CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761029Orig1s000

REMS

Initial REMS approval: 05/2016

BLA 761029 ZINBRYTA™ (daclizumab)

Alpha subunit, Interleukin-2 antagonist

Biogen Inc.

225 Binney Street, Cambridge, MA 02142

Phone: 781-464-2000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(s)

To mitigate the risks of severe and fatal hepatic injury and serious immune mediated disorders associated with ZINBRYTA by:

- Ensuring that prescribers are educated on the following:
  - the potential risks of severe and fatal hepatic injury and serious immune mediated disorders associated with the use of ZINBRYTA
  - the need to counsel patients about these risks and the need for appropriate baseline and monthly monitoring
- Ensuring that prescribers are educated on and adhere to:
  - required baseline and monthly monitoring and evaluation of patients who receive ZINBRYTA
- Ensuring that patients are informed about:
  - the potential risks of severe and fatal hepatic injury and serious immune mediated disorders associated with the use of ZINBRYTA
  - appropriate baseline and monthly monitoring
- Enrollment of all patients in a registry to further support long-term safety and safe use of ZINBRYTA

II. ELEMENTS

A. Communication Plan

Biogen must implement the following communication plan to healthcare providers likely to prescribe ZINBRYTA:

1. REMS Letters

Biogen must send a *ZINBRYTA REMS Program Letter for Healthcare Providers* within 60 calendar days of the approval of the REMS. Biogen must send a second and third mailing of the *ZINBRYTA REMS Program Letter for Healthcare Providers* at 12 and 24 months from the date of the REMS approval. The REMS Letter must address the risks of severe and fatal hepatic injury and serious immune mediated disorders as well as support implementation of the REMS Program.

Reference ID: 3938318

The REMS Letter must be distributed by mail. A copy of the Prescribing Information must accompany each *REMS Program Letter for Healthcare Providers*. Biogen must make the *ZINBRYTA REMS Program Letter for Healthcare Providers* available via a link from the ZINBRYTA REMS Program Website (www.zinbrytarems.com) and through Biogen field based sales and medical representatives upon request for one year after the initial approval of the REMS.

REMS letters must be mailed in hard copy letter format. If a mailed letter is returned as undeliverable, Biogen must send an email, within 10 business days after the letter is returned for those healthcare providers for whom an email address is available.

The intended audience for the *ZINBRYTA REMS Program Letter for Healthcare Providers* must be prescribers who have written at least one prescription within the previous 2 years for a prescription drug indicated for the treatment of multiple sclerosis.

The following materials are part of the REMS and are appended:
ZINBRYTA REMS Program Letter for Healthcare Providers

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe ZINBRYTA must be specially certified.

    a. To become specially certified to prescribe ZINBRYTA, healthcare providers must:

        i. Review the Prescribing Information for ZINBRYTA

        ii. Review the *ZINBRYTA REMS Program Overview* and *ZINBRYTA REMS Program Prescriber Training* and successfully complete the *ZINBRYTA REMS Program Prescriber Knowledge Assessment*

        iii. Enroll in the ZINBRYTA REMS Program by signing and completing the *ZINBRYTA REMS Program Prescriber Enrollment Form* and submitting it to the ZINBRYTA REMS Program

    b. As a condition of certification, prescribers must:

        i. Enroll each patient in the ZINBRYTA REMS Program by performing the following:

            1) Counsel the patient about the risks of severe and fatal hepatic injury, serious immune mediated disorders associated with ZINBRYTA, and the need for baseline and monthly monitoring, and provide the *ZINBRYTA REMS Program Patient Guide* and *ZINBRYTA REMS Program Patient Wallet Card.*

            2) Complete the *ZINBRYTA REMS Program Patient Enrollment Form* for each patient and provide a completed copy to the patient. Submit the completed form to the ZINBRYTA REMS Program and store a copy in the patient's records.

ii. Report any adverse events suggestive of hepatic injury and immune mediated disorders to the ZINBRYTA REMS Program

iii. Perform the baseline monitoring as described in the Prescribing Information and attest that this monitoring will be completed and evaluated prior to the patient's first dose of ZINBRYTA on the *ZINBRYTA REMS Program Patient Enrollment Form*

iv. Perform monthly monitoring as described in the Prescribing Information

v. Submit a *ZINBRYTA REMS Program Patient Status Form* by fax or by mail to the REMS Program indicating completion and evaluation of each patient's monthly monitoring every 90 calendar days during treatment and every 90 calendar days for 6 months after discontinuation of the drug

vi. Inform Biogen if an enrolled patient is no longer under your care or has discontinued therapy

c. Biogen must:

i. Ensure that healthcare providers who prescribe ZINBRYTA are specially certified, in accordance with the requirements described above

ii. Provide all the following mechanisms for healthcare providers to complete the certification process for the ZINBRYTA REMS Program: fax and mail

iii. Ensure that healthcare providers are notified when they have been certified by the ZINBRYTA REMS Program

iv. Maintain a validated, secure database of healthcare providers who are certified to prescribe ZINBRYTA in the ZINBRYTA REMS Program

v. Ensure that healthcare providers meet the REMS requirements and de-certify healthcare providers who do not maintain compliance with REMS requirements

vi. Ensure that certified prescribers are provided access to the database of certified pharmacies and their enrolled patients

vii. Provide all the materials listed below and the Prescribing Information to healthcare providers who (1) attempt to prescribe ZINBRYTA and are not yet certified, or (2) inquire about how to become certified

The following materials are part of the REMS and are appended:

- *ZINBRYTA REMS Program Overview*
- *ZINBRYTA REMS Program Prescriber Training*
- *ZINBRYTA REMS Program Prescriber Enrollment Form*
- *ZINBRYTA REMS Program Prescriber Knowledge Assessment*
- *ZINBRYTA REMS Program Patient Enrollment Form*
- *ZINBRYTA REMS Program Patient Status Form*
- *ZINBRYTA REMS Program Patient Guide*
- *ZINBRYTA REMS Program Patient Wallet Card*

2. Pharmacies that dispense ZINBRYTA must be specially certified.

   a. To become specially certified to dispense ZINBRYTA, pharmacies must:

      i. Designate an authorized representative to complete the enrollment process by submitting the completed *ZINBRYTA REMS Program Pharmacy Enrollment Form* on behalf of the pharmacy

      ii. Ensure that the authorized representative oversees implementation and compliance with the ZINBRYTA REMS Program requirements by the following:

         1) Review the *ZINBRYTA REMS Program Overview*

         2) Ensure all relevant staff involved in the dispensing of ZINBRYTA are trained on the ZINBRYTA REMS Program requirements as described in the *ZINBRYTA REMS Program Overview* and maintain a record of training

         3) Put processes and procedures in place to ensure the following requirements are completed prior to dispensing ZINBRYTA:

            a) Verify the prescriber is certified and the patient is enrolled and authorized by accessing the ZINBRYTA REMS Program Website, or calling the ZINBRYTA REMS Program; and
            b) Dispense no more than a one month supply of ZINBRYTA to a patient

   b. As a condition of certification, pharmacies must:

      i. Dispense ZINBRYTA to patients only after obtaining authorization by calling the ZINBRYTA REMS Program or accessing the ZINBRYTA REMS Program Website. The authorization confirms the following:

         1) The prescriber is certified and the patient is enrolled in the ZINBRYTA REMS Program

         2) The *Patient Status Form* is received by Biogen within the designated time frame

      ii. Dispense no more than a one month supply of ZINBRYTA

      iii. Recertify in the ZINBRYTA REMS Program if the pharmacy designates a new authorized representative

      iv. Report any adverse events suggestive of hepatic injury and immune mediated disorders to the ZINBRYTA REMS Program

      v. Maintain appropriate documentation that all processes and procedures are in place and are being followed for the ZINBRYTA REMS Program and provide upon request to Biogen, FDA, or a third party acting on behalf of Biogen or FDA

      vi. Comply with audits by Biogen, FDA, or a third party acting on behalf of Biogen or FDA to ensure that all processes and procedures are in place and are being followed for the ZINBRYTA REMS Program

c. Biogen must:

i. Ensure that pharmacies that dispense ZINBRYTA are specially certified, in accordance with the requirements described above

ii. Provide all the following mechanisms for pharmacies to complete certification for the ZINBRYTA REMS Program: fax and mail

iii. Ensure that pharmacies are notified when they have been certified by the ZINBRYTA REMS Program

iv. Ensure that certified pharmacies are provided access to the database of certified prescribers and enrolled and authorized patients

v. Verify every year that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified pharmacy. If different, the pharmacy must be required to recertify with a new authorized representative

vi. Maintain a database of enrolled patients and their current authorization status. Authorization to dispense requires that Biogen receives a *ZINBRYTA REMS Program Patient Status Form* within 115 calendar days (See Section 4bii.) for each patient. If not received, the patient will not be authorized for further dispensing until a *ZINBRYTA REMS Program Patient Status Form* is received.

