EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Selzentry® (maraviroc tablets – Pfizer)

TAC REVIEW DATE: 06/03/2015

LAY CRITERIA EFFECTIVE DATE: Previously in Effect

OVERVIEW

Selzentry, in combination with other antiretroviral therapy (ART), is indicated for the treatment of adults with only cysteine-cysteine chemokine receptor 5 (CCR5)-tropic human immunodeficiency virus (HIV)-1.[1] This indication is based on analyses of plasma HIV-1 RNA levels in two controlled trials of Selzentry in treatment-experienced patients and one trial in treatment-naïve patients. Both trials in treatment-experienced patients were conducted in clinically advanced, three-class ART-experienced adults with evidence of HIV-1 replication despite ongoing ART therapy. When initiating therapy with Selzentry, the following should be considered:

- Adult patients infected with only CCR5-tropic HIV-1 should use Selzentry.
- Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated ability to identify patients appropriate for use of Selzentry. Outgrowth of pre-existing low-level cysteine-X-cysteine chemokine receptor 4 (CXCR4)- or dual-mixed tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure of Selzentry.
- Use of Selzentry is not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a Phase II study.
- The safety and efficacy of Selzentry have not been established in pediatric patients.
- In treatment-naïve patients, more patients treated with Selzentry experienced virologic failure and developed lamivudine resistance compared with Sustiva® (efavirenz tablets/capsules)-treated patients.

Selzentry is the only Food and Drug Administration (FDA-approved) CCR5 antagonist and works by selectively binding to the human chemokine receptor CCR5 preventing the interaction necessary for CCR5-tropic HIV-1 to enter cells. CXCR4-tropic and dual/mixed-tropic (e.g., CCR5/CXCR4) HIV-1 entry is not inhibited by Selzentry; the antiviral activity of Selzentry against HIV-2 has not been evaluated.

Co-receptor tropism assay should be performed whenever the use of CCR5 antagonist is being considered.[2] Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available and is less expensive than phenotypic assays. Evaluation of genotypic assays is ongoing; however, data suggest that testing should be considered as an alternative assay. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist. Resistance to CCR5 antagonists in the absence of detectable CXCR4- using virus has been reported, but such resistance is uncommon. The Department of Health and Human Services (DHHS) guidelines make the following recommendations regarding co-receptor tropism assays: 1) A co-receptor tropism assay should be performed whenever the use of CCR5 co-receptor antagonist is being considered; 2) co-receptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 antagonist; 3) a phenotypic assay is

preferred to determine HIV-1 co-receptor usage; and 4) a genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage.

Two Trofile® assays are now available.[3] One Trofile assay if for patients with HIV RNA ≥ 1,000 copies/mL (Trofile) and the other is for patients with HIV RNA < 1,000 copies/mL (Trofile DNA). The Trofile assay is 100% sensitive at detecting 0.3% CXR4-using minor variant and uses the complete gp160 coding region of the HIV-1 envelope protein to ensure that all determinants of tropism are tested. The Trofile DNA is for patients with ***undetectable*** viral loads, and can be considered when a patient's viral tropism is unknown, and a CCR5 antagonist is desired. Unlike the standard Trofile assay, which uses viral RNA found in the plasma of patients with viral loads ≥ 1,000 copies/mL, Trofile DNA uses viral DNA extracted from cells in a whole blood draw. Once the viral information is obtained, Trofile DNA runs on the same clinically validated platform as the Trofile.

Clinical Efficacy

The clinical efficacy and safety of Selzentry have been established from analyses of data from three ongoing studies in adults infected with CCR5-tropic HIV-1 (two studies in ART-experienced patients[1] and one in ART-naïve patients[7]). These studies are supported by a 48-week study in ART-experienced adults infected with dual/mixed-tropic HIV-1.[4] In both treatment-experienced and treatment-naïve patients, detection of CXCR4-using virus prior to initiation of therapy has been associated with a reduced virologic response to Selzentry.[1] In the majority of cases, treatment failure on Selzentry in treatment-experienced patients with HIV-1 was associated with the detection of CXCR4- or dual/mixed-tropic virus.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Selzentry. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Selzentry is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **HIV-1 Infection with Cysteine-Cysteine Chemokine Receptor 5 (CCR5)-Tropic Virus.** Approve for patients who meet the following criteria (A and B):
   A) The patient has HIV-1 infection; AND
   B) The patient has only CCR5-tropic virus detected by an enhanced sensitivity tropism assay.

