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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 autoinjector (3)
- 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: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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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)]*.

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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 autoinjector or 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 autoinjector or 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

<u>Hepatic Assessment</u>

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)]*.

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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)]*.

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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 autoinjector.

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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5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

ZINBRYTA can cause life-threatening severe liver injury, including liver failure and autoimmune hepatitis. In controlled studies, serious drug-related hepatic injury occurred in 0.7% of ZINBRYTA-treated patients compared with 0.4% of AVONEX-treated patients (Study 1) and in 1.0% of ZINBRYTA-treated patients compared with no injury in placebo patients (Study 2). Across all clinical studies (controlled and open-label), serious drug-related hepatic injury occurred in 1% of ZINBRYTA-treated patients, with monthly monitoring of transaminases and total bilirubin. The incidence of discontinuation due to drug related hepatic injury was 5% in ZINBRYTA-treated patients and 4% in AVONEX-treated patients.

Autoimmune Hepatitis

Across all clinical studies (controlled and open-label), 0.3% of ZINBRYTA-treated patients developed autoimmune hepatitis. One fatal case of autoimmune hepatitis occurred in a patient re-initiating ZINBRYTA after a planned 6 month treatment interruption period. This patient subsequently received two doses of ZINBRYTA in the presence of persisting alanine aminotransferase levels (ALT) more than 5 times the upper limit of normal (ULN).

Transaminase and Total Bilirubin Elevations

The incidence of increases in hepatic transaminases was greater in patients taking ZINBRYTA than in those taking AVONEX or placebo. The incidence of ALT or AST elevations above 5 times the ULN was 6% in ZINBRYTA-treated patients compared with 3% in AVONEX-treated patients (Study 1) and 4% in ZINBRYTA-treated patients compared with 1% in patients on placebo (Study 2). Less than 1% of ZINBRYTA-treated patients had ALT or AST greater than 20 times the ULN. Elevations of hepatic transaminases of at least 3 times the ULN combined with elevated bilirubin at least 2 times the ULN and alkaline phosphatase less than 2 times the ULN occurred in 0.7% of ZINBRYTA-treated patients compared with 0.1% of AVONEX-treated patients. In clinical trials, serum transaminase elevations occurred during treatment and up to 4 months after the last dose of ZINBRYTA.

Monitoring

Prior to starting treatment with ZINBRYTA, obtain serum transaminases (ALT and AST) and total bilirubin levels *[see Contraindications (4)]*.

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.

Treatment modifications are recommended based on serum transaminase and total bilirubin values *[see Dosage and Administration (2.4)]*.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with ZINBRYTA, as appropriate.

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Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes, such as infection, and a specialist should evaluate the patient *[see Dosage and Administration (2.4)]*. Discontinue ZINBRYTA if autoimmune hepatitis is suspected. Treatment of autoimmune hepatitis with systemic corticosteroids and other immunosuppressant drugs may be required. Some patients may need long-term immunosuppression.

Risk of Hepatic Injury with Concomitant Use of Other Hepatotoxic Drugs

Caution should be used when using hepatotoxic drugs, including non-prescription products, concomitantly with ZINBRYTA. Also, carefully consider the need for the use of herbal products or dietary supplements that can cause hepatotoxicity *[see Drug Interactions (7.1)]*.

5.2 Immune-Mediated Disorders

Treatment with ZINBRYTA increases the risk of immune-mediated disorders, including autoimmune disorders such as autoimmune hepatitis. Across all clinical studies (controlled and open-label), immune-mediated disorders occurred in 28% of patients on ZINBRYTA, the most common of which were skin reactions and lymphadenopathy. In the active-control study (Study 1), immune-mediated disorders were observed in 32% of ZINBRYTA-treated patients compared with 12% for AVONEX-treated patients. In Study 1, serious immune-mediated disorders were observed in 4% of patients treated with ZINBRYTA compared with less than 1% for AVONEX-treated patients. In the placebo-control study (Study 2), immune-mediated disorders were observed in 13% of ZINBRYTA-treated patients compared with 7% of placebo-treated patients. In Study 2, serious immune-mediated disorders were observed in 0.5% of ZINBRYTA-treated patients and in 0.5% of placebo-treated patients. In some cases, patients had concurrent or sequential occurring disorders while taking ZINBRYTA.

Some patients required invasive procedures for diagnosis (e.g., colonoscopy, liver biopsy, kidney biopsy, lung biopsy), hospitalization for fluid replacement or blood transfusion, or prolonged treatment with systemic corticosteroids or immunosuppressant drugs. Some of these events did not resolve after stopping ZINBRYTA during study follow-up.

Prescribers should be vigilant regarding emergent immune-mediated disorders. For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes. If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to an appropriate specialist for further evaluation and treatment.

Skin Reactions

ZINBRYTA causes skin reactions. In clinical trials, skin reactions occurred in 37% of ZINBRYTA-treated patients compared with 19% of AVONEX-treated patients (Study 1) and in 18% of ZINBRYTA-treated patients compared with 13% of patients on placebo (Study 2). Skin reactions occurred at any time during treatment with ZINBRYTA. Rashes occurred in 11% of ZINBRYTA-treated patients compared to 4% of AVONEX-treated patients, and in 7% of ZINBRYTA-treated patients compared to 3% of patients on placebo. Dermatitis occurred more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients or to patients

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on placebo, and eczema was observed more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients [*see Adverse Reactions (6.1*)]. Psoriatic conditions occurred in 2% of ZINBRYTA-treated patients compared with 0.3% of AVONEX-treated patients. Photosensitivity also occurred.

Serious skin reactions occurred in 2% of patients treated with ZINBRYTA compared with 0.1% of patients on AVONEX (Study 1) and in 1% of patients treated with ZINBRYTA compared with none treated with placebo (Study 2). One death resulted from infectious complications following a serious cutaneous reaction. In patients with a history of skin conditions, including eczema or psoriasis, use of ZINBRYTA may exacerbate those conditions. Treatment of skin reactions included treatment with topical or systemic steroids or immunosuppressant drugs, including tacrolimus. In clinical trials, discontinuation because of skin reactions was 4% in ZINBRYTA-treated patients. Rashes took a mean of 3 months to resolve, some were unresolved at the time of the last evaluation.

If a patient develops a serious diffuse or inflammatory rash, it is recommended that a dermatologist evaluate the patient before the next dose of ZINBRYTA. Discontinuation of ZINBRYTA may be appropriate.

Lymphadenopathy

ZINBRYTA increases the incidence of lymphadenopathy. In controlled studies, lymphadenopathy or lymphadenitis occurred in 6% of ZINBRYTA-treated patients compared with 1% of AVONEX-treated patients (Study 1) and in 2% of ZINBRYTA-treated patients compared with 1% of placebo-treated patients (Study 2). Onset of lymphadenopathy or lymphadenitis occurred throughout the treatment period. Serious events related to lymphadenopathy or lymphadenitis included infections, benign salivary neoplasm, skin reactions, thrombocytopenia, and interstitial lung changes *[see Warnings and Precautions (5.5)]*. The majority of cases resolved with or without continued treatment with ZINBRYTA and took a mean of 3 months to resolve. Lymphadenopathy resulted in discontinuation in 0.6 % of ZINBRYTA-treated patients.

Some patients with lymphadenopathy underwent diagnostic biopsy. In the event that lymph node biopsy is considered, full diagnostic evaluation should be conducted by a specialist.

Non-Infectious Colitis

An increased incidence of serious colitis (less than 1%) was reported in patients treated with ZINBRYTA compared with none for patients treated with AVONEX or placebo in clinical trials. Consider referring patients who develop symptoms of colitis (e.g., abdominal pain, fever, prolonged diarrhea) to a specialist.

Other immune-mediated disorders

A wide variety of other immune-mediated disorders, some serious, have occurred infrequently with the use of ZINBRYTA. These include single organ or systemic multi-organ inflammatory reactions. Many events occurred in only one patient, and the relationship to ZINBRYTA is unknown *[see Adverse Reactions (6.1)]*. Some required treatment with systemic corticosteroids. Some required several months for resolution after the last dose of ZINBRYTA.

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For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes. If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to an appropriate specialist for further evaluation and treatment.

5.3 ZINBRYTA REMS Program

ZINBRYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZINBRYTA REMS Program, because of the risks of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the ZINBRYTA REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Patients must enroll in the program and comply with ongoing monitoring requirements *[see Warnings and Precautions (5.1, 5.2)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive ZINBRYTA.

Further information, including a list of qualified pharmacies/distributors, is available at 1-800--456-2255

5.4 Acute Hypersensitivity

ZINBRYTA can cause anaphylaxis, angioedema, and urticaria after the first dose or at any time during treatment. Discontinue and do not re-start ZINBRYTA if anaphylaxis or other allergic reactions occur *[see Contraindications (4)]*.

