Drug Monograph

Drug/Drug Class:	**Zinbryta® (daclizumab) solution for injection/ Multiple Sclerosis Agents**
Prepared for:	MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Zinbryta® is available in a single-dose prefilled syringe containing 150 mg daclizumab per 1 ml. Manufacturer: Biogen Inc., Cambridge, MA 02142
Summary of Findings:	Zinbryta® demonstrated efficacy in the treatment of relapsing multiple sclerosis in 2 large randomized, double-blind clinical trials. It significantly decreased the annualized relapse rate compared with interferon beta 1-a in the 144-week DECIDE trial (22% vs 39%) and compared with placebo in the 52-week SELECT trial (21% vs 46%). Daclizumab also significantly reduced the mean number of new or newly enlarging T2 hyperintense lesions at week 96 in DECIDE (4.3 vs 9.4) and at week 52 in SELECT (2.4 vs 8.1). Confirmed disability progression was not significantly improved at 12 weeks compared with interferon beta-1a (16% vs 20%) but 3-month sustained disability progression was significantly improved at 52 weeks compared with placebo (6% vs 13%). In a post-hoc analysis of SELECT, a significantly greater proportion of daclizumab patients were free of disease activity at 1 year (36% vs 11%) compared with placebo.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Relapsing-remitting multiple sclerosis (RRMS) is characterized by clearly defined attack of new or increasing neurologic symptoms. These attacks, also called relapses or exacerbations, are followed by periods of partial or complete recovery (remissions). RRMS is the most common disease course. Approximately 85% of people with multiple sclerosis are initially diagnosed with RRMS.

Dosage Form(s) [1]

Zinbryta® is available in a single-dose prefilled syringe containing 150 mg daclizumab per 1 ml.

Manufacturer [1]

Biogen Inc., Cambridge, MA 02142

Indication(s) [1]

Zinbryta® is indicated for the treatment of relapsing form of multiple sclerosis in adult patients who have had an inadequate response to at least 2 previous therapies.

Clinical Efficacy [1,2,3,4] (mechanism of action/pharmacology, comparative efficacy)

Daclizumab is a humanized monoclonal antibody that binds to the interleukin-2 receptor. The exact mechanism of action in multiple sclerosis is unknown, but it is thought to modulate the interleukin-2-mediated activation of lymphocytes by binding to the CD25 subunit on the interleukin-2 receptor.

Pharmacokinetics:

	Zinbryta®
Metabolism	Undergoes catabolism to peptides and amino acids
Elimination Half-life	21 days
Volume of distribution	6.34 L

Daclizumab significantly reduced the annualized relapse rate compared with interferon beta-1a in patients with relapsing/remitting multiple sclerosis.

STUDY DESIGN	Randomized, double-blind, active-controlled, phase 3 clinical trial

	(n=1841)
INCLUSION CRITERIA	Adults with relapse/remitting multiple sclerosis
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	Patients were randomized to receive Zinbryta 150 mg subcutaneously every 4 weeks or interferon beta-1a 30 mcg IM once weekly for up to 144 weeks.
RESULTS	The annualized relapse rate was significantly lower with Zinbryta (22%) compared with interferon beta-1a (39%). The mean number of new or newly-enlarging T2 hyperintense lesions on MRI at week 96 was significantly lower in patients receiving Zinbryta (4.3) compared to those patients receiving interferon beta-1a (9.4). There was not a significant difference found in confirmed disability progression at 12 weeks between the Zinbryta (16%) and interferon beta-1a (20%) groups.
SAFETY	Zinbryta was associated with a higher incidence of infections (65% vs 57%) and cutaneous events (37% vs 19%) compared with interferon beta-1a.

Contraindications [(1)]

- History of autoimmune hepatitis or other autoimmune condition involving the liver
- History of hypersensitivity to daclizumab or product components
- Preexisting hepatic disease or hepatic impairment (eg. ALT or AST > 2 times ULN); may exacerbate existing liver dysfunction; screening for hepatitis B and C required prior to initiation.