The following materials are part of the REMS and are appended:

- *ZINBRYTA REMS Program Pharmacy Enrollment Form*
- *ZINBRYTA REMS Program Overview*
- *ZINBRYTA REMS Program Website* (www.zinbrytarems.com)

3. ZINBRYTA must be dispensed to patients with evidence or other documentation of safe-use conditions.

a. To become enrolled in the ZINBRYTA REMS Program, a patient/caregiver must sign a *ZINBRYTA REMS Program Patient Enrollment Form* indicating that he/she has:

i. Received and has read the *ZINBRYTA REMS Program Patient Guide*

ii. Received counselling from the prescriber regarding

a. the risks of severe and fatal hepatic injury and serious immune mediated disorders;

b. required baseline and monthly monitoring

iii. Received *the ZINBRYTA REMS Program Patient Wallet Card*

b. To authorize a patient to receive ZINBRYTA under the ZINBRYTA REMS Program, a certified prescriber must complete and submit by fax or by mail to the REMS Program a *Patient Status*

Form every 90 calendar days during treatment and every 90 calendar days for 6 months after discontinuation of the drug

c. Biogen must:

i. Provide all the following mechanisms for the certified prescriber to be able to submit the completed *ZINBRYTA REMS Program Patient Enrollment Form* and *Patient Status Form* to the ZINBRYTA REMS Program: fax and mail

ii. Ensure that the certified pharmacies verify the required authorization for each patient prior to dispensing

The following materials are part of the REMS and are appended:

- *ZINBRYTA REMS Program Patient Enrollment Form*
- *ZINBRYTA REMS Program Patient Guide*
- *ZINBRYTA REMS Program Patient Wallet Card*

4. Each patient using ZINBRYTA is subject to certain monitoring.

a. The prescriber must

i. Perform the baseline and monthly monitoring for each patient as described in the Prescribing Information, and

ii. Submit by fax or mail a *ZINBRYTA REMS Program Patient Status Form* to the REMS Program indicating completion of each patient's monthly monitoring every 90 calendar days during treatment and every 90 calendar days for 6 months after discontinuation of the drug

b. Biogen must:

i. Ensure that the *ZINBRYTA REMS Program Patient Status Form* is received every 90 calendar days after the first dispensation of the drug and every 90 calendar days for 6 months after discontinuation

ii. Ensure that if the *ZINBRYTA REMS Program Patient Status Form* is not received for each patient within 95 calendar days, Biogen will attempt to contact the prescriber to receive the form. If the form has not been received within 115 calendar days then the patient will not be authorized for further dispensing until the form is received. If a form has not been received at 145 calendar days Biogen must begin de-enrollment procedures for the patient

iii. Ensure that the *ZINBRYTA REMS Program Patient Status Form* is available to certified prescribers for patient monitoring

The following materials are part of the REMS and are appended:

- *ZINBRYTA REMS Program Patient Status Form*

5. Each patient using ZINBRYTA is enrolled in a registry.
    a. Biogen must maintain a ZINBRYTA REMS Program Registry. The primary objectives of the registry are to ensure that only enrolled and authorized patients receive ZINBRYTA and to provide information on the incidence of severe and fatal hepatic injury and serious immune mediated events
    b. Biogen must ensure that certified prescribers enroll all patients in the ZINBRYTA REMS Program Registry using the ZINBRYTA *REMS Program Patient Enrollment Form*
    c. Biogen must provide all the following mechanisms for prescribers to complete patient enrollment: fax and mail
    d. Biogen must ensure that once a report for an adverse event that is required to be reported to the REMS is received, Biogen follows up with the healthcare provider to procure all necessary information to complete the report, and captures all required data for the registry

The following materials are part of the REMS and are appended:

- *ZINBRYTA REMS Program Patient Enrollment Form*

C. Implementation System

1. Biogen must ensure that ZINBRYTA is only distributed to certified pharmacies by:
    a. Ensuring that wholesalers/distributors who distribute ZINBRYTA comply with the program requirements for wholesalers/distributors. The wholesalers/distributor must:
        i. Put processes and procedures in place to verify, prior to distributing ZINBRYTA, that the pharmacies are certified
        ii. Train all relevant staff on the ZINBRYTA REMS Program requirements
        iii. Comply with audits by Biogen, FDA, or a third party acting on behalf of Biogen or FDA to ensure that all procedures are in place and are being followed for the ZINBRYTA REMS Program. In addition, wholesalers/distributors must maintain appropriate documentation and make it available for audits
        iv. Provide distribution data to the ZINBRYTA REMS Program to verify compliance with the REMS.
    b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of ZINBRYTA and provide the data to the ZINBRYTA REMS Program
2. Biogen must monitor distribution data to ensure all the processes and procedures are in place and functioning to support the requirements of the ZINBRYTA REMS Program
3. Biogen must audit the wholesalers/distributors within 180 calendar days after the wholesaler/distributor receives the first shipment of ZINBRYTA to ensure that all processes and procedures are in place and functioning to support the requirements of the ZINBRYTA REMS Program. Corrective action must be instituted by Biogen if noncompliance is identified.

4. Biogen must maintain a validated, secure database of pharmacies that are certified to dispense ZINBRYTA in the ZINBRYTA REMS Program

5. Biogen must maintain records of ZINBRYTA distribution and dispensing, certified prescribers, certified pharmacies, wholesalers/distributors, and enrolled patients, to meet REMS requirements

6. Biogen must maintain a ZINBRYTA REMS Program Call Center (800-456-2255) and ZINBRYTA REMS Program Website (www.zinbrytarems.com). The REMS Program Website must include the cabability to confirm patient authorization status, and the option to print the Prescribing Information, Medication Guide, and ZINBRYTA REMS materials. The ZINBRYTA product website must include a prominent REMS-specific link to the ZINBRYTA REMS Program Website.

7. Biogen must ensure that within 60 calendar days of REMS approval the ZINBRYTA REMS Program Website is fully operational including the online confirmation of patient authorization functionality; and the REMS materials listed in or appended to the ZINBRYTA REMS document are available through the ZINBRYTA REMS Program Website and by calling the ZINBRYTA REMS Program Call Center.

8. Biogen must monitor on an ongoing basis the certified pharmacies to ensure the requirements of the ZINBRYTA REMS Program are being met. Biogen must institute corrective action if noncompliance is identified and decertify pharmacies that do not maintain complaince with the REMS requirements.

9. Biogen must maintain an ongoing annual audit plan that involves wholesaler/distributors and certified pharmacies

10. Biogen must audit 25% of the certified pharmacies within 90 calendar days after the pharmacy places its first order of ZINBRYTA to ensure that all processes and procedures are in place and functioning to support the requirements of the ZINBRYTA REMS Program. The certified pharmacies must be included in Biogen's ongoing annual audit plan. Biogen must institute corrective action if noncompliance is identified.

11. Biogen must send monthly reminders to patients while receiving ZINBRYTA treatment and up to 6 months after discontinuing, reminding them of the requirement for ongoing monitoring

12. Biogen must take reasonable steps to improve implementation of and compliance with the requirements in the ZINBRYTA REMS Program based on monitoring and evaluation of the ZINBRYTA REMS Program

III. Timetable for Submission of Assessments

Biogen must submit REMS assessments to the FDA at 6 months, 1 year, and annually thereafter from the date of the intial approval of the REMS (May 27, 2016). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Biogen must submit each assessment so that it will be received by the FDA on or before the due date.

Zinbryta™
(daclizumab)

Phone: 1-800-456-2255 Fax: 1-855-474-3067

May 2016

ZINBRYTA REMS Program Letter for Healthcare Providers

Subject: Risk of severe liver injury including life-threatening events, liver failure and autoimmune hepatitis and other immune-mediated disorders with ZINBRYTA (daclizumab)

Dear Healthcare Provider:

The purpose of this letter is to inform you about serious risks associated with ZINBRYTA (daclizumab) injection and the need for monitoring for these risks. 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.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of ZINBRYTA outweigh the serious risks. ZINBRYTA is available only through the ZINBRYTA REMS Program, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the Program are able to prescribe, dispense, and receive ZINBRYTA.

Serious Risks of ZINBRYTA

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.

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.

If a patient develops a serious immune 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.

Biogen abbvie

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(daclizumab)

Phone: 1-800-456-2255 Fax: 1-855-474-3067

ZINBRYTA Healthcare Provider Training

It is important that healthcare providers understand the serious risks associated with ZINBRYTA. As part of the REMS, healthcare providers must be trained and specially certified to prescribe ZINBRYTA.

ZINBRYTA REMS Program training materials for healthcare providers may be obtained at www.zinbrytarems.com or by calling 1-800-456-2255.

Reporting Adverse Events

Healthcare providers and patients are encouraged to report adverse events in patients taking ZINBRYTA to Biogen at 1-800-456-2255. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Healthcare providers should report any adverse events suggestive of hepatic injury and immune-mediated disorders with the use of ZINBRYTA to Biogen at 1-800-456-2255.

All REMS information/materials may be accessed at www.zinbrytarems.com or by calling 1-800-456-2255.

Please see the enclosed Prescribing Information for ZINBRYTA.

Sincerely,

Biogen abbvie

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ZIN-US-0403

Reference ID: 3938318

ZINBRYTA REMS (Risk Evaluation and Mitigation Strategy) Program Overview

This overview describes the requirements of the ZINBRYTA REMS Program and the responsibilities of prescribers, pharmacies and patients.

To learn more about ZINBRYTA, please visit www.zinbrytarems.com. You can also call us at 1-800-456-2255, Monday to Friday, 8:30AM to 8:00PM (ET)

Please see Prescribing Information, including BOXED WARNING, for additional Important Safety Information.

Zinbryta™
(daclizumab)
150 mg Subcutaneous Injection

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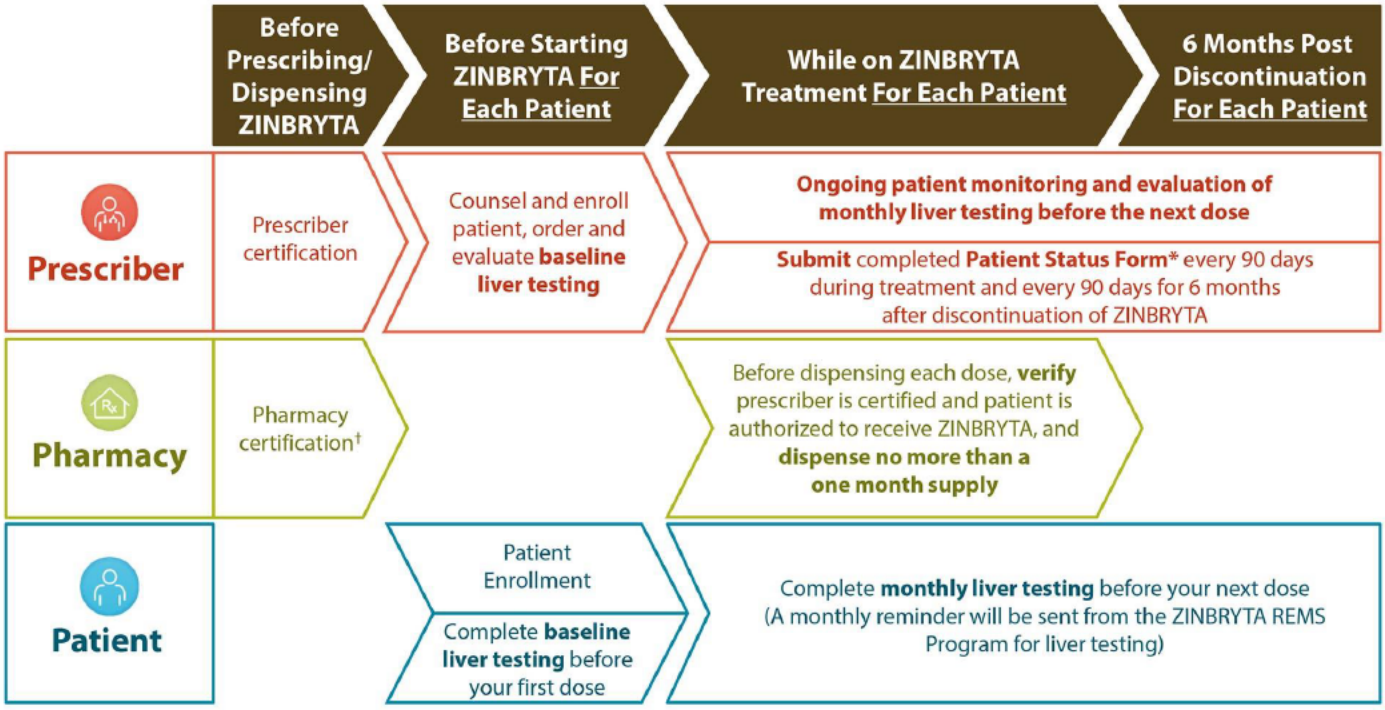
What is the ZINBRYTA REMS Program?

- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug continue to outweigh its risks.
- **Due to the risks of severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis, and other immune -mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis, ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program.**

How Does the ZINBRYTA REMS Program Work?



* Every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA, the ZINBRYTA REMS Program will send an individualized Patient Status Form to the certified prescriber for completion.
† Recertify if there is a change in authorized representative.

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What are the Requirements of the ZINBRYTA REMS Program?

- In order to receive ZINBRYTA, prescribers, patients, and pharmacies must comply with the requirements of the ZINBRYTA REMS Program.

Prescribers

To prescribe ZINBRYTA:

1. **Become certified** by completing a one-time certification process
2. As you start patients on ZINBRYTA, **counsel and enroll** them into the ZINBRYTA REMS Program, complete the prescription, and order and evaluate baseline liver testing
3. **Perform** ongoing patient monitoring, evaluate **monthly liver testing** prior to each patient's next dose, and complete the ZINBRYTA REMS Program Patient Status Forms for each patient every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA

Pharmacies

To dispense ZINBRYTA*:

1. **Designate an authorized representative, become certified,** and **recertify** if there is a change in the authorized representative
2. **Train** staff and **comply** with REMS requirements
3. Before dispensing each dose, **verify** prescriber is certified and patient is authorized to receive ZINBRYTA, and **dispense no more than a one month supply**

Patients

To receive ZINBRYTA:

1. **Understand the risks** associated with ZINBRYTA
2. **Enroll** in the ZINBRYTA REMS Program by completing the ZINBRYTA REMS Program Patient Enrollment Form with your doctor
3. **Complete** baseline liver testing before your first dose and monthly liver testing before your next dose of ZINBRYTA. A monthly reminder will be sent from the ZINBRYTA REMS Program for liver testing

* ZINBRYTA is not available to all pharmacies. If you have any questions about the ZINBRYTA REMS Program or how to obtain ZINBRYTA, call 1-800-456-2255, Monday to Friday, 8:30AM to 8:00PM (ET).

Prescribers and pharmacies must report any adverse events suggestive of hepatic injury and immune-mediated disorders to the ZINBRYTA REMS Program.

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Prescriber Requirements

Become Certified (One-time)

Before prescribing ZINBRYTA

1. **Review** the following educational materials on ZINBRYTA to understand the risks of severe and life-threatening hepatic injury including autoimmune hepatitis, and serious immune-mediated disorders, and the REMS Program:
   - **ZINBRYTA Prescribing Information**
   - **ZINBRYTA REMS Program Overview**
   - **ZINBRYTA REMS Program Prescriber Training**
2. **Complete** and **submit** the ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form, using the submission details at the end of this document
3. Once completed, the ZINBRYTA REMS Program will contact you to finish certification

Enroll Your Patients

Before starting each patient on ZINBRYTA

1. **Counsel** your patient about the risks associated with ZINBRYTA and the need for baseline and monthly liver testing before the next dose and share the resources below
   - **ZINBRYTA REMS Program Patient Guide**
   - **ZINBRYTA REMS Program Patient Wallet Card**
2. **Order and evaluate** the baseline liver testing before each patient's first dose of ZINBRYTA
3. **Submit** a completed ZINBRYTA REMS Program Patient Enrollment Form and prescription for each patient, store a copy in the patient's records. Your patient can expect to be contacted by the ZINBRYTA REMS Program

Monitor Your Patients

Once your patient is on ZINBRYTA

1. **Monitor** your ZINBRYTA patients on an ongoing basis. Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Transaminase levels and total bilirubin should be followed monthly for 6 months after the last dose of ZINBRYTA
2. **Submit** a completed ZINBRYTA REMS Program Patient Status Form* for each patient **every 90 days** during treatment and **every 90 days for 6 months after discontinuation** of ZINBRYTA using the submission details at the end of this document
3. **Report** any adverse events suggestive of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders to the ZINBRYTA REMS Program. You may be contacted for more information about these events
4. **Inform** the ZINBRYTA REMS Program if a patient is no longer under your care or has discontinued ZINBRYTA

* Every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA, the ZINBRYTA REMS Program will send an individualized Patient Status Form to the certified prescriber for completion.

The completed forms should be faxed to the ZINBRYTA REMS Program at **1-855-474-3067**, or mailed to the ZINBRYTA REMS Program at **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**.

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Pharmacy Requirements

Become Certified

Before dispensing ZINBRYTA

1. **Designate** an authorized representative for the pharmacy. He or she will need to review the ZINBRYTA REMS Program Overview and will oversee implementation and ensure compliance with the ZINBRYTA REMS Program requirements
2. **Have the authorized representative complete and submit** the ZINBRYTA REMS Pharmacy Enrollment Form using the submission details at the end of this document
   - Once this step is completed, the ZINBRYTA REMS Program will contact you to complete certification
3. **Have the authorized representative ensure** that all relevant staff involved in the dispensing of ZINBRYTA are trained on the ZINBRYTA REMS Program requirements and that a record of training is maintained by the pharmacy

Ensure Compliance With REMS Requirements

When dispensing ZINBRYTA

1. Before dispensing each dose, **verify** that the prescriber is certified and the patient is authorized to receive ZINBRYTA by calling the ZINBRYTA REMS Program. **Do not dispense more than a one month supply per patient**
2. **Report** any adverse events suggestive of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders to the ZINBRYTA REMS Program. You may be contacted for more information about these events
3. **Maintain** appropriate documentation that all processes and procedures are in place and are being followed so that it can be provided upon request to Biogen, the FDA, or a third party acting on behalf of Biogen or the FDA
4. **Recertify** in the ZINBRYTA REMS Program if a new authorized representative is designated by completing and submitting the ZINBRYTA REMS Pharmacy Enrollment Form

ZINBRYTA is not available to all pharmacies. If you have questions about the ZINBRYTA REMS Program or how to obtain ZINBRYTA, call 1-800-456-2255, Monday to Friday, 8:30AM to 8:00PM (ET).

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Patient Requirements

Enroll and Complete Baseline Liver Testing

Before starting ZINBRYTA

1. **Discuss** with your doctor and understand
   - The risk of serious liver problems and immune system problems
   - The required monthly liver testing
2. **Receive and read** the
   - **ZINBRYTA REMS Program Patient Guide**
   - **ZINBRYTA REMS Program Patient Wallet Card** (fill in your name and your doctor's information)
3. **Complete** the **ZINBRYTA REMS Program Patient Enrollment Form** with your doctor
4. **Complete liver testing** before your first dose of ZINBRYTA

Complete Monthly Liver Testing and Report Side Effects

After starting ZINBRYTA

1. **Complete** monthly liver testing (before your next dose) during ZINBRYTA treatment and for 6 months after discontinuation of ZINBRYTA
2. **Inform your doctor** if you have any side effects, reactions or symptoms after receiving ZINBRYTA
3. **Show** the **ZINBRYTA REMS Program Patient Wallet Card** to your doctor when you have any medical treatment, even if it is not for your MS
4. **Notify** the ZINBRYTA REMS Program if you **change your ZINBRYTA doctor**, if your **contact information changes,** or if you **discontinue treatment with ZINBRYTA**