5.5 Infections

ZINBRYTA increases the risk for infections. In controlled trials, infections occurred in 65% of ZINBRYTA-treated patients compared with 57% of AVONEX-treated patients (Study 1) and in 50% of ZINBRYTA-treated patients compared with 44% of patients taking placebo (Study 2). Serious infections occurred in 4% of ZINBRYTA-treated patients compared with 2% of AVONEX-treated patients (Study 1) and in 3% of ZINBRYTA-treated patients compared with none on placebo (Study 2).

The most common types of infections observed were upper respiratory tract infections, urinary tract infections and viral infections.

In clinical trials, cases of tuberculosis occurred in countries where tuberculosis is endemic. Evaluate high-risk patients for tuberculosis infection prior to initiating treatment with ZINBRYTA. For patients testing positive for tuberculosis, treat by standard medical practice prior to therapy with ZINBRYTA *[see Dosage and Administration (2.3)]*.

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Avoid initiating ZINBRYTA in patients with severe active infection until the infection is fully controlled. If serious infection develops, consider withholding treatment with ZINBRYTA until the infection resolves.

Vaccinations

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 discontinuation of ZINBRYTA *[see Dosage and Administration (2.3)]*.

5.6 Depression and Suicide

Depression-related events occurred more frequently in patients receiving ZINBRYTA than in patients receiving AVONEX or placebo. In controlled trials, depression-related events occurred in 10% of ZINBRYTA-treated patients compared with 8% of AVONEX-treated patients (Study 1) and in 7% of ZINBRYTA-treated patients compared with 2% of patients taking placebo (Study 2). In Study 1, serious events related to depression, including suicidal ideation or suicide attempt, occurred in 0.4% of ZINBRYTA-treated patients and in 0.7% of AVONEX-treated patients. None occurred in Study 2 (placebo-controlled).

Administer ZINBRYTA with caution to patients with previous or current depressive disorders. Advise patients and/or caregivers to immediately report any symptoms of new or worsening depression and/or suicidal ideation to their healthcare provider.

If a patient develops severe depression and/or suicidal ideation, consider discontinuation of ZINBRYTA.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Disorders *[see Warnings and Precautions (5.2)]*
- Acute Hypersensitivity *[see Warnings and Precautions (5.4)]*
- Infections *[see Warnings and Precautions (5.5)]*
- Depression and Suicide [*see Warnings and Precautions (*5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ZINBRYTA cannot be directly compared with rates in clinical trials of other drugs and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials performed in patients with relapsing multiple sclerosis, 2236 patients received ZINBRYTA for a total of 5214 person-years. Of these patients, 1576 received ZINBRYTA for at least 1 year, 1259 for at least 2 years, and 888 for at least 3 years. In

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the controlled studies, approximately 67% were female, 92% were Caucasian, and the mean age was 36 years at study entry.

In the active-controlled study (Study 1), 919 patients received ZINBRYTA (150 mg SQ, every 4 weeks) and 922 patients received AVONEX (interferon beta-1a 30 mcg IM, weekly) for a minimum of 2 years and up to 3 years, with 1952 person-years of exposure to ZINBRYTA; the median length of treatment was approximately 27 months. The adverse reactions from Study 1 are presented in Table 2.

In the placebo-controlled study (Study 2), 417 patients received ZINBRYTA with 423 person-years of exposure, of which 208 received 150 mg, and 204 received placebo every 4 weeks for up to 1 year; the median length of treatment was approximately 11 months. The adverse reactions from Study 2 are presented in Table 3.

The most common adverse reactions (incidence at least 5% and at least 2% higher incidence than comparator) that occurred in ZINBRYTA-treated patients 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.

The most common adverse reactions leading to discontinuation in up to 5% of patients treated with ZINBRYTA were hepatic events including elevations of serum transaminases and cutaneous events.

Patients were excluded from the clinical studies for abnormal laboratory values including hemoglobin, complete blood count with differential, serum transaminases, or serum creatinine. Patients were excluded if they had a history of seizure disorder or of having a seizure within 6 months of beginning the study, or suicidal ideation or severe depression within 3 months of beginning the study. During Study 1, concomitant use of ZINBRYTA with the hepatotoxic drugs valproic acid, carbamazepine, lamotrigine, phenytoin, isoniazid, and propylthiouracil was not permitted except in patients already receiving the drugs at the time of study entry.

In clinical studies, serum chemistry was evaluated at baseline and monthly. Hematology was evaluated at baseline, monthly for 6 months, and then every 3 months. Thyroid function was measured at baseline and every 6 months.

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Table 2: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than AVONEX 30 mcg IM Once Weekly (Study 1)

Adverse Reaction	ZINBRYTA 150 mg SQ Every 4 Weeks N=919 %	AVONEX 30 mcg IM Once Weekly N=922 %
Nasopharyngitis	25	21
Upper respiratory tract infection [1]	17	14
Rash[2]	11	4
Influenza	9	6
Dermatitis [3]	9	2
Oropharyngeal pain	8	4
Bronchitis	7	5
Eczema [4]	5	2
Lymphadenopathy	5	<1
Tonsillitis	4	2
Acne	3	<1

[1] includes upper respiratory tract infection and viral upper respiratory tract infection
[2] includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
[3] includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis
[4] includes dyshidrotic eczema, eczema, and nummular eczema

Table 3: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than Placebo (Study 2)

Adverse Reaction	ZINBRYTA 150 mg SQ Every 4 Weeks N=208 %	Placebo N=204 %
Upper respiratory tract infection	9	7
Depression[1]	7	2
Rash[2]	7	3
Pharyngitis	6	4
Increased ALT	5	2
Rhinitis	4	1
Anemia	3	<1
Pyrexia	3	<1
Increased AST	3	<1
Dermatitis [3]	3	<1

[1] includes depressed mood and depression
[2] includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
[3] includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis

Other clinically relevant adverse reactions observed at <2% difference included abnormal liver function test, decreased lymphocyte count, diarrhea, dry skin, erythema, folliculitis, increased

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hepatic enzyme, laryngitis, lymphadenitis, pneumonia, pruritus, psoriasis, respiratory tract infection, skin exfoliation, toxic skin eruption, and viral infection.

Seizures

In Study 1, seizures occurred in 1% of ZINBRYTA-treated patients, compared with 0.3% of AVONEX-treated patients. In Study 2, no seizures occurred in either treatment group.

Immune-mediated disorders

Types of immune-mediated or autoimmune conditions that were observed in 2 or more ZINBRYTA-treated patients include type I diabetes, celiac disease, autoimmune thyroiditis, immune hemolytic anemia, thrombocytopenia, pancreatitis, glomerulonephritis, sarcoidosis, rheumatoid arthritis, thyroiditis, and sialadenitis [*see Warnings and Precautions (5.2)]*. The relationship of these events to ZINBRYTA is unknown.

Breast Cancer

In controlled studies, 1 ZINBRYTA-treated woman developed breast cancer compared with none in the AVONEX-treated group. Across all controlled and open-label clinical studies, 8 of 1485 (0.5%) ZINBRYTA-treated women developed breast cancer, and 1 of 751 (0.1%) ZINBRYTA-treated men developed breast cancer. It is unclear whether this represents an incidence increase over background rate.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In Study 1, patients were tested for anti-drug (daclizumab) antibodies at Week 4 and approximately every 3 months thereafter. Anti-drug antibodies and neutralizing antibodies were observed in 19% (175/913) and 8% (71/913) of patients, respectively. Anti-drug antibody responses were transient in 12% (110/913) of patients and persistent in 7% (65/913) of patients. Anti-drug and neutralizing antibody responses predominantly occurred during the first year of treatment, and their frequency declined with continued ZINBRYTA treatment.

In patients with neutralizing antibodies, daclizumab clearance was increased on average by 19% *[see Clinical Pharmacology (12.3)]*. There was no apparent correlation of anti-drug antibody or neutralizing antibody development to clinical response, adverse reactions, or pharmacodynamic profile of ZINBRYTA.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to daclizumab with the incidence of antibodies to other products may be misleading.

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7 DRUG INTERACTIONS

7.1 Hepatotoxic Drugs

Caution should be used when using hepatotoxic drugs, including non-prescription products, concomitantly with ZINBRYTA. Carefully consider the need for the use of herbal products or dietary supplements that can cause hepatotoxicity [*see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with use of ZINBRYTA in pregnant women.

Administration of ZINBRYTA to monkeys during gestation resulted in embryofetal death and reduced fetal growth at maternal exposures greater than 30 times that expected clinically *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

In monkeys administered ZINBRYTA (0, 10, 50, or 200 mg/kg) weekly by subcutaneous injection during organogenesis (gestation days 20 through 50), there was a decrease in fetal body weight and crown-rump length, and an increase in embryofetal death at the highest dose tested. Plasma exposure (AUC) at the no-effect dose of 50 mg/kg was approximately 30 times that in humans at the recommended human dose (RHD) of 150 mg.