Warnings and Precautions [(1)]

- Severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis with fatalities, may occur at any time during treatment and up to 4 months after the last dose; close monitoring recommended and treatment interruption or discontinuation may be required
- Immune-mediated disorders such as skin reactions, lymphadenopathy, and noninfectious colitis may occur and include concurrent or sequentially occurring disorders; monitoring recommended; consider discontinuation for serious reactions and referral to a specialist for evaluation and treatment.
- Concomitant use of hepatotoxic drugs, including nonprescription products, herbal products, or dietary supplements, may increase the risk for hepatic injury.
- Vaccination with live vaccines is not recommended during treatment and up to 4 months after discontinuation.
- Skin reactions such as rash, dermatitis, eczema, psoriatic conditions, and photosensitivity

have been reported at any time during therapy, including serious reactions with infectious complications and fatalities; evaluation and potential discontinuation recommended for serious diffuse or inflammatory rash.

- History of skin conditions, including eczema or psoriasis; may be exacerbated.
- Elevations in ALT, AST, and total bilirubin have been reported during treatment and up to 4 months after the last dose; monitoring recommended monthly before each dose and monthly for 6 months following the last dose; treatment interruption or discontinuation may be required; discontinue if autoimmune hepatitis is suspected.
- Lymphadenopathy and lymphadenitis have been reported, with serious associated events including infections, benign salivary neoplasm, skin reactions, thrombocytopenia, and interstitial lung changes; monitoring recommended; consider discontinuation for serious reactions and referral to a specialist for evaluation and treatment.
- Single organ or systemic multi-organ inflammatory reactions have been reported.
- Acute hypersensitivity, including anaphylaxis, angioedema, and urticaria, may occur after the first dose or at any time during treatment; discontinue and do not restart if any allergic reaction occurs.
- An increased risk for infections has been reported, including upper respiratory tract, urinary tract, and viral infections that may be serious; avoid initiation in patients with serious active infections until infection is fully controlled and withhold therapy until resolution if a serious infection develops.
- Depression-related events, including suicidal ideation or suicide attempt, have been reported; consider discontinuation if severe depression and/or suicidal ideation develops.
- History of previous or current depressive disorders; use with caution.
- TB has been reported in TB endemic countries; screen high-risk TB patients prior to initiation and if positive, treat TB prior to use.

Adverse Effects [(1)]

Most common, > 2 % more than comparator	Zinbryta® (n=202)	Interferon beta-1a (n=231)
Nasopharyngitis	25%	21%
Upper respiratory infection	17%	14%
Rash	11%	4%
Influenza	9%	6%
Dermatitis	9%	2%
Oropharyngeal pain	8%	4%
Bronchitis	7%	5%
Eczema	5%	2%
Lymphadenopathy	5%	<1%
Tonsillitis	4%	2%
Acne	3%	<1%

Drug Interactions [1]

- Hepatotoxic drugs

Dosage and Administration [1]

The FDA recommended dose is 150 mg injected subcutaneously once every month.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ MONTH
Daclizumab	Zinbryta	Abbvie	150 mg single dose prefilled syringe	150 mg every 4 weeks	$6,901.66 *
Interferon beta-1a	Avonex	Biogen Idec	30 mcg single dose prefilled syringe	30 mcg once weekly	$5,879.20 *
Peginterferon beta-1a	Plegridy	Biogen Idec	125 mcg single dose prefilled syringe	125 mcg every 14 days	$5,879.21*

*Maximum Allowable Cost

Conclusion

Zinbryta® is a humanized monoclonal antibody that is self-administered as a subcutaneous injection once monthly for the treatment of relapsing forms of multiple sclerosis. Zinbryta® is reserved for patients who have had an inadequate response to at least 2 prior therapies because of its safety profile. Due to the risk of severe hepatic injury and other immune-mediated disorders Zinbryta®, is available only through a Risk Evaluation and Mitigation Strategy program. Liver function must be closely monitored prior to therapy, monthly during therapy, and monthly for 6 months following discontinuation.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1. Product Information: Zinbryta™, daclizumab injection, Abbvie Inc, North Chicago, IL, 05/2016.
2. Kappos L, Wiendl H, Selmaj K et al: Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2015; 873(15): 1418-1428.
3. Gold R, Giovannoni G, Selmaj K et al: Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomized, double-blind, placebo-controlled trial. Lancet 2013; 381(9884):2167-2175

4. Havrdova E, Giovannoni G, Stefoski D et al: Disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with daclizumab high-yield process in the SELECT study. Mult Scler 2014; 20(4): 464-470.

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Date: November 22, 2016