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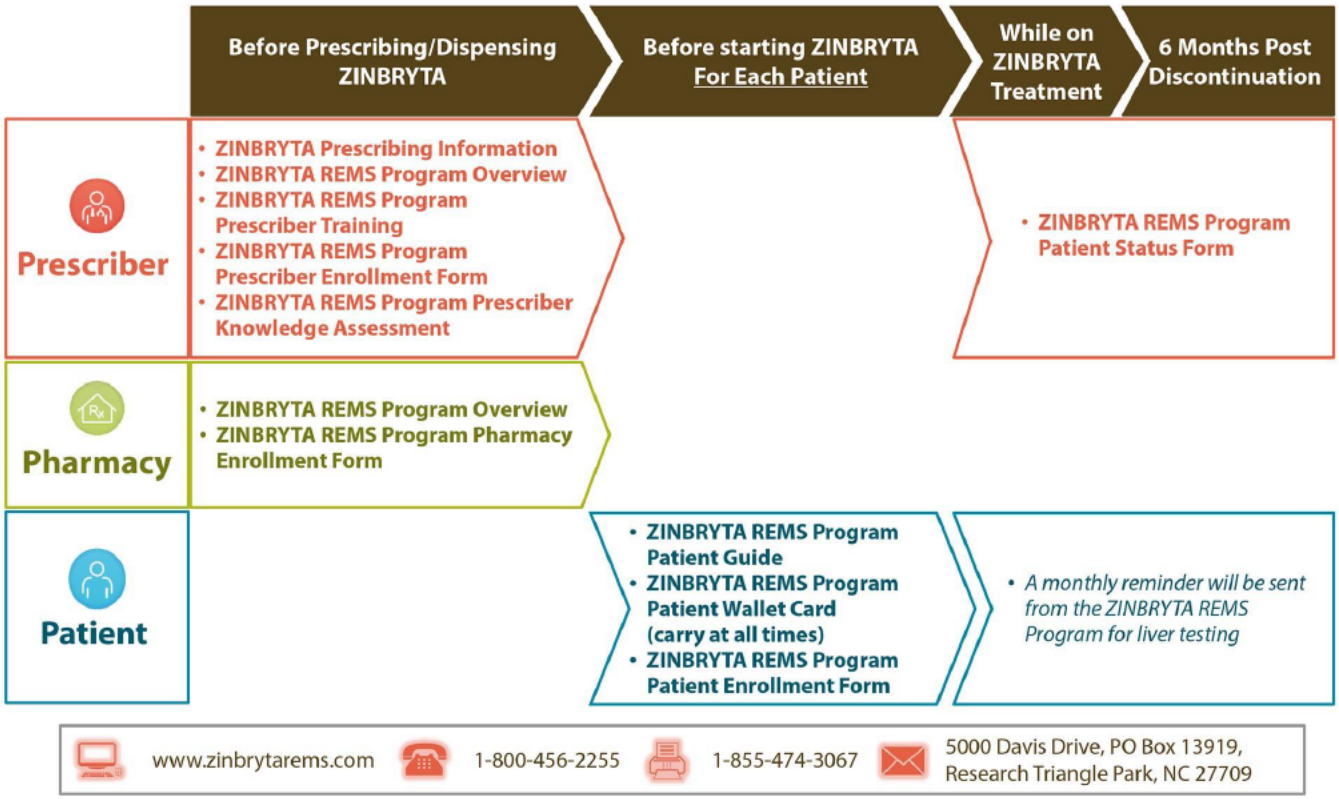
ZINBRYTA REMS Program Resources



ZINBRYTA is indicated for the treatment of 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.

Please see Prescribing Information, including BOXED WARNING, for additional Important Safety Information.

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If you have any questions regarding the ZINBRYTA REMS Program,
visit www.zinbrytarems.com or call: **1-800-456-2255**
Fax: **1-855-474-3067**
Mail: **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**

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Reference ID: 3938318

ZINBRYTA REMS (Risk Evaluation and Mitigation Strategy) Program Prescriber Training

This training includes information about:

- Risks of life-threatening, severe hepatic injury and serious immune-mediated disorders associated with ZINBRYTA
- Requirements for monthly monitoring and evaluation of your patient
- The ZINBRYTA REMS Program requirements

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The review of this document is necessary to successfully pass the ZINBRYTA REMS Program Prescriber Knowledge Assessment in order to prescribe ZINBRYTA

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What Is ZINBRYTA?

- ZINBRYTA is indicated for the treatment of 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.
- Please see Prescribing Information, including BOXED WARNING, for additional Important Safety Information.

Risks Associated With ZINBRYTA: *Hepatic Injury*

Observations in the Clinical Trials

- **ZINBRYTA can cause life-threatening severe hepatic injury, including liver failure and autoimmune hepatitis.**

  - Elevations of serum transaminases and severe hepatic injury have occurred in patients treated with ZINBRYTA. In clinical trials, serum transaminase elevations occurred during treatment and up to 4 months after the last dose of ZINBRYTA.
  - An increased incidence of elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times the upper limit of normal (ULN) was reported in ZINBRYTA-treated patients compared with placebo-treated patients (4% vs 1%) and compared with AVONEX-treated patients (6% vs 3%).
  - Serious events, including acute hepatic failure and hepatitis including autoimmune hepatitis, were observed in 1% of patients.
  - In a clinical trial, a case of fatal autoimmune hepatitis occurred in a patient reinitiating treatment with daclizumab after a planned 6-month treatment interruption period.
  - The incidence of drug discontinuation due to hepatic disorders was 5% in ZINBRYTA-treated patients and 4% in AVONEX-treated patients.

Risks Associated With ZINBRYTA: *Immune-mediated Disorders*

Observations in the Clinical Trials

- **Immune-mediated disorders including 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.**
  - Treatment with ZINBRYTA can increase the risk of immune-mediated disorders, including autoimmune disorders such as autoimmune hepatitis.
  - Immune-mediated disorders including skin reactions, lymphadenopathy, and non-infectious colitis occurred in patients treated with ZINBRYTA. Additionally, a wide variety of other immune-mediated disorders have occurred infrequently with the use of ZINBRYTA. Many were single events and some were serious. The relationship to ZINBRYTA is unknown. These include single organ or systemic multi-organ inflammatory reactions.
  - Overall in clinical trials, immune-mediated conditions occurred in 28% of patients on ZINBRYTA, the most common of which were skin reactions and lymphadenopathy.
  - In the active controlled study, immune-mediated disorders were observed in 32% of ZINBRYTA-treated patients compared with 12% for AVONEX-treated patients.
  - Serious immune-mediated disorders were observed in 4% of patients treated with ZINBRYTA compared with less than 1% for AVONEX-treated patients.
- **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.**

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Risks Associated With ZINBRYTA: *Immune-mediated Disorders*

Observations in the Clinical Trials

1. Skin Reactions

- In clinical trials, skin reactions occurred in 18% of ZINBRYTA-treated patients compared to 13% of patients on placebo, and in 37% of ZINBRYTA-treated patients compared to 19% of AVONEX-treated patients.
- Skin reactions occurred at any time during treatment with ZINBRYTA.
- The most common skin reactions were dermatitis and eczema.
- Serious skin reactions occurred in 2% of subjects treated with ZINBRYTA and 0.1% of patients on AVONEX. 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.

Risks Associated With ZINBRYTA: *Immune-mediated Disorders*

Observations in the Clinical Trials

2. Lymphadenopathy

- In clinical trials, ZINBRYTA increased the incidence of lymphadenopathy, with onset occurring throughout the treatment period. In a controlled trial, 6% of ZINBRYTA-treated patients compared to 1% of AVONEX-treated patients developed lymphadenopathy or lymphadenitis.
- Serious events related to lymphadenopathy or lymphadenitis included infections, benign salivary neoplasm, skin reactions, thrombocytopenia, and interstitial lung changes.

3. Non-Infectious Colitis

- An increased incidence of serious colitis (less than 1%) was reported in patients treated with ZINBRYTA compared with placebo and AVONEX in clinical trials.
- Consider referring patients who develop symptoms of colitis (e.g. abdominal pain, fever, prolonged diarrhea) to a specialist.

Risks Associated With ZINBRYTA: *Immune-mediated Disorders*

Observations in the Clinical Trials

4. Other immune-mediated disorders

- A wide variety of other immune-mediated disorders have occurred infrequently with the use of ZINBRYTA. Many were single events and some were serious. The relationship to ZINBRYTA is unknown. These include single organ or systemic multi-organ inflammatory reactions.
- Some required treatment with systemic corticosteroids and required several months for resolution after the last dose of ZINBRYTA.

Additional Risks and Safety Information

- The information presented in this training program does not include a complete list of all safety information for ZINBRYTA.
- To review the complete safety information on ZINBRYTA, please refer to the Prescribing Information, including BOXED WARNING, for ZINBRYTA at www.zinbrytarems.com.

Clinical Considerations and Assessment

Reference ID: 3938318

Assessment Prior to Initiating ZINBRYTA

Baseline Tests Required

- Prior to starting ZINBRYTA, obtain and evaluate serum transaminases (ALT and AST) and total bilirubin levels.
- In clinical trials, baseline assessments were performed within 4 weeks of the initial dose of ZINBRYTA.

Contraindications

ZINBRYTA is contraindicated for patients with:

- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN.
- A history of autoimmune hepatitis or other autoimmune condition involving the liver.
- A history of hypersensitivity to daclizumab or any other components of the formulation.

ULN=upper limit of normal.

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Upon Initiation of ZINBRYTA: *Monitoring for Hepatic Injury*

Ongoing Tests Required

- Testing of serum transaminase (ALT and AST) levels and total bilirubin should be done monthly and assessed before the next dose of ZINBRYTA. Transaminase levels and total bilirubin should be followed 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.

Evaluating Monthly Lab Tests

Lab values	Recommendations
ALT, AST >5x ULN **OR** Total bilirubin >2x ULN **OR** ALT, AST >3 but <5x ULN and total bilirubin >1.5 but <2x ULN	Interrupt ZINBRYTA therapy and investigate for other etiologies of abnormal lab values 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 <2x ULN and total bilirubin is ≤ to ULN*

Monitoring and Evaluation

- If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (eg, 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.
- In patients with prolonged elevations of serum transaminases, evaluate for other possible causes, such as infection, and a specialist should evaluate the patient.
- Discontinue ZINBRYTA if autoimmune hepatitis is suspected. Treatment of autoimmune hepatitis with systemic corticosteroids and other immunosuppressant drugs may be appropriate. Some patients may need long-term immunosuppression.

* 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.

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Upon Initiation of ZINBRYTA: *Monitoring for Immune-mediated Disorders*

Monitoring and Evaluation

- For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes.
- Monitor for signs and symptoms such as fever, a serious diffuse or inflammatory rash, lymphadenopathy, symptoms of colitis (eg, abdominal pain, prolonged diarrhea) and other organ-specific symptoms.
- Some patients required invasive procedures for diagnosis (eg, 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.
- If a patient develops a serious immune disorder consider stopping ZINBRYTA and refer the patient to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment.

Introduction to the ZINBRYTA REMS Program

Reference ID: 3938318

What Is the ZINBRYTA REMS Program?

- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug continue to outweigh its risks.
- **Due to the risks of severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis, and other immune -mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis, ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program.**

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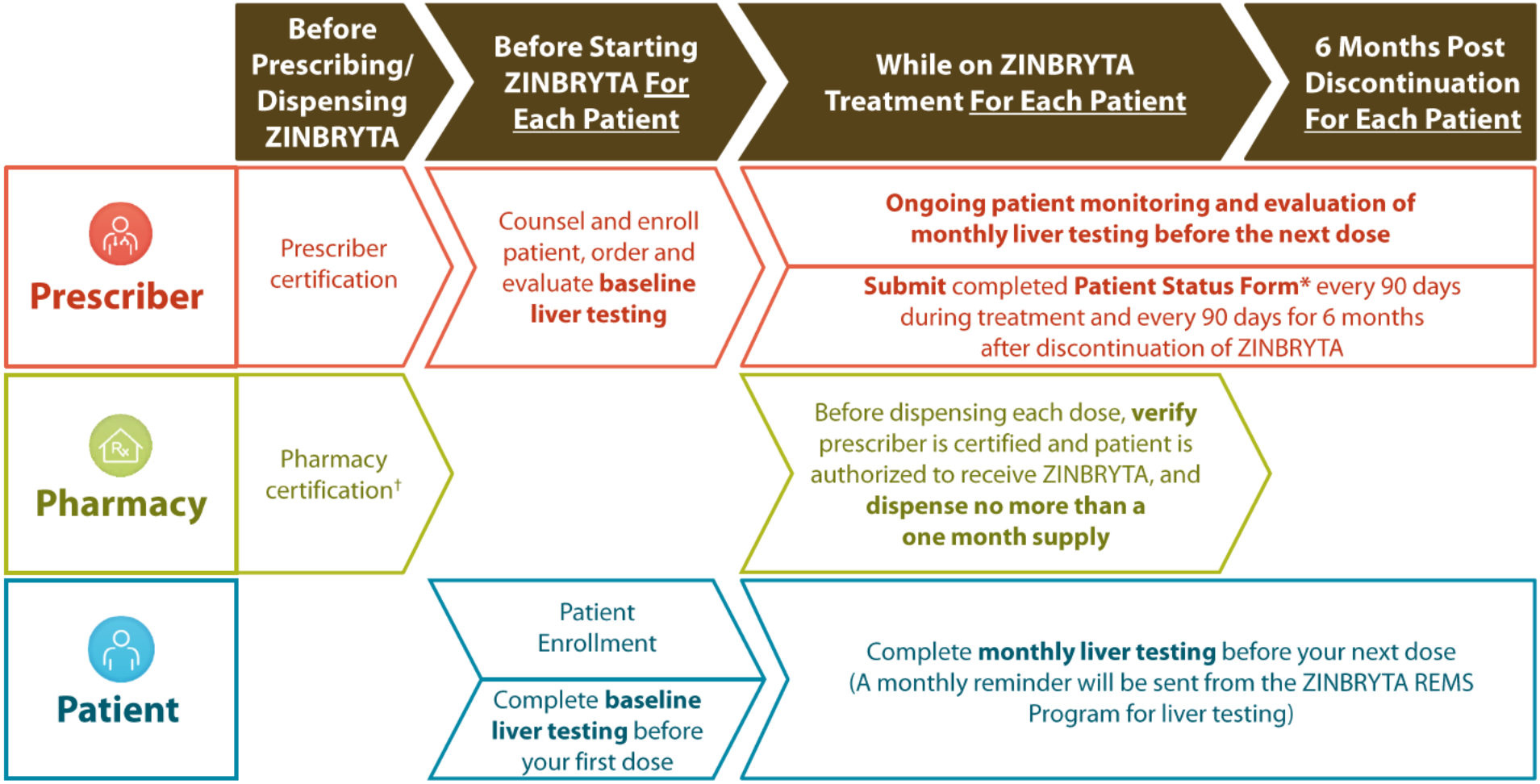
How Does the ZINBRYTA REMS Program Work?



* Every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA, the ZINBRYTA REMS Program will send an individualized Patient Status Form to the certified prescriber for completion.

† Recertify if there is a change in authorized representative.

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Requirements and Roles of Prescribers, Pharmacies, and Patients

Reference ID: 3938318

What are the Requirements of the ZINBRYTA REMS Program?

Prescribers

To prescribe ZINBRYTA:

1. **Become certified** by completing a one-time certification process
2. As you start patients on ZINBRYTA, **counsel and enroll** them into the ZINBRYTA REMS Program, complete the prescription, and order and evaluate baseline liver testing
3. **Perform** ongoing patient monitoring, evaluate **monthly liver testing** prior to each patient's next dose, and complete the ZINBRYTA REMS Program Patient Status Forms for each patient every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA

Pharmacies

To dispense ZINBRYTA:

1. **Designate an authorized representative, become certified,** and **recertify** if there is a change in the authorized representative
2. **Train** staff and **comply** with REMS requirements
3. Before dispensing each dose, **verify** prescriber is certified and patient is authorized to receive ZINBRYTA, and **dispense no more than a one month supply**

Patients

To receive ZINBRYTA:

1. **Understand the risks** associated with ZINBRYTA
2. **Enroll** in the ZINBRYTA REMS Program by completing the ZINBRYTA REMS Program Patient Enrollment Form with your doctor
3. **Complete** baseline liver testing before your first dose and monthly liver testing before your next dose of ZINBRYTA. A monthly reminder will be sent from the ZINBRYTA REMS Program for liver testing

- Prescribers and Pharmacies must report any adverse events suggestive of severe hepatic injury and serious immune-mediated disorders to the ZINBRYTA REMS Program

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How Does a Prescriber Become Certified in the Program?

Become Certified (One-time) → **Enroll Your Patients** → **Monitor Your Patients**

Before prescribing ZINBRYTA

1. **Review** the following educational materials on ZINBRYTA to understand the risks of severe and life-threatening hepatic injury including autoimmune hepatitis, and serious immune-mediated disorders, and the REMS Program:
   - **ZINBRYTA Prescribing Information**
   - **ZINBRYTA REMS Program Overview**
   - **ZINBRYTA REMS Program Prescriber Training**
2. **Complete** and **submit** the ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form, using the submission details at the end of this presentation
3. Once completed, the ZINBRYTA REMS Program will contact you to finish certification. Within 2 business days upon receipt of your form, you will receive correspondence from the ZINBRYTA REMS Program. Correspondence will include:
   - How to retake the **ZINBRYTA REMS Program Prescriber Knowledge Assessment**, if necessary

   OR

   - A confirmation of your enrollment and certification in the ZINBRYTA REMS Program

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How Does a Prescriber Enroll Appropriate Patients in the Program?

Become Certified (One-time) → **Enroll Your Patients** → **Monitor Your Patients**

Before starting each patient on ZINBRYTA

1. **Counsel** your patient about the risks associated with ZINBRYTA and the need for baseline and monthly liver testing before the next dose and share the resources below
   - **ZINBRYTA REMS Program Patient Guide**
   - **ZINBRYTA REMS Program Patient Wallet Card**
2. **Order and evaluate** the baseline liver testing before each patient's first dose of ZINBRYTA
3. **Submit** a completed ZINBRYTA REMS Program Patient Enrollment Form and prescription for each patient, store a copy in the patient's records. Your patient can expect to be contacted by the ZINBRYTA REMS Program

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What Are the Monitoring Requirements for Prescribers After Starting a Patient on ZINBRYTA?

Become Certified (One-time) → **Enroll Your Patients** → **Monitor Your Patients**

Once your patient is on ZINBRYTA

1. **Monitor** your ZINBRYTA patients on an ongoing basis. Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Transaminase levels and total bilirubin should be followed monthly for 6 months after the last dose of ZINBRYTA
2. **Submit** a completed ZINBRYTA REMS Program Patient Status Form* for each patient **every 90 days** during treatment and **every 90 days for 6 months after discontinuation** of ZINBRYTA using the submission details at the end of this presentation
3. **Report** any adverse events suggestive of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders to the ZINBRYTA REMS Program. You may be contacted for more information about these events
4. **Inform** the ZINBRYTA REMS Program if a patient is no longer under your care or has discontinued ZINBRYTA

* Every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA, the ZINBRYTA REMS Program will send an individualized Patient Status Form to the certified prescriber for completion.

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Overview of ZINBRYTA REMS Program Forms

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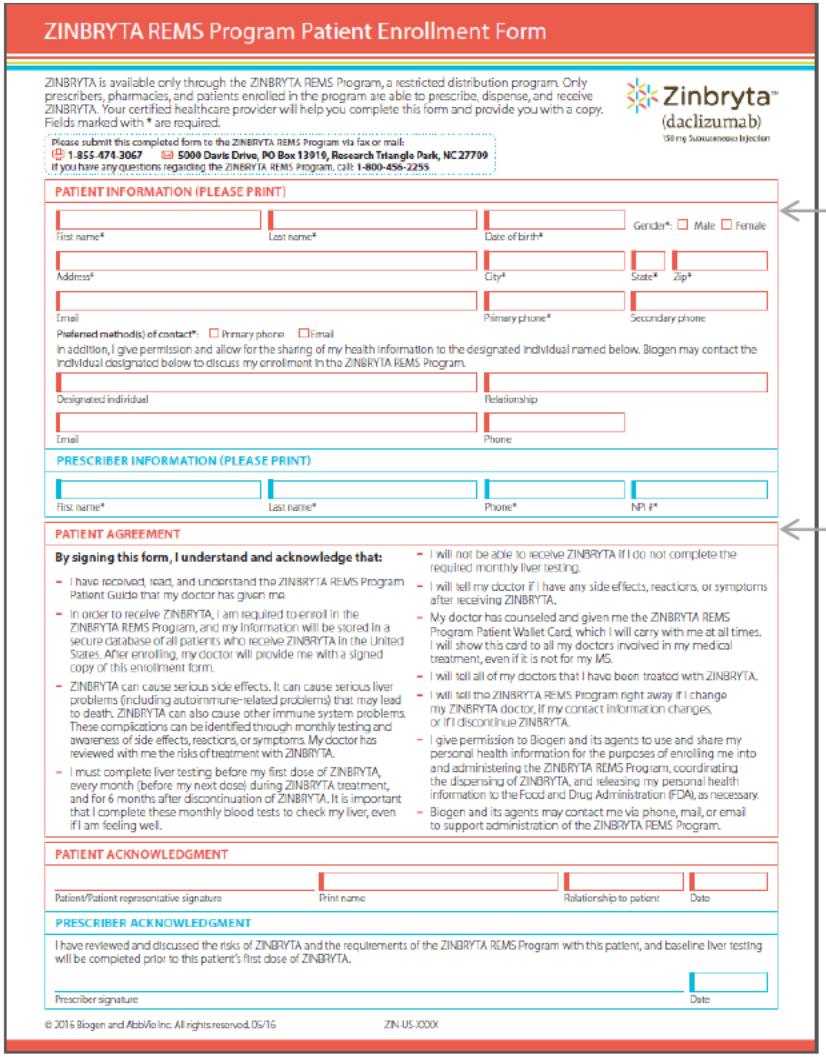
Prescribers Must Enroll Each Patient in the ZINBRYTA REMS Program



ZINBRYTA REMS Program Patient Enrollment Form

ZINBRYTA is available only through the ZINBRYTA REMS Program, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program are able to prescribe, dispense, and receive ZINBRYTA. Your certified healthcare provider will help you complete this form and provide you with a copy. Fields marked with * are required.