In monkeys administered ZINBRYTA (50 mg/kg) weekly by subcutaneous injection from gestation day 50 to birth, there were no effects on pre- or postnatal development for up to 6 months after birth. Plasma exposure (AUC) at the administered dose was 55 times that in humans at the RHD.

8.2 Lactation

Risk Summary

There are no data on the presence of daclizumab in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Daclizumab was excreted in the milk of ZINBRYTA-treated monkeys.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZINBRYTA and any potential adverse effects on the breastfed child from ZINBRYTA or from the underlying maternal condition.

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8.4 Pediatric Use

Safety and effectiveness of ZINBRYTA in patients less than 17 years old have not been established. Use of ZINBRYTA is not recommended in pediatric patients due to the risks of hepatic injury and immune-mediated disorders *[see Warnings and Precautions (5.1, 5.2)]*.

8.5 Geriatric Use

Clinical studies of ZINBRYTA did not include a sufficient number of patients aged 65 and over to determine whether they respond differently than younger patients.

8.6 Hepatic Impairment

Clinical trials did not include patients with ALT or AST more than two times the ULN. Patients with signs and symptoms of hepatic impairment may be at increased risk for hepatotoxicity from ZINBRYTA *[see Dosage and Administration (2.3, 2.4), Contraindications (4), and Warnings and Precautions (5.1)]*.

11 DESCRIPTION

Daclizumab is a humanized monoclonal antibody that binds to the alpha subunit of the interleukin-2 receptor (IL-2Rα, CD25). Daclizumab is composed of two humanized gamma-1 heavy chains and two humanized kappa light chains and has a molecular weight of approximately 144 kilodaltons (kDa).

ZINBRYTA injection is supplied as a sterile, preservative-free, colorless to slightly yellow, clear to slightly opalescent solution for subcutaneous use in a single-dose prefilled autoinjector and syringe. Each 1 mL prefilled autoinjector and syringe contains 150 mg daclizumab; polysorbate 80, USP (0.3 mg); sodium chloride (5.84 mg); sodium succinate, anhydrous (5.94 mg); succinic acid (0.35 mg); and Water for Injection, USP. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which daclizumab exerts therapeutic effects in multiple sclerosis is unknown but is presumed to involve modulation of IL-2 mediated activation of lymphocytes through binding to CD25, a subunit of the high-affinity IL-2 receptor.

12.2 Pharmacodynamics

During ZINBRYTA treatment, mean cell counts for the major immune subsets (T, B, and NK cells) remained within normal ranges. Total lymphocyte, T and B cell counts decreased less than 10% from baseline during the first year of treatment. Total lymphocyte counts returned to baseline levels approximately 8-12 weeks after the last dose of ZINBRYTA (150 mg).

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12.3 Pharmacokinetics

The pharmacokinetics of ZINBRYTA are similar for healthy volunteers and patients with multiple sclerosis (MS).

Absorption

Following a single subcutaneous injection of ZINBRYTA, the maximum concentration occurred between 5 and 7 days. At steady state, daclizumab mean maximum serum concentration (Cmax) was 30 µg/mL, minimum serum concentration (Cmin) was 15 µg/mL, and area under the serum concentration-time curve over the dosing interval (AUCtau) values were approximately 640 µg-days per mL. The absolute bioavailability of 150 mg subcutaneous daclizumab was approximately 90%.

After administration of ZINBRYTA 150 mg subcutaneously every 4 weeks, serum daclizumab concentrations reached steady state by the fourth dose. Daclizumab accumulated to a level approximately 2.5-fold compared with a single dose.

The coefficient of variation between individual patients was approximately 35-40% for exposure (Cmax and AUC) and 27-51% for clearance and volume of distribution.

Distribution

In multiple sclerosis patients taking 150 mg subcutaneous doses of ZINBRYTA every 4 weeks, the estimated steady-state volume of distribution of daclizumab was approximately 6.34 liters.

Metabolism and Elimination

Because it is a protein, daclizumab is expected to undergo catabolism to peptides and amino acids in the same manner as endogenous IgG proteins without renal elimination. The estimated clearance of daclizumab is 0.212 liters per day with an elimination half-life of 21 days. Daclizumab clearance in patients who developed neutralizing antibodies was 19% higher *[see Adverse Reactions (6.2)]*.

Specific Populations

Clinical studies did not identify significant differences in pharmacokinetic parameters between Japanese and Caucasian healthy volunteers. Covariate analyses did not identify significant differences in pharmacokinetic parameters based on gender, age, or weight for patients with relapsing forms of multiple sclerosis.

Drug Interaction Studies

ZINBRYTA 150 mg administered subcutaneously every 4 weeks for 12 weeks in patients with multiple sclerosis did not significantly affect the systemic exposure of concomitantly administered oral midazolam (CYP3A substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), omeprazole (CYP2C19 substrate), or caffeine (CYP1A2 substrate).

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of ZINBRYTA has not been assessed.

Mutagenesis

Genetic toxicology studies of ZINBRYTA have not been conducted.

Impairment of Fertility

ZINBRYTA (0, 10, 50, or 200 mg/kg) administered biweekly by subcutaneous injection to monkeys had no adverse effect on male (sperm motility, concentration, and morphology or testosterone levels) or female (estrus cycle length or estradiol/progesterone patterns) fertility endpoints. At the highest dose tested, plasma exposures (AUC) in males and females were 100 and 85 times, respectively, that at the recommended human dose (RHD) of 150 mg.

13.2 Animal Toxicology and/or Pharmacology

There was a dose-dependent increase in microglial aggregates in the brain and spinal cord of monkeys at subcutaneous doses greater than 10 mg/kg administered biweekly for up to 39 weeks. Microglial aggregates were, in some animals, associated with microhemorrhage; however, no evidence of neuronal injury was observed. There was evidence of reversibility by 12 weeks after the last dose.

14 CLINICAL STUDIES

The efficacy of ZINBRYTA was demonstrated in two randomized, double-blind, controlled studies (Study 1 and Study 2). Both studies evaluated 150 mg of subcutaneous ZINBRYTA taken once every four weeks in patients with relapsing multiple sclerosis (RMS).

Study 1: Active-Controlled Trial in RMS

Study 1 compared ZINBRYTA to 30 mcg weekly intramuscular doses of AVONEX in 1841 patients. The study included RMS patients who had either: 1) at least 2 relapses during the prior 3 years and at least one relapse in the year prior to randomization; or 2) one or more clinical relapses and one or more new T1 gadolinium (Gd)-enhancing or T2 hyperintense MRI lesions within the prior 2 years with at least one of these events in the prior 12 months. Patients with progressive forms of multiple sclerosis or an Expanded Disability Status Scale (EDSS) score greater than 5 were excluded. Treatment continued for up to 144 weeks until the last enrolled patient completed 96 weeks of treatment. Clinical assessments were to occur every 12 weeks and after relapse events. MRI scans were performed at Week 24 and Week 96.

The primary outcome measure of Study 1 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients relapsed, the proportion of patients who experienced confirmed disability progression, and the number of new or newly enlarging T2 hyperintense lesions. Confirmed disability progression was defined as at least a 1 point increase

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from baseline EDSS (1.5 point increase for patients with baseline EDSS of 0) sustained for 12 weeks.

In Study 1, randomization assigned 919 patients to ZINBRYTA and 922 patients to AVONEX; 71% of ZINBRYTA- and 70% of AVONEX-treated patients completed at least 96 weeks of treatment with the assigned drug. At baseline, the mean age of patients was 36 years, the mean disease duration since diagnosis was 4.2 years, the mean EDSS score was 2.5, and the mean number of relapses in the prior year was 1.6. At baseline, 68% of patients were female, 46% of patients had MRI scans with T1 Gd-enhancing lesions and 41% of patients had previously taken one or more non-steroid treatments for MS.

ZINBRYTA had a statistically significant effect on the annualized relapse rate and on the number of new or newly enlarging T2 hyperintense lesions. There was no statistically significant effect on 12-week confirmed disability progression.

Results for Study 1 are shown in Table 4 and Figure 1, below.

