HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZINBRYTA™ safely and effectively. See full prescribing information for ZINBRYTA.

ZINBRYTA (daclizumab) injection, for subcutaneous use
Initial U.S. Approval: 2016

WARNING: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS
See full prescribing information for complete boxed warning.

Hepatic Injury Including Autoimmune Hepatitis
- **ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. Obtain transaminase and bilirubin levels before initiation of ZINBRYTA. Monitor and evaluate transaminase and bilirubin levels monthly and up to 6 months after the last dose (2 3, 2.4, 5 1).**
- **ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment (4, 5.1).**

Other Immune-Mediated Disorders
- **Immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur with ZINBRYTA (5.2).**

These conditions may require treatment with systemic corticosteroids or immunosuppressive medication (5 1, 5.2).

ZINBRYTA is available only through a restricted distribution program called the ZINBRYTA REMS Program (5.3).

INDICATIONS AND USAGE

ZINBRYTA is an interleukin-2 receptor blocking antibody indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of 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. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 150 milligrams once monthly (2.1)
- For subcutaneous use only (2.1)
- Train patients in the proper technique for self-administration (2.2)
- Conduct laboratory tests at baseline and at periodic intervals to monitor for early signs of potentially serious adverse reactions (2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/mL solution in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN (4)
- History of autoimmune hepatitis or other autoimmune condition involving the liver (4)
- History of hypersensitivity to daclizumab or any other component of the formulation (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Risk of anaphylaxis and angioedema. Discontinue and do not re-start ZINBRYTA if anaphylaxis or other allergic reactions occur (5.4)
- Infections: Increased risk of infections. If serious infection develops, consider withholding ZINBRYTA until infection resolves (5.5)
- Depression and Suicide: Advise patients to immediately report symptoms of depression and/or suicidal ideation to their health care provider. Consider discontinuation if severe depression and/or suicidal ideation occur (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and ≥2% higher incidence than comparator) reported for ZINBRYTA were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema and lymphadenopathy compared with AVONEX; and upper respiratory tract infection, depression, rash, pharyngitis, and increased alanine aminotransferase (ALT) compared with placebo (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Hepatotoxic Drugs: Evaluate potential for increased risk of hepatotoxicity with concomitant use (7.1)

See 17 **for PATIENT COUNSELING INFORMATION and Medication Guide**

Revised: 05/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS

- **Hepatic Injury Including Autoimmune Hepatitis**

  ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. In clinical trials, 1 patient died due to autoimmune hepatitis. Liver injury, including autoimmune hepatitis, can occur at any time during treatment with ZINBRYTA, with cases reported up to 4 months after the last dose of ZINBRYTA.

  ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

  Prior to starting ZINBRYTA, obtain serum transaminases (ALT and AST) and bilirubin levels *[see Dosage and Administration (2.3)]*.

  Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Follow transaminase levels and total bilirubin monthly for 6 months after the last dose of ZINBRYTA. In case of elevation in transaminases or total bilirubin, treatment interruption or discontinuation may be required *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]*.

- **Other Immune-Mediated Disorders**

  In addition to autoimmune hepatitis, immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis can occur in patients treated with ZINBRYTA. Overall, serious immune-mediated conditions were observed in 5% of patients treated with ZINBRYTA *[see Warnings and Precautions (5.2)]*.

- **If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment.**

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 *[see Warnings and Precautions (5.1, 5.2)]*.

Because of the risks of hepatic injury, including autoimmune hepatitis, and other immune-mediated disorders, ZINBRYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZINBRYTA REMS Program *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

ZINBRYTA is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dosage of ZINBRYTA is 150 milligrams injected subcutaneously once monthly *[see Dosage and Administration (2.3, 2.4)]*.

Instruct patients to inject a missed dose as soon as possible but no more than two weeks late. After two weeks, skip the missed dose and take the next dose on schedule. Administer only one dose at a time.

2.2 Important Administration Instructions

ZINBRYTA is for subcutaneous use only.

Train patients in the proper technique for self-administering subcutaneous injections using the prefilled syringe.

