



PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Zinbryta™ (daclizumab injection for subcutaneous use)

TAC APPROVAL DATE: 06/08/2016

LAY CRITERIA EFFECTIVE DATE: 07/12/2016

OVERVIEW

Zinbryta, an interleukin-2 receptor blocking antibody, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS).¹ Due to its safety profile, use of Zinbryta should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS. The recommended dose of Zinbryta is 150 mg given by subcutaneous (SC) injection once monthly. If appropriate, patients can be trained to self-administer the medication. Before initiating Zinbryta, obtain and evaluate serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels. Also, evaluate patients at high risk for tuberculosis (TB) infection prior to initiating treatment. Prior to initiating therapy, screen patients for hepatitis B and hepatitis C. Zinbryta is contraindicated in patients with pre-existing hepatic disease. Test transaminase and total bilirubin levels monthly and assess before the next dose of Zinbryta. Follow transaminase levels and total bilirubin monthly for 6 months following the last Zinbryta dose. Two pivotal trials assessed the efficacy of Zinbryta in patients with relapsing MS.¹⁻² DECIDE compared Zinbryta 150 mg SC once every 4 weeks with Avonex® (interferon beta-1a for intramuscular [IM] injection) 30 mcg IM once weekly (QW) in 1,841 patients with relapsing MS. Approximately 41% of patients had received previous disease-modifying MS therapies and 70% of patients completed at least 96 weeks of treatment. Patients given Zinbryta had an annualized relapse rate of 0.216 compared with 0.393 among those given Avonex, a 45% relative reduction (P < 0.0001).¹⁻² SELECT compared Zinbryta with placebo in patients with relapsing MS in which patients were randomized to receive Zinbryta 150 mg SC once every 4 weeks (n = 208), Zinbryta 300 mg SC once every 4 weeks (n = 209) or placebo (n = 204) for 52 weeks.^{1,3} Approximately 25% of patients had received disease-modifying treatment for MS. The annualized relapse rate was 0.211 for patients given Zinbryta 150 mg SC once every 4 weeks compared with 0.458 for patients randomized to placebo, a 54% relative reduction (P < 0.0001).

Risk Evaluation and Mitigation Strategy (REMS)

Zinbryta is available only through a restricted REMS program called the ZINBRYTA REMS Program due to the risks of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders.¹ Some program requirements include that prescribers must be certified with the program by enrolling and completing training. Also, patients must enroll in the program and comply with ongoing monitoring requirements. Pharmacies are required to be certified with the program and must only dispense Zinbryta to patients authorized to receive Zinbryta.

Multiple Sclerosis (MS)

MS is a chronic disabling disease of the central nervous system (CNS) characterized by inflammation, demyelination, and degenerative changes.⁴⁻⁵ Patients experience relapses followed by remission of neurological symptoms. MS lesions occur in many different parts of the CNS and the symptoms and clinical course of the disease are highly variable. Some common signs and symptoms of the disease include vision problems (e.g., nystagmus), ambulation problems, pain, fatigue, spasticity, cognitive

dysfunction, depression, ataxia, sensory loss, bladder disturbances, bowel dysfunction, dizziness, and vertigo.⁴ In general, patients with MS may have diminished ratings on vitality and physical functions.⁵ Most people with MS are diagnosed between the ages of 20 and 50 years, but MS can manifest in young children and older adults.⁴ Approximately 450,000 people are living with MS in the US.⁵ Women are impacted two to three times more commonly than men, and MS is more predominant in Caucasians compared with other racial groups.

Four different clinical courses of MS have been delineated.⁴ A relapse is defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least one month. Relapsing-remitting MS (RRMS) is characterized by acute attacks usually followed by almost complete recovery with limited progression. Disease progression is minimal between attacks. Approximately 85% of people are initially diagnosed with RRMS. Secondary progressive MS (SPMS) begins as a relapsing-remitting course but the disease transitions in many patients to a steadily progressive form with increased loss of function. Of the 85% of patients who initially have RRMS, more than 50% of patients will develop to SPMS within 10 years and 90% of patients within 25 years. Primary-progressive MS (PPMS) is noted by a steady decline in function from the onset without noted relapses. Around 10% of patients are diagnosed with primary-progressive. Progressive-relapsing MS (PRMS) starts with disease progression at onset with occasional acute relapses and continued disease progression. Only a small minority of patients (< 5%) have PRMS. About 10% of the MS population has a benign disease course, which is generally determined retrospectively. Among those with relapsing forms of MS, the severity, duration, and frequency of relapses vary widely among patients. The Expanded Disability Scale Score (EDSS) is the scale most often used to assess neurologic disability and evaluates cerebellar, pyramidal, brainstem, sensory, bowel, bladder, visual, and mental functional systems on a scale that ranges from 0 (normal neurologic examination) to 10 (death due to MS). Magnetic resonance imaging (MRI) evaluations are used to assess current MS disease activity, as well as to monitor for permanent neurologic damage.

