 infection, including opportunistic infections. You
869 should remain under the care of a doctor when using SELZENTRY.

870

871 Avoid doing things that can spread HIV-1 infection.

- 872 • **Do not share needles or other injection equipment.**

- 873 • **Do not share personal items that can have blood or body fluids on them,**
874 **like toothbrushes and razor blades.**
- 875 • **Do not have any kind of sex without protection.** Always practice safe sex
876 by using a latex or polyurethane condom to lower the chance of sexual contact
877 with semen, vaginal secretions, or blood.

878

879 **How does SELZENTRY work?**

880 HIV-1 enters cells in your blood by attaching itself to structures on the surface of
881 the cell called receptors. SELZENTRY blocks a specific receptor called CCR5 that
882 CCR5-tropic HIV-1 uses to enter CD4 or T-cells in your blood. Your healthcare
883 provider will do a blood test to see if you have been infected with CCR5-tropic
884 HIV-1 before prescribing SELZENTRY for you.

885

- 886 • When used with other anti-HIV medicines, SELZENTRY may:
- 887 • reduce the amount of HIV-1 in your blood. This is called “viral load”.
 - 888 • increase the number of white blood cells called T (CD4) cells.

889

890 SELZENTRY does not work in all people with CCR5-tropic HIV-1 infection.

891

892 **Who should not take SELZENTRY?**

893 People with severe kidney problems or who are on hemodialysis and are taking
894 certain other medications should not take SELZENTRY. Talk to your healthcare
895 provider before taking this medicine if you have kidney problems.

896

897 **What should I tell my healthcare provider before taking SELZENTRY?**

898

899 **Before you take SELZENTRY, tell your healthcare provider if you:**

- 900 • have liver problems including a history of hepatitis B or C.
 - 901 • have heart problems.
 - 902 • have kidney problems.
 - 903 • have low blood pressure or take medicines to lower blood pressure.
 - 904 • have any other medical condition.
 - 905 • are pregnant or plan to become pregnant. It is not known if SELZENTRY may
906 harm your unborn baby.
- 907 **Antiretroviral Pregnancy Registry.** There is a pregnancy registry for women
908 who take antiviral medicines during pregnancy. The purpose of the registry is to
909 collect information about the health of you and your baby. Talk to your
910 healthcare provider about how you can take part in this registry.
- 911 • are breastfeeding or plan to breastfeed. **Do not breastfeed.** We do not know if
912 SELZENTRY can be passed to your baby in your breast milk and whether it could

913 harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1
914 can be passed to the baby in the breast milk. Talk with your healthcare provider
915 about the best way to feed your baby.

916

917 **Tell your healthcare provider about all the medicines you take**, including
918 prescription and non-prescription medicines, vitamins, and herbal supplements.
919 Certain other medicines may affect the levels of SELZENTRY in your blood. Your
920 healthcare provider may need to change your dose of SELZENTRY when you take it
921 with certain medicines.

922

923 The levels of SELZENTRY in your blood may change and your healthcare provider
924 may need to adjust your dose of SELZENTRY when taking any of the following
925 medications together with SELZENTRY:

926

- | | | |
|-----|---|--|
| 927 | - darunavir (PREZISTA [®]) | - delavirdine (RESCRIPTOR [®]) |
| 928 | - lopinavir/ritonavir (KALETRA [®] , NORVIR [®]) | - ketoconazole (NIZORAL [®]) |
| 929 | - atazanavir (REYATAZ [®]) | - itraconazole (SPORANOX [®]) |
| 930 | - saquinavir (INVIRASE [®]) | - clarithromycin (BIAXIN [®]) |
| 931 | - nelfinavir (VIRACEPT [®]) | - nefazodone (SERZONE [®]) |
| 932 | - indinavir (CRIXIVAN [®]) | - telithromycin (Ketek [®]) |
| 933 | - fosamprenavir (LEXIVA [®]) | - efavirenz (SUSTIVA [®] , ATRIPLA [®]) |
| 934 | - etravirine (INTELENCE [®]) | - rifampin (RIFADIN [®] , RIFATER [®]) |
| 935 | - carbamazepine (TEGRETOL [®]) | - phenobarbital (LUMINAL [®]) |
| 936 | - phenytoin (DILANTIN [®]) | |
| 937 | - ritonavir (NORVIR [®]) | |

938

939 **Do not take products that contain St. John's wort (*Hypericum perforatum*).**
940 **St. John's wort may lower the levels of SELZENTRY in your blood so that it**
941 **will not work to treat your CCR5-tropic HIV-1 infection.**

942

943 **Know the medicines you take.** Keep a list of your medicines. Show the list to
944 your healthcare provider and pharmacist when you get a new medicine.

945

946 **How should I take SELZENTRY?**

947

948 **Take SELZENTRY exactly as prescribed by your healthcare provider.**
949 SELZENTRY comes in 150-mg and 300-mg tablets. Your healthcare provider will
950 prescribe the dose that is right for you.

- 951 • Take SELZENTRY 2 times a day.
- 952 • Swallow SELZENTRY tablets whole. Do not chew the tablets.