Thirty minutes prior to injection, remove ZINBRYTA from the refrigerator to allow the drug to warm to room temperature. Do not use external heat sources such as hot water to warm ZINBRYTA. Do not place ZINBRYTA back into the refrigerator after allowing it to warm to room temperature *[see How Supplied/Storage and Handling (16.2)]*.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZINBRYTA is a colorless to slightly yellow, clear to slightly opalescent solution. Do not use ZINBRYTA if it is cloudy or there are visible particles.

Sites for injection include the thigh, abdomen, and back of the upper arm.

Use each prefilled syringe one time and then place in a sharps disposal container for disposal according to community guidelines *[see How Supplied/Storage and Handling (16.3)]*.

2.3 Assessment Prior to Initiating ZINBRYTA

Hepatic Assessment

Prior to initiating ZINBRYTA, obtain and evaluate the following:

- Serum transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and total bilirubin levels. Initiation of ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment including ALT or AST at least 2 times the ULN *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Assessment for Tuberculosis and Other Infections

- Evaluate patients at high risk for tuberculosis infection prior to initiating treatment with ZINBRYTA *[see Warnings and Precautions (5.5)]*. For patients testing positive for tuberculosis, treat tuberculosis by standard medical practice prior to therapy with ZINBRYTA.
- Avoid initiating ZINBRYTA in patients with tuberculosis or other severe active infection *[see Warnings and Precautions (5.5)]*.
- Prior to initiation of ZINBRYTA, screen patients for Hepatitis B and C. ZINBRYTA is contraindicated in patients with pre-existing hepatic disease *[see Contraindications (4)]*.

Vaccinations

Because vaccination with live vaccines is not recommended during treatment and up to 4 months after discontinuation of treatment, consider any necessary immunization with live vaccines prior to treatment with ZINBRYTA *[see Warnings and Precautions (5.5)]*.

2.4 Laboratory Testing and Monitoring to Assess Safety after Initiating ZINBRYTA

Conduct the following laboratory tests at periodic intervals to monitor for early signs of potentially serious adverse effects:

Liver Tests

Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Follow transaminase levels and total bilirubin monthly for 6 months after the last dose of ZINBRYTA. As shown in Table 1, interruption or discontinuation of ZINBRYTA therapy is recommended for management of certain liver test abnormalities *[see Warnings and Precautions (5.1)]*.

Table 1: ZINBRYTA Treatment Modification for Liver Test Abnormalities

Elevated Transaminases and/or Total Bilirubin *[see Warnings and Precautions (5.1)]*	
Lab Value(s)	**Recommendations**
ALT or AST greater than 5 times ULN OR Total bilirubin greater than 2 times ULN OR ALT or AST greater than or equal to 3 but less than 5 times ULN and total bilirubin greater than 1.5 but less than 2 times ULN	• Interrupt ZINBRYTA therapy and investigate for other etiologies of abnormal lab value(s). • If no other etiologies are identified, then discontinue ZINBRYTA. • If other etiologies are identified, re-assess the overall risk-benefit profile of ZINBRYTA in the patient and consider whether to resume ZINBRYTA when both AST or ALT are less than 2 times ULN and total bilirubin is less than or equal to ULN.

In clinical trials, permanent discontinuation of therapy was required if the patient had liver test abnormalities resulting in suspension of study treatment for at least 8 consecutive weeks.

ULN = upper limit of normal

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/mL solution in a single-dose prefilled syringe.

ZINBRYTA is a sterile, preservative-free, colorless to slightly yellow, clear to slightly opalescent solution.

4 CONTRAINDICATIONS

ZINBRYTA is contraindicated in patients with:

- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN, because ZINBRYTA could exacerbate existing liver dysfunction *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- A history of autoimmune hepatitis or other autoimmune condition involving the liver *[see Warnings and Precautions (5.1)]*.
- A history of hypersensitivity to daclizumab or any other components of the formulation. Use in such patients may result in anaphylaxis or life-threatening multi-organ hypersensitivity *[see Warnings and Precautions (5.4)]*.

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