PDL DRUG REVIEW

Proprietary Name: Zinbryta®
Common Name: daclizumab
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Avonex	Preferred
Plegridy	Non-Preferred
Rebif	Preferred

Summary

Pharmacology: Daclizumab, the active ingredient of Zinbryta®, is a humanized monoclonal antibody that binds to the alpha sub-unit of the interleukin-2 receptor (IL-2Rα, CD25). While the exact mechanism of action for use in MS is not known, it is thought to involve modulation of IL-2 mediated activation of lymphocytes through binding to CD25, a subunit of the high-affinity IL-2 receptor.

Indications and Usage: For the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Due to its safety profile, the use of Zinbryta® should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

There are no adequate data on the developmental risk associated with use of Zinbryta® in pregnant women. Use in animal studies during gestation resulted in embryo-fetal death and reduced fetal growth at maternal exposures greater than 30 times that expected clinically. The safety and efficacy of use in children under the age of 17 years have not been established.

Dosage Forms: Injection, in a single-dose prefilled syringe as a sterile, preservative-free solution: 150mg/ml

Recommended Dosage: Inject 150mg SC QM, injecting into the thigh, abdomen, or back of the upper arm. Patients should be educated for self-administering SC injections. It is recommended that 30 minutes prior to injection to Zinbryta® be removed from the refrigerator to allow the drug to warm to room temperature.

Prior to starting treatment, it is recommended to obtain serum transaminases (ALT and AST) and total bilirubin levels. Levels should be obtained monthly and for 6 months after the last dose. Interruption or discontinuation of treatment is recommended for managing certain liver test abnormalities. Due to the risks of hepatic injury, including autoimmune hepatitis and other immune-mediated disorders, Zinbryta® is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Zinbryta® REMS Program. Prescribers, patients, and pharmacies must all enroll in this program.

It is also recommended to assess patients at high risk for TB infection prior to starting Zinbryta® treatment. Zinbryta® should be avoided in patients with TB or other severe active infection until the infection is fully controlled. Patients should also be screened for Hepatitis B and C prior to starting treatment. Last, it is recommended to consider any necessary immunizations with live vaccines prior to starting treatment with Zinbryta®.

Drug Interactions: It is recommended to use caution when using hepatotoxic drugs, including non-prescription products, concomitantly with Zinbryta®. In addition, carefully consider the need for herbal products or dietary supplements that can cause hepatotoxicity. The safety of immunization with live viral vaccines during treatment with Zinbryta® has not been studied. Vaccination with live vaccines is not recommended during treatment and up to 4 months after the discontinuation of Zinbryta®.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zinbryta®) minus reported % incidence for Avonex® 30mcg IM QW. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included nasopharyngitis (4%), upper respiratory tract infection (3%), rash (7%), influenza (3%), dermatitis (7%), oropharyngeal pain (4%), bronchitis (2%), eczema (3%), lymphadenopathy (>4%), tonsillitis (2%), seizures (0.7%), and acne (>2%). Skin reactions were also reported (8%). If a serious diffuse or inflammatory rash develops, it is recommended a dermatologist assess the patient before the next dose.

In controlled studies, 1 woman treated with Zinbryta® developed breast cancer as compared with none in the Avonex®-treated group. Across all controlled and open-label studies, 0.5% of Zinbryta®-treated women (N=8/1485) developed breast cancer and 0.1% of Zinbryta®-treated men (N=1/751) developed breast cancer. It is not clear if this represents an increase incidence over background rate.

Zinbryta® has a box warning regarding the increased risk of hepatic injury, including autoimmune hepatitis and other immune-mediated disorders. Zinbryta® can cause severe liver injury, including life-threatening events, liver failure and autoimmune hepatitis. It is therefore recommended to obtain serum transaminases (ALT and AST) and total bilirubin levels prior to starting treatment, and then monthly for 6 months after the last dose of Zinbryta®. In addition to autoimmune hepatitis, immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis can occur in patients can occur in patients treated with Zinbryta®. If a serious immune-mediated disorder develops, consider discontinuing treatment and refer the patient to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment. Furthermore, the box warning adds that some patients required systemic corticosteroids or other immunosuppressant treatment for autoimmune hepatitis or other immune-mediated disorders and continued this treatment after the last dose of Zinbryta®. The box warning ends by discussing that Zinbryta® is only available through a restricted program called the Zinbryta® REMS Program.