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Please submit this completed form to the ZINBRYTA REMS Program via fax or mail:
1-855-474-3067 | 5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709
If you have any questions regarding the ZINBRYTA REMS Program, call: 1-800-456-2255

PATIENT INFORMATION (PLEASE PRINT)

First name* | Last name* | Date of birth* | Gender*: ☐ Male ☐ Female
Address* | City* | State* | Zip*
Email | Primary phone* | Secondary phone
Preferred method(s) of contact*: ☐ Primary phone ☐ Email

In addition, I give permission and allow for the sharing of my health information to the designated individual named below. Biogen may contact the individual designated below to discuss my enrollment in the ZINBRYTA REMS Program.

Designated individual | Relationship
Email | Phone

PRESCRIBER INFORMATION (PLEASE PRINT)

First name* | Last name* | Phone* | NPI #*

PATIENT AGREEMENT

By signing this form, I understand and acknowledge that:

- I have received, read, and understand the ZINBRYTA REMS Program Patient Guide that my doctor has given me.
- In order to receive ZINBRYTA, I am required to enroll in the ZINBRYTA REMS Program, and my information will be stored in a secure database of all patients who receive ZINBRYTA in the United States. After enrolling, my doctor will provide me with a signed copy of this enrollment form.
- ZINBRYTA can cause serious side effects. It can cause serious liver problems (including autoimmune-related problems) that may lead to death. ZINBRYTA can also cause other immune system problems. These complications can be identified through monthly testing and awareness of side effects, reactions, or symptoms. My doctor has reviewed with me the risks of treatment with ZINBRYTA.
- I must complete liver testing before my first dose of ZINBRYTA, every month (before my next dose) during ZINBRYTA treatment, and for 6 months after discontinuation of ZINBRYTA. It is important that I complete these monthly blood tests to check my liver, even if I am feeling well.
- I will not be able to receive ZINBRYTA if I do not complete the required monthly liver testing.
- I will tell my doctor if I have any side effects, reactions, or symptoms after receiving ZINBRYTA.
- My doctor has counseled and given me the ZINBRYTA REMS Program Patient Wallet Card, which I will carry with me at all times. I will show this card to all my doctors involved in my medical treatment, even if it is not for my MS.
- I will tell all of my doctors that I have been treated with ZINBRYTA.
- I will tell the ZINBRYTA REMS Program right away if I change my ZINBRYTA doctor, if my contact information changes, or if I discontinue ZINBRYTA.
- I give permission to Biogen and its agents to use and share my personal health information for the purposes of enrolling me into and administering the ZINBRYTA REMS Program, coordinating the dispensing of ZINBRYTA, and releasing my personal health information to the Food and Drug Administration (FDA), as necessary.
- Biogen and its agents may contact me via phone, mail, or email to support administration of the ZINBRYTA REMS Program.

PATIENT ACKNOWLEDGMENT

Patient/Patient representative signature | Print name | Relationship to patient | Date

PRESCRIBER ACKNOWLEDGMENT

I have reviewed and discussed the risks of ZINBRYTA and the requirements of the ZINBRYTA REMS Program with this patient, and baseline liver testing will be completed prior to this patient's first dose of ZINBRYTA.

Prescriber signature | Date

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- Form includes:
  - Patient information and acknowledgment of REMS requirements.
  - Prescriber information, acknowledgment that this patient was counselled on the risks associated with ZINBRYTA and that baseline testing will be completed prior to patient's first dose of ZINBRYTA.

- Missing information will prompt a follow-up from the ZINBRYTA REMS Program.
- Prescriber will be notified upon successful enrollment of each patient.

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ZINBRYTA REMS Program Patient Status Form: To Be Completed by Prescriber Every 90 Days While on Therapy and Every 90 Days for 6 Months Post Discontinuation

- Prescribers will receive an individualized ZINBRYTA REMS Program Patient Status Form for completion every 90 days during treatment and every 90 days for 6 months post discontinuation of ZINBRYTA.
- A ZINBRYTA certified prescriber or delegate may complete and submit this form on behalf of the certified Prescriber of record. The certified Prescriber of record is responsible for compliance with the ZINBRYTA REMS Program requirements, including monitoring, evaluation, and management of each patient under his/her care.

Is the above-named patient still under the care of <Prescriber Name>? ☐ Yes ☐ No

If No, please indicate the name of the prescriber now responsible for this patient's care

Prescriber Name _____ Prescriber Number _____ ☐ Unknown

PATIENT STATUS

1. This patient has completed required liver testing during the last 90 days: ☐ Yes ☐ No
2. Has this patient been diagnosed with any of the following that you have *not already* reported to Biogen in the last 90 days?
   a. Hepatic injury ☐ Yes ☐ No
      - *May include elevated liver enzymes and/or total bilirubin:*
        - *ALT or AST >5x ULN* ***OR***
        - *Total bilirubin >2x ULN* ***OR***
        - *ALT or AST ≥3xULN but <5xULN and total bilirubin >1.5xULN but <2xULN*
      - *Or a suspected or confirmed diagnosis (e.g. autoimmune hepatitis)*

   b. Immune-mediated disorders ☐ Yes ☐ No
      - *May include skin reactions, lymphadenopathy, non-infectious colitis or other suspected or newly diagnosed single or multi-organ immune-mediated disorder or systemic inflammatory reaction*
3. (On-Therapy patients only) This patient will continue to receive ZINBRYTA: ☐ Yes ☐ No

   If no, ZINBRYTA REMS will begin the de-enrollment process for the patient, the patient ***will not be eligible to receive ZINBRYTA****, and you will be contacted for patient status information every 90 days for 6 months post-therapy discontinuation.*

- Prescribers will be contacted to obtain missing information, based on responses provided, or if the form is not received.
- Please note that if the prescriber does not submit the form, it may result in a delay of the patient receiving ZINBRYTA.

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If you have any questions regarding the ZINBRYTA REMS Program,
visit www.zinbrytarems.com or call: **1-800-456-2255**
Fax: **1-855-474-3067**
Mail: **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**

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ZINBRYTA REMS Program Prescriber Enrollment Form

ZINBRYTA is available only through the ZINBRYTA REMS Program, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the Program are able to prescribe, dispense, and receive ZINBRYTA.

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Instructions:

1. Review the ZINBRYTA Prescribing Information, the ZINBRYTA REMS Program Overview, and the ZINBRYTA REMS Program Prescriber Training
2. Complete the ZINBRYTA REMS Program Prescriber Knowledge Assessment and this ZINBRYTA REMS Program Prescriber Enrollment Form
3. Submit the ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form. Please complete all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the ZINBRYTA REMS Program will contact you to finish certification.

Please submit this completed form to the ZINBRYTA REMS Program via fax or mail:
1-855-474-3067 **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**
If you have any questions regarding the ZINBRYTA REMS Program, call: **1-800-456-2255**

PRESCRIBER INFORMATION (PLEASE PRINT)

Last Name* | First Name* | Email

Address*

City* | State* | ZIP*

Office Phone Number* | Fax Number* | Mobile Phone Number

Clinical/Hospital Affiliation

National Provider Identification (NPI) Number*

Best time(s) to contact: ☐ Morning ☐ Afternoon ☐ Evening

Preferred method(s) of contact: ☐ Phone ☐ Email ☐ Fax

State License # | Tax ID #

*Mandatory Field

OFFICE CONTACT INFORMATION (PLEASE PRINT)

Office Contact Name | Office Contact Email | Office Contact Phone

ZINBRYTA REMS Program Prescriber Enrollment Form *(cont'd)*

PRESCRIBER AGREEMENT

By completing this form, I understand and agree that:

- ZINBRYTA is only available through the ZINBRYTA REMS Program and I must comply with the program requirements in order to prescribe ZINBRYTA.
- I have reviewed the ZINBRYTA Prescribing Information, ZINBRYTA REMS Program Overview, and ZINBRYTA REMS Program Prescriber Training and must successfully complete the ZINBRYTA REMS Program Knowledge Assessment.
- By completing the certification requirements and signing this ZINBRYTA REMS Program Prescriber Enrollment Form, I will be enrolled in the ZINBRYTA REMS Program and can prescribe ZINBRYTA.
- In order to prescribe ZINBRYTA to a patient, I must enroll the patient in the ZINBRYTA REMS Program by:
  - i. Counseling each patient about the risks of severe and fatal hepatic injury and serious immune mediated disorders associated with ZINBRYTA and the need for baseline and monthly liver testing, using the ZINBRYTA REMS Program Patient Guide and ZINBRYTA REMS Program Patient Wallet Card, and providing a copy of each to the patient.
  - ii. Completing and submitting the ZINBRYTA REMS Program Patient Enrollment Form for each patient to the ZINBRYTA REMS Program, storing a copy in the patient's records, and providing a copy to the patient.
- I understand the risks of severe and fatal hepatic injury and serious immune-mediated disorders associated with the use of ZINBRYTA, and the requirement for baseline and monthly monitoring in order to identify and mitigate these risks.
- I am responsible for ordering and evaluating serum transaminases (ALT and AST) and total bilirubin levels prior to each patients' first dose of ZINBRYTA.
- I am responsible for ordering and evaluating ALT, AST and total bilirubin every month (prior to the next dose) during treatment and monthly for 6 months after the last dose of ZINBRYTA. A patient who does not complete the required liver testing cannot receive ZINBRYTA.
- I will report any adverse events suggestive of hepatic injury or immune-mediated disorders to the ZINBRYTA REMS Program.
- I will complete and submit the ZINBRYTA REMS Program Patient Status Form every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA.
- I will notify the ZINBRYTA REMS Program if an enrolled patient is no longer under my care or if the patient discontinues treatment with ZINBRYTA.
- If I do not maintain compliance with the requirements of the ZINBRYTA REMS Program, I will no longer be able to prescribe ZINBRYTA.
- Biogen and its agents may contact me via phone, mail, fax, or email to support administration of the ZINBRYTA REMS Program.