- 953 • Take SELZENTRY tablets with or without food.
954 • Always take SELZENTRY with other anti-HIV drugs as prescribed by your
955 healthcare provider.

956

957 **Do not change your dose or stop taking SELZENTRY or your other anti-HIV**
958 **medicines without first talking with your healthcare provider.**

959

- 960 • If you take too much SELZENTRY, call your healthcare provider or the poison
961 control center right away.
962 • If you forget to take SELZENTRY, take the next dose of SELZENTRY as soon as
963 possible and then take your next scheduled dose at its regular time. If it is less
964 than 6 hours before your next dose, do not take the missed dose. Wait and take
965 the next dose at the regular time. Do not take a double dose to make up for a
966 missed dose.
967 • It is very important to take all your anti-HIV medicines as prescribed. This can
968 help your medicines work better. It also lowers the chance that your medicines
969 will stop working to fight HIV-1 (drug resistance).
970 • When your SELZENTRY supply starts to run low, ask your healthcare provider or
971 pharmacist for a refill. This is very important because the amount of virus in
972 your blood may increase and SELZENTRY could stop working if it is stopped for
973 even a short period of time.

974

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

976

977 **There have been serious side effects when SELZENTRY has been given with**
978 **other anti-HIV drugs including:**

- 979 • **Liver problems.** See “What is the most important information I should know
980 about SELZENTRY?”
981 • **Serious skin rash and allergic reactions.** Severe and potentially life-
982 threatening skin reactions and allergic reactions have been reported in some
983 patients taking SELZENTRY. If you develop a rash with any of the following
984 symptoms, stop using SELZENTRY and contact your doctor right away:
985 o fever
986 o generally ill feeling
987 o muscle aches
988 o blisters or sores in your mouth
989 o blisters or peeling of the skin
990 o redness or swelling of the eyes
991 o swelling of the mouth or face or lips
992 o problems breathing

- 993 ○ yellowing of the skin or whites of your eyes
- 994 ○ dark or tea colored urine
- 995 ○ pain, aching, or tenderness on the right side below the ribs
- 996 ○ loss of appetite
- 997 ○ nausea/vomiting
- 998 • **Heart problems** including heart attack.
- 999 • **Low blood pressure when standing up (postural hypotension).** Low blood
1000 pressure when standing up can cause dizziness or fainting. Do not drive a car or
1001 operate heavy machinery if you have dizziness while taking SELZENTRY.
- 1002 • **Changes in your immune system.** A condition called Immune Reconstitution
1003 Syndrome can happen when you start taking HIV medicines. Your immune
1004 system may get stronger and could begin to fight infections that have been
1005 hidden in your body such as pneumonia, herpes virus, or tuberculosis. Tell your
1006 healthcare provider if you develop new symptoms after starting your HIV
1007 medicines.
- 1008 • **Possible chance of infection or cancer.** SELZENTRY affects other immune
1009 system cells and therefore may possibly increase your chance for getting other
1010 infections or cancer.

1011

1012 **The most common side effects of SELZENTRY include** colds, cough, fever,
1013 rash, and dizziness.

1014

1015 Tell your healthcare provider about any side effect that bothers you or does not go
1016 away.

1017

1018 These are not all of the side effects with SELZENTRY. For more information, ask
1019 your healthcare provider or pharmacist.

1020

1021 Call your doctor for medical advice about side effects. You may report side effects
1022 to FDA at 1-800-FDA-1088.

1023

1024 **How should I store SELZENTRY?**

1025 • Store SELZENTRY tablets at room temperature from 59°F to 86°F (15°C to
1026 30°C).

1027 • Safely throw away medicine that is out of date or that you no longer need.

1028

1029 **Keep SELZENTRY and all medicines out of the reach of children.**

1030

1031 **General information about SELZENTRY**

1032 Medicines are sometimes prescribed for conditions that are not mentioned in
1033 Medication Guides. Do not use SELZENTRY for a condition for which it was not
1034 prescribed. Do not give SELZENTRY to other people, even if they have the same
1035 symptoms you have. It may harm them.

1036

1037 This Medication Guide summarizes the most important information about
1038 SELZENTRY. If you would like more information, talk with your healthcare provider.
1039 You can ask your healthcare provider or pharmacist for more information about
1040 SELZENTRY that is written for health professionals.
1041 For more information, go to www.selzentry.com.

1042

1043 **What are the ingredients in SELZENTRY?**

1044 **Active ingredient:** maraviroc

1045 **Inactive ingredients:** microcrystalline cellulose, dibasic calcium phosphate
1046 (anhydrous), sodium starch glycolate, magnesium stearate

1047 **Film-coat:** FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol
1048 (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide

1049

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1051 and are not trademarks of ViiV Healthcare. The makers of these brands are not
1052 affiliated with and do not endorse ViiV Healthcare or its products.

1053

1054 This Medication Guide has been approved by the US Food and Drug Administration.

1055

1056

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1058

1059 ViiV Healthcare

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1061

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1065

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