Table 4: Clinical and MRI Results of Study 1

	ZINBRYTA 150 mg SQ Every 4 Weeks N=919	**AVONEX 30 mcg IM Once Weekly N=922**	**p-value**
Clinical Results[1]			
Annualized relapse rate Relative reduction Proportion Relapse Free	0.216 45% 67%	0.393 51%	<0.0001
Proportion with 12-week confirmed disability progression	16%	20%	0.16
MRI Results[2]			
Mean number of new or newly enlarging T2 hyperintense lesions Relative reduction	4.31 54%	9.44	<0.0001

[1]Values refer to results up to144 weeks
[2] MRI analysis used evaluable dataset and values reflect results at 96 weeks

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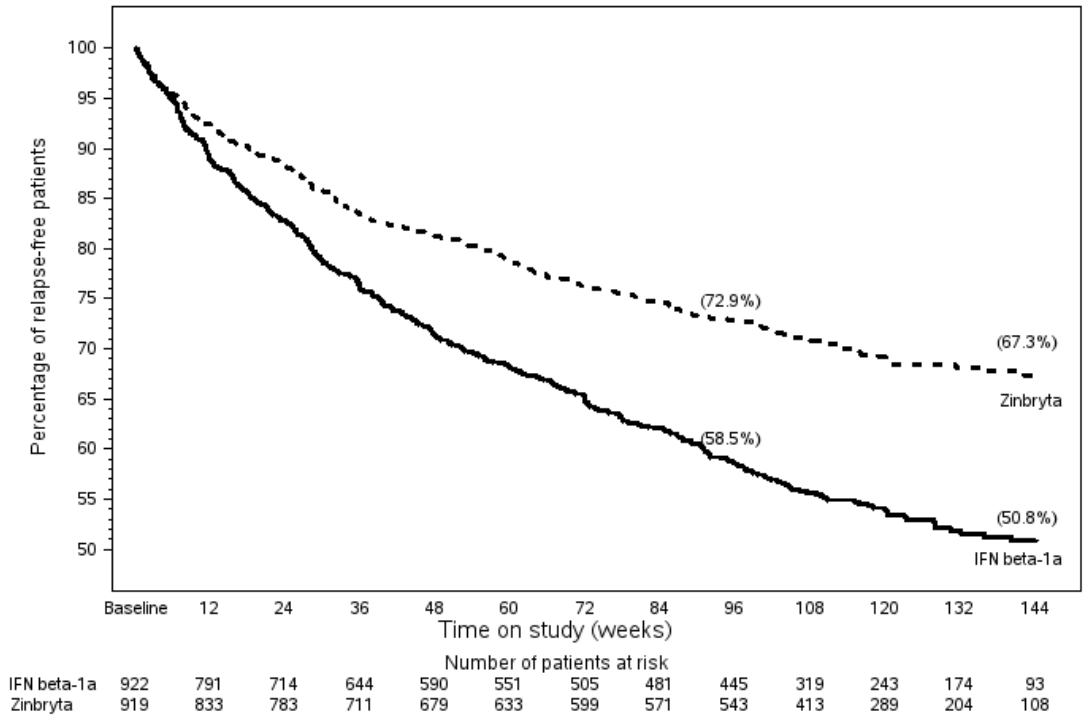
Figure 1: Study 1 Percentage of Relapse-Free Patients



In a subgroup analysis of Study 1, a reduction was observed compared with AVONEX on annualized relapse rate across patient subgroups (based on gender, age, prior multiple sclerosis disease modifying therapy, and disease activity levels).

Study 2: Placebo-Controlled Trial in RMS

Study 2 compared ZINBRYTA to placebo in 412 patients. The study included RMS patients who had experienced at least one relapse in the year prior to randomization or who had one or more T1 Gd-enhancing MRI lesions within 6 weeks of randomization. Patients with progressive forms of multiple sclerosis or an EDSS score greater than 5 were excluded. Treatment duration was 52 weeks. Clinical assessments were to occur every 12 weeks and after relapse events. MRI scans were performed at weeks 24, 36, and 52 in all patients and every 4 weeks in a subset of patients.

The primary outcome measure of Study 2 was the annualized relapse rate (ARR) at Week 52. Additional outcome measures included new T1 Gd-enhancing lesions between Week 8 and Week 24, the proportion of patients relapsed, the proportion of patients who experienced 12-week confirmed disability progression (as defined in Study 1) and the number of new or newly enlarging T2 hyperintense lesions.

In Study 2, randomization assigned 208 patients to receive ZINBRYTA (150 mg) and 204 patients to receive placebo; 91% of ZINBRYTA patients and 91% of placebo patients completed treatment. At baseline, the mean age of patients was 36 years, the mean disease duration since

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diagnosis was 4.3 years, the mean EDSS score was 2.8, and the mean number of relapses in the prior year was 1.4. At baseline, 65% of patients were female, 48% of patients had MRI scans with T1 Gd-enhancing lesions and 21% of patients had previously taken one or more non-steroid treatments for MS.

ZINBRYTA had a statistically significant effect on the annualized relapse rate, 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 results for Study 2 are shown in Table 5.

Table 5: Clinical and MRI Results of Study 2

	ZINBRYTA 150 mg SQ Every 4 Weeks N=208	**Placebo N=204**	**p-value**
Clinical Results[1]			
Annualized relapse rate	0.211	0.458	
Relative reduction	54%		<0.0001
Proportion Relapse Free	81%	64%	
Proportion with 12-week confirmed disability progression[3]	6%	13%	
Relative risk reduction	57%		
MRI Results[2]			
Mean number of new or newly enlarging T2 hyperintense lesions[1]	2.4	8.1	
Relative reduction	70%		<0.0001
Mean number of new T1 Gd-enhancing lesions	1.46	4.79	
Relative reduction	69%		<0.0001

[1] Values refer to results at 52 weeks
[2] MRI analyses used evaluable dataset for each endpoint; T1 Gd-enhancing: MRI intensive population, between 8-24 weeks
[3] The proportion of patients with 12-week confirmed disability progression was an exploratory measure in Study 2. As the proportion of patients with 12-week confirmed disability was used as a key secondary outcome in Study 1, and is one of the main outcome measures in MS studies, the disability progression results are presented for Study 2. The nominal p value for that comparison, p=0.02, is not adjusted for multiple comparisons.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZINBRYTA injection is a sterile, colorless to slightly yellow, clear to slightly opalescent solution for subcutaneous injection. ZINBRYTA is provided in a 29 gauge, 0.5 inch staked (pre-affixed) needle syringe with a rubber plunger stopper and rigid needle shield that are not made with natural rubber latex.

Two presentations are provided for ZINBRYTA injection, a single-dose prefilled autoinjector and a single-dose prefilled syringe.

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ZINBRYTA PEN Single-Dose Prefilled Autoinjector

The ZINBRYTA PEN is available in a carton containing a single-dose prefilled disposable autoinjector, which contains a syringe providing 1 mL of 150 mg/mL of daclizumab. The NDC is 0074-0034-01.

ZINBRYTA Single-Dose Prefilled Syringe

The ZINBRYTA prefilled syringe is available in a carton containing a single-dose prefilled disposable syringe providing 1 mL of 150 mg/mL of daclizumab. The NDC is 0074-0033-01.

16.2 Storage and Handling

Store in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or expose to temperatures above 30°C (86°F). Discard if frozen.

If refrigeration is unavailable, ZINBRYTA may be stored protected from light up to 30°C (86°F) for a period up to 30 days. Do not place ZINBRYTA back into the refrigerator after allowing it to warm to room temperature. Discard after 30 days without refrigeration.

16.3 Instructions for Disposal

Dispose in a sharps container or other hard plastic or metal sealable container. Always follow local regulations for disposal.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hepatic Injury

Inform the patient of the risk of severe hepatic injury associated with ZINBRYTA. Advise patients of the symptoms of hepatic dysfunction, and instruct patients to report such symptoms to their health care provider immediately *[see Warnings and Precautions (5.1)]*.

Discuss with the patient the importance of measuring hepatic laboratory values and having them evaluated by the health care provider monthly while taking ZINBRYTA and for up to 6 months after the last dose of ZINBRYTA.

Discuss with the patient the risk of concomitant use of other hepatotoxic medications, over the counter medications, herbal products, or dietary supplements.

Inform the patient that they will be given a ZINBRYTA Patient Wallet Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Advise the patient to show the ZINBRYTA Patient Wallet Card to other treating health care providers.

Immune-Mediated Disorders

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Advise patients that ZINBRYTA can cause their immune system to attack healthy cells in their body and that this can affect any organ system.

Skin Reactions
Advise patients that ZINBRYTA can cause dermatologic reactions that can range from mild rashes to serious reactions that could require treatment with other medications or result in hospitalization. Instruct patients to seek immediate medical attention if dermatologic reactions occur *[see Warnings and Precautions (5.2)]*.

Lymphadenopathy
Inform patients that ZINBRYTA may cause lymphadenopathy that can range from mild events that can resolve on their own to serious lymphadenopathy that may require invasive procedures for diagnosis. Inform patients of the symptoms and instruct patients to contact their health care provider if they develop lymphadenopathy *[see Warnings and Precautions (5.2)]*.

Non-Infectious Colitis
Inform patients that ZINBRYTA may cause gastrointestinal reactions that may be serious and could require treatment. Advise patients of the symptoms of colitis and instruct patients to promptly contact their healthcare provider if they experience these symptoms *[see Warnings and Precautions (5.2)]*.

ZINBRYTA REMS Program

ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program *[see Warnings and Precautions (5.3)]*. Inform the patient of the following notable requirements:

- Patients must enroll in the program and comply with ongoing monitoring requirements *[see Warnings and Precautions (5.1, 5.2)]*.