Other Disease-Modifying Drug Therapies for Multiple Sclerosis

Interferon beta therapies indicated for use in relapsing forms of MS include Avonex,⁶ Rebif[®] (interferon beta-1a for SC injection),⁷ and Betaseron[®]/Extavia[®] (interferon beta-1b for SC injection).⁸⁻⁹ Dosing of these products is IM QW, SC three times weekly (TIW), and SC every other day, respectively. Plegridy[™] (peginterferon beta-1a for SC injection) is a pegylated interferon beta-1a product that is also indicated for the treatment of relapsing forms of MS and is dosed SC every 14 days.¹⁰ Another self-injectable MS therapy is Copaxone[®] (glatiramer acetate injection for SC use), which can be dosed SC either once daily (QD) or TIW.¹¹ Glatopa[™] (glatiramer acetate injection for SC use) is the generic for Copaxone and is available in the 20 mg dose only.¹² Although some differences in efficacy have been observed in clinical trials among the interferon beta products, in general, these self-injectable MS therapies appear to reduce the annualized relapse rate by approximately one-third.¹³ Copaxone and several interferon beta products have been available for over 20 years with established efficacy and known safety. Oral therapies indicated in relapsing forms of MS include Aubagio[®] (teriflunomide tablets),¹⁴ Gilenya[™] (fingolimod capsules),¹⁵ and Tecfidera[™] (dimethyl fumarate delayed-release capsules).¹⁶ Compared with placebo, these agents lead to reductions in the annualized relapse rate of approximately 31% with Aubagio, 54% with Gilenya, and 44% to 53% with Tecfidera.⁵ Several therapies are given by intravenous (IV) infusion. Tysabri[®] (natalizumab for IV infusion)¹⁷ and mitoxantrone injection,¹⁸ are administered once every 4 weeks (over 1 hour), and once every 3 months (over 5 to 15 minutes), respectively. These therapies have also demonstrated benefits in patients with MS with the effect of the annualized relapse rate being reduced by approximately 67%.⁵ However, Tysabri must be used cautiously due to the risk of progressive multifocal leukoencephalopathy (PML).¹⁷ Due to toxicities (e.g., cardiotoxicity, increased risk of developing secondary acute myeloid leukemia) the role of mitoxantrone is limited to a carefully selected

patient population who have not responded to other therapies.¹⁹ Lemtrada™ (alemtuzumab injection for IV use) is indicated for use for the treatment of MS in patients with relapsing forms of MS but due to its safety profile it should be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS. Lemtrada is given by IV infusion over 4 hours for two treatment courses: first course is 12 mg/day on 5 consecutive days and the second course is 12 mg/day on 3 consecutive days 12 months after the first treatment course. Lemtrada has a REMS program related to its Boxed Warning regarding autoimmunity, infusion reactions, and malignancies.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zinbryta. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zinbryta, as well as the monitoring required for adverse events and long-term efficacy, approval requires Zinbryta to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. Multiple Sclerosis (MS).

- A) Initial therapy.** Approve for 3 years if the patient meets all of the following criteria (i, ii, iii, and iv):
- i.** The patient is ≥ 17 years of age; AND
 - ii.** The patient has a relapsing form of multiple sclerosis (MS) [relapsing forms of MS are relapsing-remitting MS {RRMS}, secondary-progressive MS {SPMS} with relapses, and progressive-relapsing MS {PRMS}]; AND
 - iii.** According to the prescribing physician the patient has had an inadequate response, or is unable to tolerate, at least two of the following medications for MS: Avonex (interferon beta-1a for intramuscular injection), Rebif (interferon beta-1 for subcutaneous injection), Betaseron (interferon beta-1b for subcutaneous injection), Extavia (interferon beta-1b for subcutaneous injection), Plegridy (peginterferon beta-1a for subcutaneous injection), Copaxone (glatiramer injection for subcutaneous use), Glatopa (glatiramer injection for subcutaneous use), Gilenya (fingolimod capsules), Aubagio (teriflunomide tablets), Tecfidera (dimethyl fumarate delayed-release capsules), Tysabri, (natalizumab injection for intravenous use) or Lemtrada (alemtuzumab injection for intravenous use); AND
 - iv.** Zinbryta is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist.
- B) Patients currently receiving therapy.** Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
- i.** The patient is ≥ 17 years of age; AND
 - ii.** The patient has a relapsing form of multiple sclerosis (MS) [relapsing forms of MS are relapsing-remitting MS {RRMS}, secondary-progressive MS {SPMS} with relapses, and progressive-relapsing MS {PRMS}]; AND

- iii. Zinbryta is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist.