   Selzentry is indicated for use in combination with other antiretroviral agents, for patients infected with only CCR5-tropic HIV-1.[1] Only patients with CCR5-tropic HIV-1 should use Selzentry tablets.[1]

   The DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents recommend the use of coreceptor tropism assays in clinical practice whenever the use of a CCR5 inhibitor is being considered.[2] Although Selzentry may be active against some HIV-2 isolates, there are no approved assays to determine HIV-2 coreceptor tropism. Further, HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4.

Other Uses with Supportive Evidence

2. **Patients with HIV-1 Infection Already Started on Selzentry.** Approve.

   In the professional opinion of a specialist physician, we have adopted this criterion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Selzentry has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **HIV-1 Infection with CXCR4- or CCR5/CXCR4-Tropic Virus**. Selzentry is not indicated in patients with CXCR4- or CCR5/CXCR4-tropic virus. CXCR4-tropic and dual-tropic (CCR5/CXCR4) HIV-1 entry is not inhibited by Selzentry.

   The efficacy of Selzentry in patients with non-CCR5-tropic HIV-1 was not demonstrated in a Phase IIb study.[1,4] In treatment-experienced patients with non-CCR5-tropic HIV-1 from baseline to Week 24, patients who received placebo demonstrated a mean decrease in HIV-1 RNA levels of 0.97 $\log_{10}$ copies/mL, compared with mean decreases of 0.91 and 1.20 $\log_{10}$ copies/mL for those who were treated with Selzentry once daily (QD) or twice daily (BID), respectively; the difference between the two groups was not statistically significant (P = 0.83 and P = 0.38, for QD and BID vs. placebo, respectively). Mean increases in CD4 cell counts were 36 cells/µL, 60 cells/µL, and 62 cells/µL, for patients who received placebo, Selzentry QD, and Selzentry BID, respectively. In patients with CXCR4 mixed or dual-tropic HIV-1, treatment with Selzentry did not demonstrate superiority to placebo and failed to demonstrate non-inferiority to placebo.[4]

2. **HIV-1 Infection Initiating Therapy with Selzentry with Unknown CCR5-Tropic Status.** Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for Selzentry use (i.e., CCR5-tropic HIV-1).[1] DHHS and Infectious Diseases Society of America (IDSA) guidelines endorse tropism testing prior to initiation of therapy with a CCR5 antagonist (i.e., Selzentry).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Selzentry® tablets [prescribing information]. New York, NY: Pfizer; April 2015.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Co-Receptor Tropism Assays. Last updated February 12, 2013. Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed on May 19, 2015.
3. Tropism assays. Monogram Biosciences. Copyright © 2014. Available at: http://www.monogrambio.com/hiv-tests/tropism. Accessed on May 19, 2015.
4. Saag M, Goodrich J, Fätkenheuer G, et al; A4001029 Study Group. A double-blind, placebo-controlled trial of maraviroc in treatment-experienced patients infected with non-R5 HIV-1. *J Infect Dis*. 2009;199(11):1638-1647.
5. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1429-1441.

OTHER REFERENCES UTILIZED

- Latinovic O, Kuruppu J, Davis C, et al. Pharmacotherapy of HIV-1 infection: Focus on CCR5 antagonist maraviroc, *Clin Med Ther*. 2009;1:1497-1510.
- McGovern RA, Thielen, Mo T, et al. Population-based V3 genotypic tropism assay: a retrospective analysis using screening samples from the A4001029 and MOTIVATE studies. *AIDS*. 2010;24:2517-2525.
- Gilliam BL, Riedel DJ and Redfield RR. Clinical uses of CCR5 inhibitors in HIV and beyond. *J Transl Med*. 2010;9(Suppl 1):S9-14.
- Mortier V, Dauwe K, Vancoillie L, et al. Frequency and predictors of HIV-1 co-receptor switch in treatment naïve patients. *PLoS One*. 2013;8(11):e80259-e80259.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
Integrated policy	--	06/20/2012	--
Annual revision	--	06/12/2013	--
Annual revision	No changes	06/11/2014	Previously in effect
Selected revision	3 year approval duration	08/06/2014	08/26/2014
Annual revision	No changes	06/03/2015	Previously in effect

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.