ZINBRYTA is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Allergic Reactions and Anaphylaxis
Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur *[see Warnings and Precautions (5.4)]*.

Risk of Infections
Inform patients that they may be more likely to get infections when taking ZINBRYTA, and that they should contact their health care provider if they develop symptoms of infection *[see Warnings and Precautions (*5.5*)]*.

Depression and Suicide
Advise patients of the symptoms of depression and suicidal ideation as they have occurred with the use of ZINBRYTA and instruct patients to report symptoms of depression or thoughts of suicide to their health care provider immediately *[see Warnings and Precautions (5.6)]*.

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Instructions for Self-Injection Technique and Procedures

Provide appropriate instruction for methods of self-injection, including careful review of the ZINBRYTA Instructions for Use. Instruct the patient in the use of aseptic technique when administering ZINBRYTA.

Inform the patient that a health care provider should show them or their caregiver how to inject ZINBRYTA before administering the first dose. Tell the patient not to re-use needles, pens or syringes, and instruct the patient on safe disposal procedures. Inform the patient to dispose of used needles, pens and syringes in a puncture-resistant container.

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North Chicago, IL 60064

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Medication Guide
ZINBRYTA® (zin-bry-tuh)
(daclizumab)
injection, for subcutaneous use

What is the most important information I should know about ZINBRYTA?
ZINBRYTA can cause serious side effects, including:

- **Liver problems**. ZINBRYTA may cause serious liver problems (including autoimmune-related liver problems) that may lead to death. Your healthcare provider should do blood tests to check your liver before you start using ZINBRYTA, every month while you are using ZINBRYTA, and monthly for 6 months after you stop using ZINBRYTA. Your healthcare provider should check your test results before your next dose.
  Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - nausea or vomiting
  - stomach pain
  - unusual tiredness
  - not wanting to eat
  - yellowing of the skin or whites of your eyes
  - dark urine
- **Immune system problems.** Some people using ZINBRYTA develop immune-mediated disorders (a condition where the body's immune system attacks healthy cells in their body) and other immune system problems.
  Call your healthcare provider right away if you have any of the following symptoms:
  - skin reactions such as rash or skin irritation
  - tender, painful, or swollen lymph nodes
  - intestinal problems (colitis). Symptoms can include fever, stomach pain, blood in your stools, or diarrhea that does not go away
  - any new and unexplained symptoms affecting any part of your body

Because of the risk of serious liver problems (including autoimmune-related liver problems) and other immune system problems, ZINBRYTA is only available through a restricted program called the ZINBRYTA Risk Evaluation and Mitigation (REMS) Program.

- Before you begin using ZINBRYTA, you must enroll in the ZINBRYTA REMS Program. Talk to your healthcare provider about how to enroll in the ZINBRYTA REMS Program.
- ZINBRYTA can only be given at a certified pharmacy that participates in the ZINBRYTA REMS Program. Your healthcare provider can give you information on how to find a certified pharmacy.
- Your healthcare provider or pharmacist will give you a ZINBRYTA Patient Wallet Card along with this Medication Guide. It has important information about ZINBRYTA and should be carried with you at all times. Show the ZINBRYTA Patient Wallet Card to all of your healthcare providers so that they know you are being treated with ZINBRYTA.

What is ZINBRYTA?
ZINBRYTA is a prescription medicine used to treat adults with relapsing forms of multiple sclerosis (MS). Because of its risks, ZINBRYTA is generally used in people who have tried 2 or more MS medicines that have not worked well enough**.**
It is not known if ZINBRYTA is safe and effective for use in children under 18 years of age.

Do not use ZINBRYTA if you:

- have liver problems
- have or have had autoimmune-related liver problems including autoimmune hepatitis
- are allergic to daclizumab or any of the other ingredients in ZINBRYTA. See the end of this Medication Guide for a complete list of ingredients in ZINBRYTA.

Before using ZINBRYTA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had liver problems
- have or have had skin problems including eczema or psoriasis
- have tuberculosis
- have an active infection
- are planning to receive a vaccine
- have or have had depression
- are pregnant or plan to become pregnant. It is not known if ZINBRYTA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZINBRYTA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use ZINBRYTA.

Tell your health care provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Using ZINBRYTA with other medicines can cause serious side effects.

How should I use ZINBRYTA?

- Use ZINBRYTA exactly as your healthcare provider tells you. A healthcare provider should show you how to inject ZINBRYTA before you use it for the first time.
- Inject ZINBRYTA 1 time every month.
- ZINBRYTA is for use under the skin (subcutaneous injection) of your thigh, stomach (abdomen), or back of the upper arm.
- If you miss a dose of ZINBRYTA, inject your dose of ZINBRYTA as soon as possible within 2 weeks of the missed dose. If it is more than 2 weeks after your missed dose, skip the missed dose. Inject your next dose at your regular time the

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next month. Do not inject more than 1 dose of ZINBRYTA at a time.

- Your healthcare provider should do blood tests before you start ZINBRYTA, every month during your treatment with ZINBRYTA, and monthly for 6 months after you have stopped using ZINBRYTA to check for side effects. Your healthcare provider should check your test results before your next dose.
- ZINBRYTA comes as a:
  - Single-Dose Prefilled Autoinjector (ZINBRYTA Pen)
  - Single-Dose Prefilled Syringe

  Your healthcare provider will decide which one is best for you. See the **Instructions for Use** that come with ZINBRYTA for detailed instructions on using ZINBRYTA the right way.

Always use a new, unopened, single-dose prefilled autoinjector or single-dose prefilled syringe for each injection. Throw away any unused medicine**. Do not** re-use any syringes, needles or pens.

What are the possible side effects of ZINBRYTA?

ZINBRYTA can cause serious side effects, including:

- See "**What is the most important information I should know about ZINBRYTA?**"
- **Allergic reactions or serious problems that may affect different parts of the body such as your liver, kidneys, heart or blood.** These can be very serious and can cause death. Call your healthcare provider right away if you have any of the following symptoms while using ZINBRYTA:
  - fever
  - rash
  - swelling of the face, tongue or throat
  - trouble breathing
- **Infections**. Some people who use ZINBRYTA may get an infection, such as an upper respiratory tract infection or a urinary tract infection. Some infections may be serious. Call your healthcare provider if you have symptoms of an infection. Talk to your healthcare provider before you get vaccinations while using ZINBRYTA.
- **Depression and suicide.** Some people who use ZINBRYTA may develop depression, depressed mood, or suicidal thoughts. Call your healthcare provider right away if you have ever been treated for depression or have any of the following symptoms while using ZINBRYTA:
  - feel sad or have crying spells
  - are sleeping a lot more or a lot less than usual
  - feel hopeless or helpless
  - are more irritable, angry or aggressive than usual
  - have trouble paying attention
  - feel tired or sleepy all the time
  - have thoughts about hurting yourself or ending your life

The most common side effects of ZINBRYTA include:

- upper respiratory tract infection
- flu
- pain or swelling in your nose, throat, or mouth
- bronchitis
- abnormal liver function tests
- dry, itchy, scaly, or inflamed skin (eczema)
- rash
- depression and depressed mood
- swollen lymph glands

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ZINBRYTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZINBRYTA?

- Store ZINBRYTA in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton.
- **Do not** freeze ZINBRYTA. **Do not** use ZINBRYTA that has been frozen.
- **Do not** store ZINBRYTA at temperatures above 86°F (30°C).
- Keep ZINBRYTA away from light.
- If you cannot refrigerate ZINBRYTA, you can store ZINBRYTA at room temperature for up to 30 days.
- If ZINBRYTA has reached room temperature, **do not** put it back in the refrigerator. Throw away ZINBRYTA that has been outside of the refrigerator for more than 30 days.

Keep ZINBRYTA and all medicines out of the reach of children.

General Information about the safe and effective use of ZINBRYTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZINBRYTA for a condition for which it was not prescribed. Do not give ZINBRYTA to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ZINBRYTA that is written for health professionals. For more information, go to zinbryta.com or call 1-800-456-2255.

What are the ingredients in ZINBRYTA?

Active ingredient: daclizumab

Inactive ingredients:

- **Single-Dose Prefilled Autoinjector:** sodium succinate, anhydrous; succinic acid; sodium chloride; polysorbate 80 and water for injection.
- **Single-Dose Prefilled Syringe:** sodium succinate, anhydrous; succinic acid; sodium chloride; polysorbate 80 and water for injection.

Manufactured by: Biogen Inc., Cambridge, MA 02142; Distributed by: AbbVie Inc., North Chicago, IL 60064
ZINBRYTA is a registered trademark of Biogen. ©2016-2017 Biogen

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 05/2017

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INSTRUCTIONS FOR USE
ZINBRYTA® (zin-bry-tuh) PEN
(daclizumab)
Injection, for Subcutaneous Use
Single-Dose Prefilled Autoinjector
150 mg/mL

Do not remove the cap until you are ready to inject.