Zinbryta is indicated for the treatment of patients with relapsing forms of MS. Due to its safety profile, Zinbryta should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS.¹ The safety and efficacy of Zinbryta in pediatric patients < 17 years of age have not been established. Many MS medications are available with established efficacy and a known safety profile. The criteria for patients currently receiving therapy do not have the requirement of two prior MS therapies to allow for continuation of therapy among patients who have started treatment with Zinbryta.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zinbryta 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. **Current Use of Zinbryta with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Zinbryta should not be given in combination with other disease-modifying agents used for MS (e.g., Avonex, Betaseron, Extavia, Rebif, Plegridy, Copaxone, Glatopa, Gilenya, Aubagio, Tecfidera, Tysabri or Lemtrada). Zinbryta is not indicated for use in combination with other MS disease-modifying therapies and the safety and efficacy have not been adequately established.¹
2. **Hepatic Disease, Hepatic Impairment or Autoimmune Hepatitis (Patients With).** Use of Zinbryta is contraindicated in patients with pre-existing hepatic disease or hepatic impairment, including ALT or AST at least two times the upper limit of normal (ULN), because Zinbryta may exacerbate existing liver dysfunction.¹ Also, Zinbryta is contraindicated in patients with a history of autoimmune hepatitis or other autoimmune condition involving the liver.
3. **Primary Progressive (Chronic Progressive) Multiple Sclerosis (MS).** The safety and efficacy of Zinbryta have not been studied in patients with primary progressive (chronic progressive) MS. Zinbryta is indicated in patients with relapsing forms of MS.¹
4. 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. Zinbryta™ injection for subcutaneous use [prescribing information]. Cambridge, MA and North Chicago, IL: Biogen and AbbVie; May 2016.
2. Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Eng J Med.* 2015;373:1418-1428. [supplementary appendix].
3. Gold R, Giovannoni G, Selmaj K, for the SELECT study investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomized, double-blind, placebo-controlled trial. *Lancet.* 2013;381:2167-2175.
4. Clinical bulletin. Information for health professionals. Overview of multiple sclerosis. Rosalind Kalb and Nancy Reitman. © 2012 National Multiple Sclerosis Society.
5. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. July 2014. Available at:

http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on June 1, 2016.

6. Avonex® injection [prescribing information]. Cambridge, MA: Biogen Idec; May 2016.
7. Rebif® injection [prescribing information]. Rockland, MA and New York, NY: EMD Serono and Pfizer; November 2015.
8. Betaseron® injection [prescribing information]. Whippany, NJ: Bayer; April 2016.
9. Extavia® injection [prescribing information]. East Hanover, NJ: Novartis; May 2016.
10. Plegridy™ injection [prescribing information]. Cambridge, MA: Biogen, Inc.; October 2015.
11. Copaxone® injection [prescribing information]. Kansas City, MO: Teva Neuroscience; January 2014.
12. Glatopa™ injection [prescribing information]. Princeton, NJ: Sandoz; January 2016.
13. McGraw CA, Lublin FD. Interferon beta and glatiramer acetate therapy. *Neurotherapeutics*. 2013;10:2-18.
14. Aubagio® tablets [prescribing information]. Cambridge, MA: Genzyme (a Sanofi Corporation); October 2014.
15. Gilenya® capsules [prescribing information]. East Hanover, NJ: Novartis; February 2016.
16. Tecfidera® delayed-release capsules [prescribing information]. Cambridge, MA: Biogen Idec; February 2016.
17. Tysabri® injection [prescribing information]. Cambridge, MA: Biogen Idec; May 2016.
18. Mitoxantrone injection [prescribing information]. Irvine, CA: Teva Parenteral Medicines, Inc.; May 2012.
19. Lemtrada™ injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme Corporation; November 2014.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
New Policy	Not applicable.	06/08/2016	07/12/2016

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