Depression-related events occurred more in clinical trials with Zinbryta®-treated patients (10%) than in patients with Avonex® (8%). It is recommended to use with caution in patients with previous or current depressive disorders.

Contraindications: Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the upper limit of normal (ULN); A history of autoimmune hepatitis or other autoimmune condition involving the liver; A history of hypersensitivity to daclizumab or any component of the formulation

Manufacturer: AbbVie

Analysis: The efficacy of Zinbryta® was assessed in two randomized, double-blind, controlled studies in patients with relapsing MS.

Study 1 (N=1841) was an active-controlled study that compared Zinbryta® with Avonex® in patients who had either ≥2 relapses during the prior 3 years and ≥1 relapse in the year prior to randomization OR who had ≥1 clinical relapses and ≥1 new T1 gadolinium (Gd)-enhancing or T2 hyperintense MRI lesions within the prior 2 years with ≥1 of these events in the prior 12 months. Patients were excluded if they had progressive forms of MS or an Expanded Disability Status Scale (EDSS) score >5. The primary outcome was the annualized relapse rate (ARR).

Results suggested that Zinbryta® had a statistically significant effect on the ARR and on the number of new or newly enlarging T2 hyperintense lesions as compared with Avonex; however, statistically significant effects on 12-week confirmed disability progression was not observed. The table below, adapted from the prescribing information, illustrates the results.

	Zinbryta®	Avonex® 30mcg	p-value
Clinical results			
Annualized Relapse Rate	0.216	0.393	
Relative Reduction	45%		<0.0001
Proportion Relapse Free	67%	51%	
Proportion w/12-week confirmed disability progression	16%	20%	0.16
MRI Results			
Mean number of new or newly enlarging T2 hyperintense lesions	4.31	9.44	
Relative reduction	54%		<0.0001

Study 2 (N=412) compared Zinbryta® with placebo in patients with relapsing MS who had experienced ≥1 relapse in the year prior to randomization or who had ≥1 T1 Gd-enhancing MRI lesions within 6 months of randomization. Treatment duration was 52 weeks. The primary outcome was the annualized relapse rate (ARR) at week 52. Results suggested that Zinbryta® had a statistically significant effect on the ARR, the proportion of patients relapse free, the number of new T1 Gd-enhancing lesions, and the number of new or newly enlarging T2 hyperintense lesions. The table below, adapted from the prescribing information, illustrates the results.

	Zinbryta® (N=208)	Placebo (N=204)	p-value
Clinical results			
Annualized Relapse Rate	0.211	0.458	
Relative Reduction	54%		<0.0001
Proportion Relapse Free	81%	64%	
Proportion w/12-week confirmed disability progression*	6%	13%	0.02
Relative risk reduction	57%		
MRI Results			
Mean number of new or newly enlarging T2 hyperintense lesions	2.4	8.1	
Relative reduction	70%		<0.0001
Mean number of new T1 Gd-enhancing lesion	1.46	4.79	
Relative reduction	69%		<0.0001

*An exploratory measure in this study

Place in Therapy: Zinbryta® is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Due to its safety profile, the use of Zinbryta® should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. Box warnings and contraindications do limit the use of Zinbryta® in certain populations. Furthermore, Zinbryta® is only available through a restricted program called the Zinbryta® REMS Program.

There is some evidence at this time to support that Zinbryta® is more effective than the currently available Avonex® in regards to the annualized relapse rate. Nevertheless, as it is indicated that use should generally be reserved for patients who have had an inadequate response to two or more drugs, it is recommended that Zinbryta® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on two or more preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Zinbryta [package insert]. North Chicago, IL: AbbVie Inc; 2016.