Read this Instructions for Use before you start using ZINBRYTA Pen and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Important information:

- **Before you use the ZINBRYTA Pen for the first time,** your healthcare provider should show you or your caregiver how to prepare and inject your ZINBRYTA Pen the right way.
- **Each ZINBRYTA Pen is for 1 time use only.**
- **Do not** share your ZINBRYTA Pen with other people. You may give an infection to them or get an infection from them.
- **Do not** inject more than 1 dose each month.

Do not use your ZINBRYTA Pen if it has been dropped or is visibly damaged. If you have dropped your ZINBRYTA Pen or it looks damaged, throw it away (dispose) and get a new one. See **"Step 8: Dispose of your ZINBRYTA Pen"**.

Supplies needed for your ZINBRYTA Pen injection (See *Figures A* and *B* below):

- 1 ZINBRYTA Pen **(See *Figure B*)**
- 1 alcohol wipe
- 1 gauze pad
- 1 adhesive bandage
- 1 sharps container for throwing away ZINBRYTA Pens. See **"Step 8: Dispose of your ZINBRYTA Pen"**

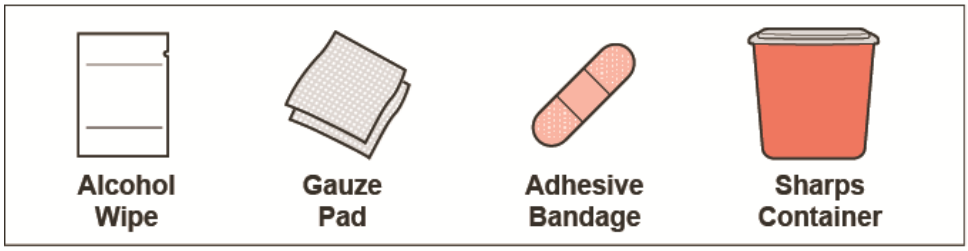

Figure A

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Before Use – Parts of your ZINBRYTA Pen (See *Figure B*)

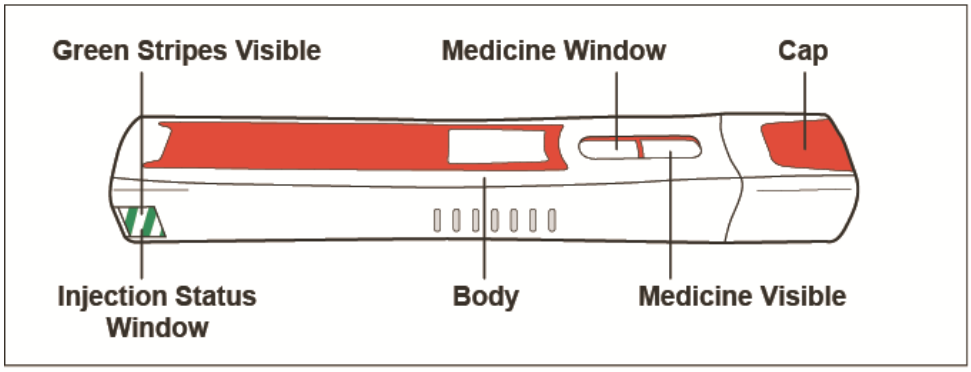

Figure B

Important: Do not remove the cap until you are ready to inject. If you remove the cap, do not recap the ZINBRYTA Pen. Recapping the ZINBRYTA Pen could cause it to lock.

Before you prepare your injection, take your ZINBRYTA Pen out of the refrigerator and let it sit at room temperature for at least 30 minutes.

- **Do not** use external heat sources such as hot water to warm the ZINBRYTA Pen.

Preparing for your injection

Step 1: Collect your supplies and wash your hands

- Find a well-lit area and a clean, flat surface, like a table, and collect all the supplies you will need to give yourself, or to receive an injection.
- Wash your hands with soap and water and dry your hands well.

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Step 2: Check your ZINBRYTA Pen (See *Figure C*)

- Check the injection status window. You should see green stripes.
  - **Do not** use if you do not see the green stripes in the injection status window.
- Check the expiration date printed on your ZINBRYTA Pen.
  - **Do not** use ZINBRYTA Pen past the expiration date.
- Check the medicine window on your ZINBRYTA Pen and make sure the ZINBRYTA medicine is colorless to slightly yellow.
  - **Do not** use ZINBRYTA Pen if the liquid is cloudy or has floating particles in it.

Note: You might see air bubbles in the medicine window. This is normal and will not affect your dose.

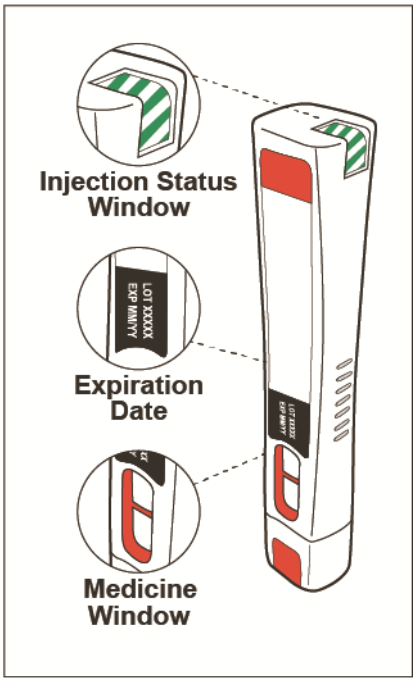

Figure C

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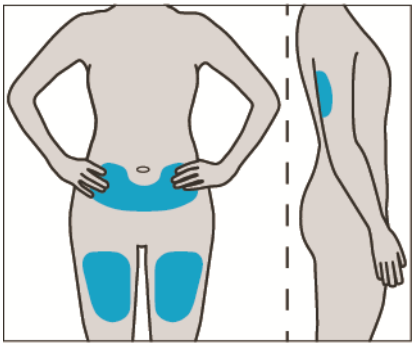
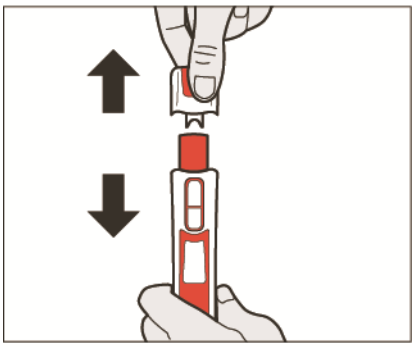
Step 3: Choose and clean your injection site	
• The ZINBRYTA Pen is used to inject ZINBRYTA under the skin only (subcutaneous). • ZINBRYTA should be injected into your thigh, abdomen, or the back of your upper arm **(See *Figure D*)**. ○ **Do not** inject directly into your belly button. ○ **Do not** inject into an area of the body where the skin is irritated, tender, red, bruised, infected, scarred, or tattooed. • **Change (rotate) your injection site** for each injection. **Do not** use the same injection site for each injection. • Choose an injection site and wipe your skin with an alcohol wipe. • Let the injection site dry on its own before injecting the dose. ○ **Do not** touch or blow on this area again before giving your injection.	 *Figure D*

Giving Your Injection

Step 4: Remove the ZINBRYTA Pen cap	
• Pull the pen cap straight off. Your ZINBRYTA Pen is now ready to inject. ○ Throw away the pen cap after your injection. **Do not** recap your ZINBRYTA Pen. This could lock the pen. • The needle is covered by the needle cover and the needle will not be seen **(See *Figure E*)**. **Do not** clean or touch the needle cover in any way. You could get a needle stick or the pen may lock.	 *Figure E*

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Step 5: Give your ZINBRYTA Pen injection

- Hold your ZINBRYTA Pen over your chosen injection site but make sure that the ZINBRYTA Pen is not touching your skin yet.
  - You should hold your ZINBRYTA Pen at 90 degrees to your injection site so that you can see the green stripes in the injection status window **(See *Figure F*)**.

Note: Do not press your pen down on your injection site until you are ready to inject. Pressing the pen down before you are ready can cause the needle cover to lock when it is removed from the site.

Firmly press and hold down your ZINBRYTA Pen on your injection site until you hear the clicking sounds start (See *Figure G*).

  - This will insert the needle and start your injection.

- Continue to hold your ZINBRYTA Pen firmly down on your injection site until the "clicking" sounds have stopped. Check injection status window for green check marks **(See *Figure H*)**.
  - **Do not** lift your ZINBRYTA Pen off your injection site until the clicking sounds stop and you see green checkmarks in the injection status window.

If you do not hear clicking sounds or you do not see green checkmarks in the injection status window after trying to inject, your pen may have locked and you should call 1-800-456-2255 for assistance.