PRESCRIBER SIGNATURE

Prescriber Signature

Date

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Reference ID: 3938318

ZINBRYTA REMS (Risk Evaluation and Mitigation Strategy) Program Prescriber Knowledge Assessment

To become a certified prescriber in the ZINBRYTA REMS Program, you must complete this ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form. You need to answer ALL 7 questions correctly to be certified.

1. Review the following materials:
   - ZINBRYTA Prescribing Information
   - ZINBRYTA REMS Program Overview
   - ZINBRYTA REMS Program Prescriber Training

2. Complete all 7 questions and print your name and National Provider Identifier (NPI).

3. Submit your completed ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form to the ZINBRYTA REMS Program via fax or mail:

   Fax: 1-855-474-3067

   Mail: 5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709

You will be contacted by the ZINBRYTA REMS Program on the status of your certification within 2 business days upon receipt. When contacted, you will receive either:

- Confirmation of your certification in the ZINBRYTA REMS Program

OR

- Instructions on how to retake the ZINBRYTA REMS Program Prescriber Knowledge Assessment, if necessary

Zinbryta™
(daclizumab)
150 mg Subcutaneous Injection

If you have any questions regarding the ZINBRYTA REMS Program, call: **1-800-456-2255**

Reference ID: 3938318

ZINBRYTA REMS Program Prescriber Knowledge Assessment

Questions 1-7

Select the one best answer.

QUESTION 1

Before starting each patient on ZINBRYTA, I should:

- ☐ a) Counsel them about the risks associated with ZINBRYTA and the need for baseline and monthly liver testing before the next dose, and provide the *ZINBRYTA REMS Program Patient Guide* and *ZINBRYTA REMS Program Patient Wallet Card*
- ☐ b) Order and evaluate baseline liver testing before each patient's first dose
- ☐ c) Complete the ZINBRYTA REMS Program Patient Enrollment Form
- ☐ d) All of the above

QUESTION 2

In order to receive ZINBRYTA, patients must enroll in the ZINBRYTA REMS Program and comply with ongoing monitoring requirements.

- ☐ a) True
- ☐ b) False

QUESTION 3

ZINBRYTA treatment initiation is not recommended in patients with pre-existing hepatic disease or hepatic impairment, including patients with ALT or AST >2 times the upper limit of normal.

- ☐ a) True
- ☐ b) False

QUESTION 4

I should monitor and evaluate my patient's liver testing:

- ☐ a) Only at baseline before the first dose
- ☐ b) At baseline before the first dose and every 3 months before the next dose
- ☐ c) At baseline before the first dose and every 6 months before the next dose
- ☐ d) At baseline before the first dose, monthly before the next dose during ZINBRYTA treatment, and for 6 months after discontinuation

QUESTION 5

I should submit a completed *ZINBRYTA REMS Program Patient Status Form* for each patient every 90 days during treatment and every 90 days for 6 months after discontinuation.

- ☐ a) True
- ☐ b) False

QUESTION 6

The most common immune-mediated reactions seen with ZINBRYTA treatment are skin reactions and lymphadenopathy.

- ☐ a) True
- ☐ b) False

QUESTION 7

Treatment should be interrupted for the following lab values:

- ☐ a) If ALT or AST is >5 times the ULN
- ☐ b) Total bilirubin is >2 times the ULN
- ☐ c) ALT or AST is ≥3 but <5 times the ULN and total bilirubin is >1.5 but <2 times the ULN
- ☐ d) All of the above

Please print your name and NPI number so we can associate your responses with your ZINBRYTA REMS Program certification.

Prescriber Name _____ Prescriber NPI _____

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Reference ID: 3938318

ZINBRYTA REMS Program Patient Enrollment Form

ZINBRYTA is available only through the ZINBRYTA REMS Program, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program are able to prescribe, dispense, and receive ZINBRYTA. Your certified healthcare provider will help you complete this form and provide you with a copy. Fields marked with * are required.

Zinbryta™ (daclizumab) 150 mg Subcutaneous Injection

Please submit this completed form to the ZINBRYTA REMS Program via fax or mail:
1-855-474-3067 **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**
If you have any questions regarding the ZINBRYTA REMS Program, call: **1-800-456-2255**

PATIENT INFORMATION (PLEASE PRINT)

First name* | Last name* | Date of birth* | Gender*: ☐ Male ☐ Female

Address* | City* | State* | Zip*

Email | Primary phone* | Secondary phone

Preferred method(s) of contact*: ☐ Primary phone ☐ Email

In addition, I give permission and allow for the sharing of my health information to the designated individual named below. Biogen may contact the individual designated below to discuss my enrollment in the ZINBRYTA REMS Program.

Designated individual | Relationship

Email | Phone

PRESCRIBER INFORMATION (PLEASE PRINT)

First name* | Last name* | Phone* | NPI #*

PATIENT AGREEMENT

By signing this form, I understand and acknowledge that:

- I have received, read, and understand the ZINBRYTA REMS Program Patient Guide that my doctor has given me.
- In order to receive ZINBRYTA, I am required to enroll in the ZINBRYTA REMS Program, and my information will be stored in a secure database of all patients who receive ZINBRYTA in the United States. After enrolling, my doctor will provide me with a signed copy of this enrollment form.
- ZINBRYTA can cause serious side effects. It can cause serious liver problems (including autoimmune-related problems) that may lead to death. ZINBRYTA can also cause other immune system problems. These complications can be identified through monthly testing and awareness of side effects, reactions, or symptoms. My doctor has reviewed with me the risks of treatment with ZINBRYTA.
- I must complete liver testing before my first dose of ZINBRYTA, every month (before my next dose) during ZINBRYTA treatment, and for 6 months after discontinuation of ZINBRYTA. It is important that I complete these monthly blood tests to check my liver, even if I am feeling well.
- I will not be able to receive ZINBRYTA if I do not complete the required monthly liver testing.
- I will tell my doctor if I have any side effects, reactions, or symptoms after receiving ZINBRYTA.
- My doctor has counseled and given me the ZINBRYTA REMS Program Patient Wallet Card, which I will carry with me at all times. I will show this card to all my doctors involved in my medical treatment, even if it is not for my MS.
- I will tell all of my doctors that I have been treated with ZINBRYTA.
- I will tell the ZINBRYTA REMS Program right away if I change my ZINBRYTA doctor, if my contact information changes, or if I discontinue ZINBRYTA.
- I give permission to Biogen and its agents to use and share my personal health information for the purposes of enrolling me into and administering the ZINBRYTA REMS Program, coordinating the dispensing of ZINBRYTA, and releasing my personal health information to the Food and Drug Administration (FDA), as necessary.
- Biogen and its agents may contact me via phone, mail, or email to support administration of the ZINBRYTA REMS Program.

PATIENT ACKNOWLEDGMENT

Patient/Patient representative signature | Print name | Relationship to patient | Date

PRESCRIBER ACKNOWLEDGMENT

I have reviewed and discussed the risks of ZINBRYTA and the requirements of the ZINBRYTA REMS Program with this patient, and baseline liver testing will be completed prior to this patient's first dose of ZINBRYTA.

Prescriber signature | Date

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Reference ID: 3938318

ZINBRYTA REMS Program Patient Status Form

This form must be completed every 90 days for all patients treated with ZINBRYTA during treatment and every 90 days for 6 months after discontinuation. Please complete this form by <DATE> and return to the ZINBRYTA REMS Program. You may also be contacted for additional information in response to answers provided on this form.

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Please submit this completed form to the ZINBRYTA REMS Program via fax or mail:
1-855-474-3067 **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**
If you have any questions regarding the ZINBRYTA REMS Program, call: **1-800-456-2255**

<Patient Therapy Status>
Patient Therapy Status

<Today's Date>
Today's Date

PRESCRIBER INFORMATION

<Prescriber Name>
Prescriber Name

<Prescriber Address>
Prescriber Address

<City> City | <State> State | <ZIP> ZIP

<Prescriber Enrollment ID>
Prescriber Enrollment ID

PATIENT INFORMATION

<Patient Name>
Patient Name

<Patient Enrollment ID>
Patient Enrollment ID

<DOB>
Patient Date of Birth

Is the above-named patient still under the care of <Prescriber Name>? ☐ Yes ☐ No

If No, please indicate the name of the prescriber now responsible for this patient's care

Prescriber Name _____ Prescriber Number _____ ☐ Unknown

PATIENT STATUS

1. This patient has completed required liver testing during the last 90 days: ☐ Yes ☐ No
2. Has this patient been diagnosed with any of the following that you have *not already* reported to Biogen in the last 90 days?
   a. Hepatic injury ☐ Yes ☐ No
      - *May include elevated liver enzymes and/or total bilirubin:*
        - *ALT or AST >5x ULN* ***OR***
        - *Total bilirubin >2x ULN* ***OR***
        - *ALT or AST ≥3xULN but <5xULN and total bilirubin >1.5xULN but <2xULN*
      - *Or a suspected or confirmed diagnosis (e.g. autoimmune hepatitis)*

   b. Immune-mediated disorders ☐ Yes ☐ No
      - *May include skin reactions, lymphadenopathy, non-infectious colitis or other suspected or newly diagnosed single or multi-organ immune-mediated disorder or systemic inflammatory reaction*
3. (On-Therapy patients only) This patient will continue to receive ZINBRYTA: ☐ Yes ☐ No

   If no, ZINBRYTA REMS will begin the de-enrollment process for the patient, the patient ***will not be eligible to receive ZINBRYTA****, and you will be contacted for patient status information every 90 days for 6 months post-therapy discontinuation.*

ZINBRYTA CERTIFIED PRESCRIBER OR DELEGATE SIGNATURE

Signature _____ Date _____

Print name _____

Please Note: A ZINBRYTA certified prescriber or delegate may complete and submit this form on behalf of the certified Prescriber of record. The certified Prescriber of record is responsible for compliance with the ZINBRYTA REMS Program requirements, including monitoring, evaluation, and management of each patient under his/her care. If you have questions on this information, please call 1-800-456-2255.