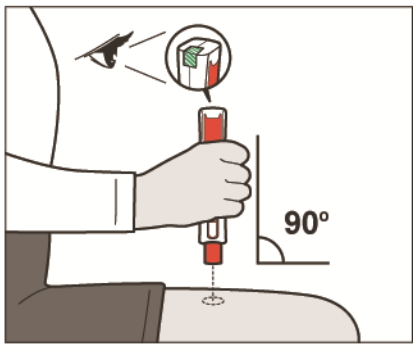

Figure F

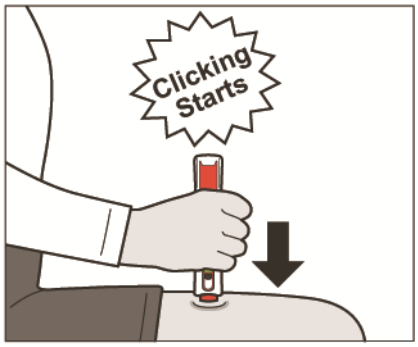

Figure G

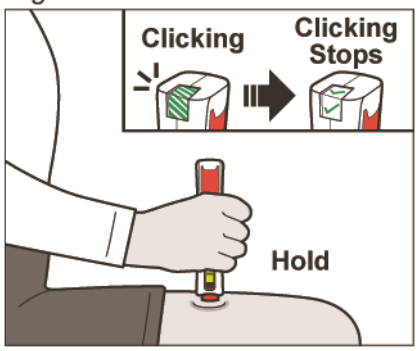

Figure H

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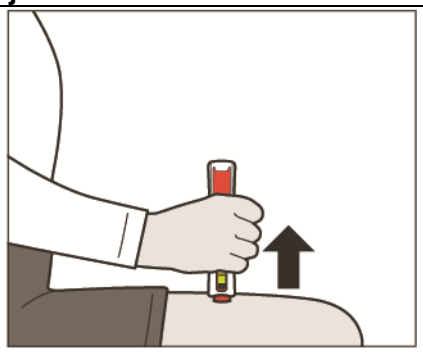
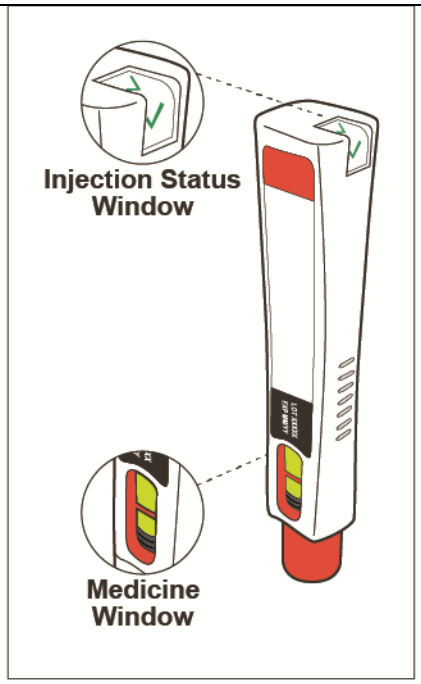
Step 6: Remove your ZINBRYTA Pen from your injection site	
• After the clicking sound has stopped, lift your ZINBRYTA Pen from your injection site. **(See*Figure I*)**.	 *Figure I*
Step 7: Check to make sure you have received your full dose of ZINBRYTA (See *Figure J*)	
• Check the injection status window. You should see green checkmarks • Check the medication window. You should see a yellow plunger**.**	 *Figure J*

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After Use – Parts of your ZINBRYTA Pen (See *Figure K*)

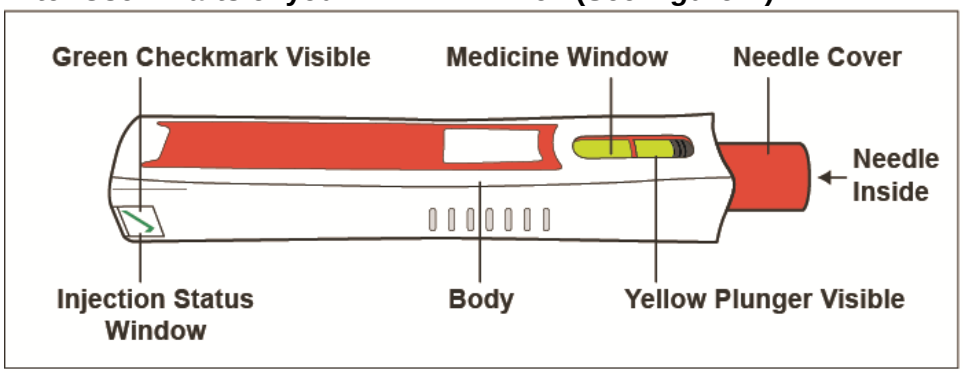

Figure K

Note: After the pen has been removed from the injection site, the needle cover will lock to help prevent a needle stick injury. **Do not** recap your pen.

After your injection

Step 8: Dispose of your ZINBRYTA Pen

- Put your used ZINBRYTA Pen and the cap in a FDA-cleared sharps disposal container right away after use **(See *Figure L*). Do not throw away (dispose of) your used ZINBRYTA Pen in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

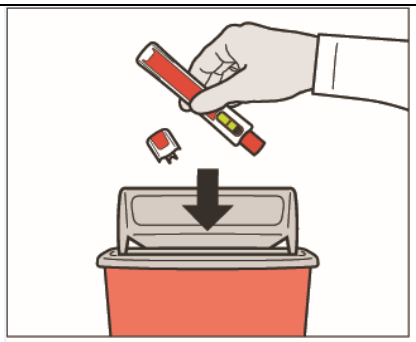

Figure L

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Step 9: Check your injection site

- If you see blood at your injection site, wipe it off with a gauze pad and apply an adhesive bandage.

How should I store ZINBRYTA?

- Store ZINBRYTA in the refrigerator between 36°F to 46°F (2°C to 8°C) in the closed original carton to protect it from light.
- **Do not** freeze ZINBRYTA or expose to temperatures above 86°F (30°C). **Do not** use ZINBRYTA that has been frozen.
- If you cannot refrigerate ZINBRYTA, you can store ZINBRYTA at room temperature in the closed original carton for up to 30 days.
- If ZINBRYTA has reached room temperature, **do not** put it back in the refrigerator.
- **Keep ZINBRYTA and all medicines out of the reach of children.**

For product or service related questions, please call 1-800-456-2255 or go to www.ZINBRYTA.com.

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Manufactured by: Biogen Inc., Cambridge, MA 02142

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INSTRUCTIONS FOR USE
ZINBRYTA® (zin-bry-tuh)
(daclizumab)
Injection, for Subcutaneous Use
Single-Dose Prefilled Syringe
150 mg

Read this Instructions for Use before you start using ZINBRYTA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Important information:

- **Before you use ZINBRYTA for the first time,** your healthcare provider should show you or your caregiver how to prepare and inject your ZINBRYTA prefilled syringe the right way.
- ZINBRYTA is for use under the skin only (subcutaneous).
- **ZINBRYTA prefilled syringe is for 1 time use only. Do not** share your ZINBRYTA prefilled syringe with other people. You may give an infection to them or get an infection from them.
- Throw away (dispose of) the ZINBRYTA prefilled syringe right away after use. See "**Disposing of ZINBRYTA prefilled syringes**" at the end of this Instructions for Use.

Supplies needed for your ZINBRYTA prefilled syringe injection (See Figure A):

- a ZINBRYTA 150 mg prefilled syringe

Figure A

Additional supplies you will need for your injection (**See Figure B**):

- alcohol wipe
- gauze pad
- adhesive bandage
  - 1 sharps container for throwing away ZINBRYTA prefilled syringes. See **"Disposing of ZINBRYTA prefilled syringes"** at the end of these instructions.
  - a well-lit area and a clean, flat surface to work on, like a table

Figure B

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Parts of your ZINBRYTA prefilled syringe (**See Figure C**):

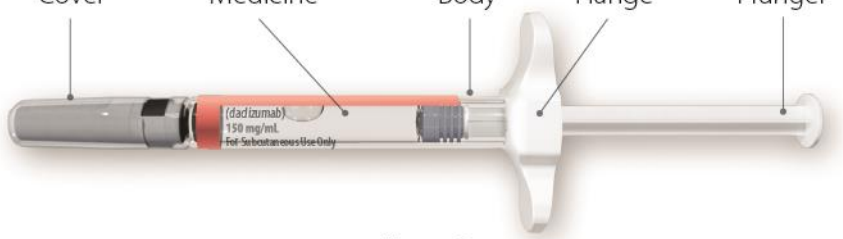

Figure C

- **Before you prepare your injection, take your ZINBRYTA prefilled syringe out of the refrigerator and let it come to room temperature for at least 30 minutes.**
  - **Do not** use external heat sources such as hot water to warm the ZINBRYTA prefilled syringe.
- **Do not** use more than 1 prefilled syringe each month.
- The finger flange will allow you to hold the prefilled syringe more firmly. **Do not** remove the finger flange.

Preparing for your injection:

Step 1: Collect your supplies and wash your hands

- Find a well-lit and clean, flat surface, like a table and collect all the supplies you will need to give yourself or to receive an injection.
- Wash your hands with soap and water and dry your hands well.

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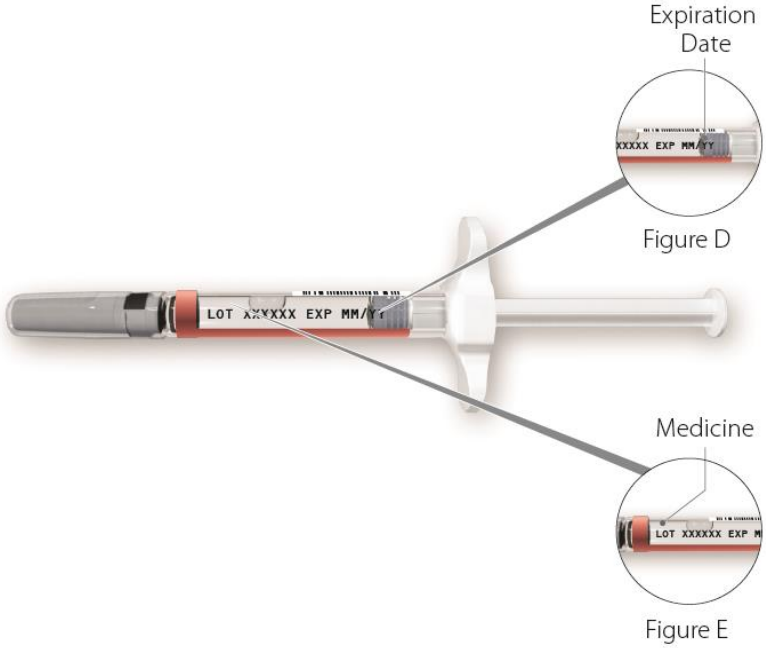
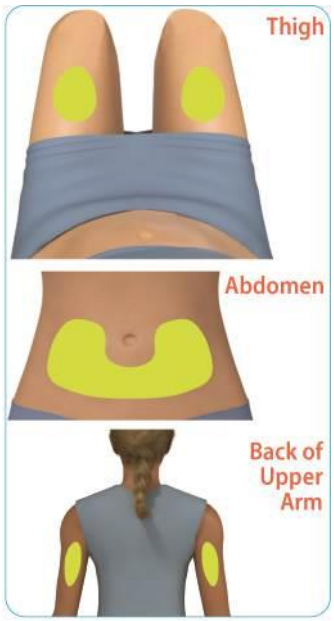
Step 2: Check your ZINBRYTA prefilled syringe	
• Check the expiration date printed on your ZINBRYTA prefilled syringe (**See Figure D**). ○ **Do not** use ZINBRYTA prefilled syringe past the expiration date.	
• Check that your ZINBRYTA medicine is clear and colorless to slightly yellow (**See Figure E**). ○ **Do not** use ZINBRYTA prefilled syringe if the liquid is cloudy, or has floating particles in it. ○ You might see air bubbles in your ZINBRYTA medicine. This is normal and will not affect your dose.	

Giving your injection:

Step 3: Choose and clean your injection site	
• ZINBRYTA prefilled syringe is used to inject ZINBRYTA under the skin only (subcutaneous). • ZINBRYTA prefilled syringe should be injected into the thigh, abdomen, or the back of the upper arm (**See Figure F**). ○ **Do not** inject directly into your belly button. ○ **Do not** inject into an area of the body where the skin is irritated, tender, red, bruised, infected, scarred, or tattooed. • Choose an injection site and wipe the skin with an alcohol wipe. • Let the injection site dry before injecting the dose. ○ **Do not** touch this area again before giving the injection.	 Figure F

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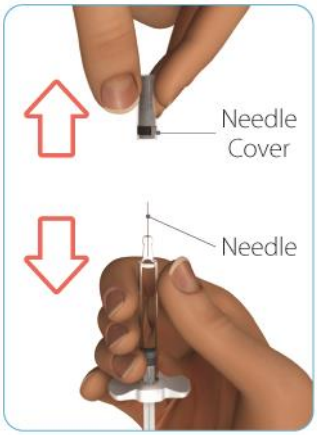
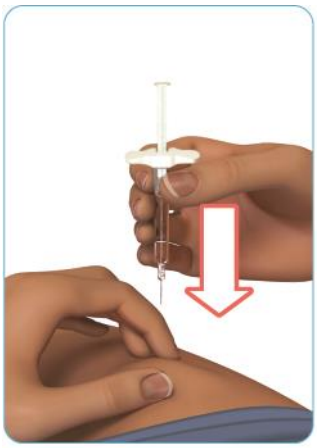
• Do not take off the ZINBRYTA prefilled syringe needle cover until you are ready to inject.	
Step 4: Remove the ZINBRYTA prefilled syringe needle cover	
• With 1 hand, hold your ZINBRYTA prefilled syringe as shown. **Do not** push on the finger flange. With your other hand, firmly hold the needle cover and pull the needle cover straight off the needle (**See Figure G**). ○ Throw away the needle cover after your injection. **Do not** recap your ZINBRYTA prefilled syringe, you could get a needle stick injury. ○ **Do not** touch the needle.	 Figure G
Step 5: Give your ZINBRYTA prefilled syringe injection	
• With 1 hand, use your thumb and first finger and pinch the skin around the cleaned injection site (**See Figure H**).	 Figure H
• With your other hand, hold your ZINBRYTA prefilled syringe like a pencil. **Use a quick dart-like motion and insert the needle at a 90° angle into your skin** (**See Figure I**). • After the needle is in, let go of your skin	 Figure I
• Slowly push the plunger down until the	

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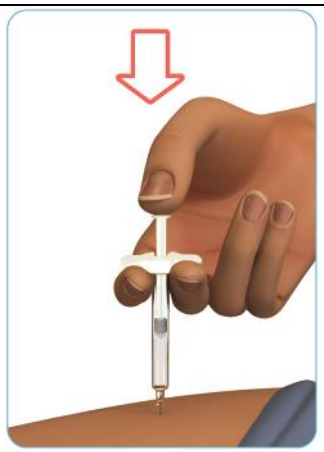
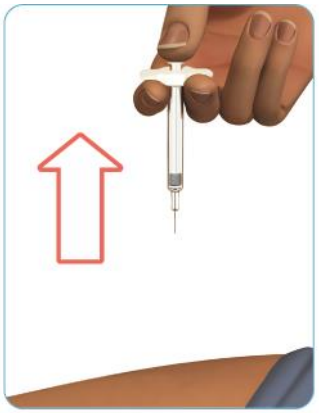
syringe is empty (**See Figure J**). ○ **Do not** pull back on the plunger. ○ **Do not** take your ZINBRYTA prefilled syringe out of your skin until you have slowly pushed the plunger all the way down.	 Figure J
Step 6: Remove the ZINBRYTA prefilled syringe from your injection site	
• Pull the needle straight out of your skin (**See Figure K**). ○ If you see blood at your injection site, wipe it off with gauze and apply an adhesive bandage. • **Do not** recap the ZINBRYTA prefilled syringe. Recapping the prefilled syringe can lead to a needle stick injury. • **Do not** reuse the ZINBRYTA prefilled syringe.	 Figure K

After your injection:

Step 7: Disposing of ZINBRYTA prefilled syringes	
• Put your used ZINBRYTA prefilled syringes in a FDA-cleared sharps disposal container right away after use (**see Figure L**). **Do not throw away (dispose of) loose needles and ZINBRYTA prefilled syringes in your household trash.** • If you do not have a FDA-cleared sharps disposal container, you may use a household container that is: ○ made of a heavy-duty plastic, ○ can be closed with a tight-fitting, puncture-resistant lid, without sharps	 Figure L

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being able to come out, ○ upright and stable during use, ○ leak resistant, and ○ properly labeled to warn of hazardous waste inside the container. • When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal. • **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.	

How should I store ZINBRYTA Prefilled Syringe?

- Store ZINBRYTA prefilled syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not** freeze ZINBRYTA prefilled syringe or expose to temperatures above 86°F (30°C). **Do not** use ZINBRYTA prefilled syringe that has been frozen.
- Keep ZINBRYTA prefilled syringe in the original carton to protect it from light.
- If you cannot refrigerate ZINBRYTA prefilled syringe, you can store ZINBRYTA at room temperature for up to 30 days.
- If ZINBRYTA prefille syringe has reached room temperature, **do not** put it back in the refrigerator.
- **Keep ZINBRYTA prefilled syringe and all medicines out of the reach of children.**

Questions?

For product or service related questions, please call 1-800-456-2255 or go to www.Zinbryta.com.

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Manufactured by: Biogen Inc., Cambridge, MA 02142

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