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Reference ID: 3938318

For Patients

ZINBRYTA REMS (Risk Evaluation and Mitigation Strategy) Program Patient Guide

Patients: Your doctor will go over this patient guide with you. It is important to ask any questions you might have. Keep this guide for important safety information about the serious risks of ZINBRYTA.

Healthcare Providers: Review this patient guide with your patient, and provide your patient a copy to take home.

To learn more about ZINBRYTA, please talk to your doctor and visit www.zinbrytarems.com. You can also call us at 1-800-456-2255, Monday to Friday, 8:30AM to 8:00PM (ET).

Zinbryta™
(daclizumab)
150 mg Subcutaneous Injection

Reference ID: 3938318

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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.

What are the most serious risks of ZINBRYTA?

ZINBRYTA can cause serious liver problems (including autoimmune-related liver problems) that may lead to death. It can also cause other immune system problems. **Contact your doctor right away and seek emergency medical care if you have any of the following symptoms:**

Liver problems. Symptoms include:

- 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 cells attack other cells or organs in the body) and other immune system problems. Symptoms include:

- 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

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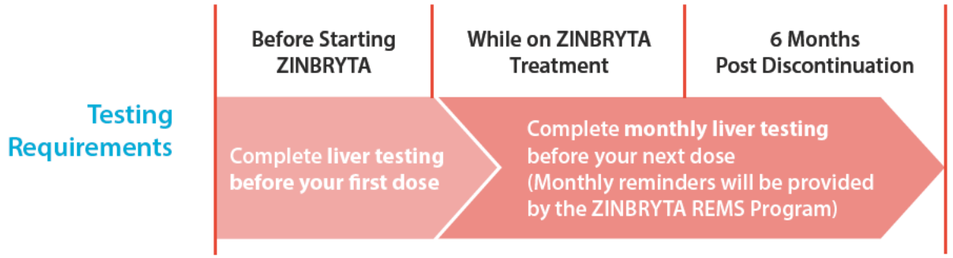
150 mg Subcutaneous Injection

What is the ZINBRYTA REMS Program?

- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug continue to outweigh its risks.
- 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.
- The ZINBRYTA REMS Program educates patients and doctors about these risks associated with ZINBRYTA.
- Requirements of the ZINBRYTA REMS Program include the following:
  - You and your doctor must be enrolled in the ZINBRYTA REMS Program in order to receive and prescribe ZINBRYTA.
  - ZINBRYTA is only available from pharmacies that participate in the ZINBRYTA REMS Program.
- Your doctor will do blood tests to check your liver before you start using ZINBRYTA, every month while you are using ZINBRYTA, and for 6 months after you stop using ZINBRYTA. Your doctor will check your test results before your next dose.



It is very important that you complete these monthly blood tests to check your liver, even if you are feeling well.

How do I enroll in the ZINBRYTA REMS Program and what is required of me?

Before starting ZINBRYTA:

☑ **Discuss** with your doctor and understand:
- The risk of serious liver problems and immune system problems.
- The required monthly liver testing.

☑ **Receive and read:**
- This **ZINBRYTA REMS Program Patient Guide**.
- The **ZINBRYTA REMS Program Patient Wallet Card** (fill in your name and your doctor's information).

☑ **Complete** the **ZINBRYTA REMS Program Patient Enrollment Form** with your doctor.

☑ **Complete liver testing** before your first dose of ZINBRYTA.

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How do I enroll in the ZINBRYTA REMS Program and what is required of me? (cont'd)

Your doctor will help you fill out the ZINBRYTA REMS Program Patient Enrollment Form mentioned on the previous page. You will be asked to acknowledge the following:

- I have received, read, and understand the ZINBRYTA REMS Program Patient Guide that my doctor has given me.
- In order to receive ZINBRYTA, I am required to enroll in the ZINBRYTA REMS Program, and my information will be stored in a secure database of all patients who receive ZINBRYTA in the United States. After enrolling, my doctor will provide me with a signed copy of this enrollment form.
- ZINBRYTA can cause serious side effects. It can cause serious liver problems (including autoimmune-related liver problems) that may lead to death. ZINBRYTA can also cause other immune system problems. These complications can be identified through monthly testing and awareness of side effects, reactions, or symptoms. My doctor has reviewed with me the risks of treatment with ZINBRYTA.
- I must complete liver testing before my first dose of ZINBRYTA, every month (before my next dose) during ZINBRYTA treatment, and for 6 months after discontinuation of ZINBRYTA. It is important that I complete these monthly blood tests to check my liver, even if I am feeling well.
- I will not be able to receive ZINBRYTA if I do not complete the required monthly liver testing.
- I will tell my doctor if I have any side effects, reactions, or symptoms after receiving ZINBRYTA.
- My doctor has counseled and given me the ZINBRYTA REMS Program Patient Wallet Card, which I will carry with me at all times. I will show this card to all my doctors involved in my medical treatment, even if it is not for my MS.
- I will tell all of my doctors that I have been treated with ZINBRYTA.
- I will tell the ZINBRYTA REMS Program right away if I change my ZINBRYTA doctor, if my contact information changes, or if I discontinue ZINBRYTA.
- I give permission to Biogen and its agents to use and share my personal health information for the purposes of enrolling me into and administering the ZINBRYTA REMS Program, coordinating the dispensing of ZINBRYTA, and releasing my personal health information to the Food and Drug Administration (FDA), as necessary.
- Biogen and its agents may contact me via phone, mail, or email to support administration of the ZINBRYTA REMS Program.

After enrolling, what are the next steps? And how will I receive ZINBRYTA?

Upon enrollment:

1. A Biogen representative from the ZINBRYTA REMS Program will contact you to get you started.
2. The pharmacy will call you to schedule a shipment of ZINBRYTA that will come right to your home.
   - ZINBRYTA is only available from pharmacies that participate in the ZINBRYTA REMS Program.
   - The pharmacy will dispense only a one month supply at a time.
3. Once you start taking ZINBRYTA, it will be important for you to complete your liver testing every month before your next dose.

After starting ZINBRYTA:

☑ **Complete** monthly liver testing (before your next dose) during ZINBRYTA treatment and for 6 months after discontinuation.

☑ **Inform your doctor** if you have any side effects, reactions or symptoms after receiving ZINBRYTA.

☑ **Show** the **ZINBRYTA REMS Program Patient Wallet Card** to your doctor when you have any medical treatment, even if it is not for your MS.

☑ **Notify** the ZINBRYTA REMS Program if you **change your ZINBRYTA doctor**, if your **contact information changes**, or if you **discontinue treatment with ZINBRYTA.**

Zinbryta™
(daclizumab)
150 mg Subcutaneous Injection

If you have any questions regarding the ZINBRYTA REMS Program,
visit www.zinbrytarems.com or call: **1-800-456-2255**
Fax: **1-855-474-3067**
Mail: **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**

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150 mg Subcutaneous Injection

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ZINBRYTA REMS Program Patient Wallet Card

Carry this card with you at all times and show it to any doctor involved in your health care.

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Reference ID: 3938318

Emergency contact info

Patient Name

ZINBRYTA Doctor Name

ZINBRYTA Doctor's Phone Number

Reference ID: 3938318

Zinbryta™
(daclizumab)
150 mg Subcutaneous Injection

Important Safety Information for Patients taking ZINBRYTA

ZINBRYTA can cause serious liver problems (including autoimmune-related liver problems) that may lead to death. It can also cause other immune system problems.

Contact your doctor right away and seek emergency medical care if you have any of the following symptoms:

Zinbryta™
(daclizumab)
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Reference ID: 3938318

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:

- 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

Important Information for the Treating Physician

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This patient has been prescribed ZINBRYTA for the treatment of relapsing multiple sclerosis (MS). ZINBRYTA increases the risk of serious liver problems and immune system problems.

- If these conditions are suspected, please contact the ZINBRYTA prescribing physician as soon as possible.
- For more information about ZINBRYTA, please see the Prescribing Information, including BOXED WARNING, at www.zinbrytarems.com.
- Please report any adverse events to the ZINBRYTA REMS Program at 1-800-456-2255.

Zinbryta™

(daclizumab)

150 mg Subcutaneous Injection

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ZINBRYTA REMS Program Pharmacy Enrollment Form

ZINBRYTA is available only through the ZINBRYTA REMS Program, a restricted distribution program. Only prescribers, pharmacies, patients enrolled in the Program are able to prescribe, dispense, and receive ZINBRYTA. An authorized representative of the pharmacy must enroll the pharmacy in the ZINBRYTA REMS Program.

Submit the completed form to the ZINBRYTA REMS Program using the submission details below. ZINBRYTA REMS Program will notify Pharmacy upon successful certification.

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Please submit this completed form to the ZINBRYTA REMS Program via fax or mail:
1-855-474-3067 **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**
If you have any questions regarding the ZINBRYTA REMS Program, call: 1-800-456-2255

☐ New Certification ☐ Recertification with New Authorized Representative

PHARMACY INFORMATION (PLEASE PRINT) - ALL FIELDS MANDATORY

Name of Pharmacy

NCPDP Number

National Provider Identification (NPI) Number

Address

City

State

ZIP

Name of Authorized Representative

Title

Phone Number

Fax Number

Email Address

PHARMACY AGREEMENT

I am the authorized representative designated by my Pharmacy to coordinate the activities of the ZINBRYTA REMS Program. By signing this form, I agree, on behalf of myself and Pharmacy, to comply with the following program requirements:

- I will oversee implementation of and ensure my pharmacy's compliance with the ZINBRYTA REMS Program requirements.
- I have reviewed the ZINBRYTA REMS Program Overview and will ensure that all relevant staff involved in the dispensing of ZINBRYTA are trained on the ZINBRYTA REMS Program requirements (as described in the ZINBRYTA REMS Program Overview) and that a record of training is maintained.
- I understand that upon completing the certification requirements and signing this ZINBRYTA REMS Program Pharmacy Enrollment Form, this pharmacy will be enrolled in the ZINBRYTA REMS Program, upon confirmation from the ZINBRYTA REMS Program. I understand that my pharmacy will only dispense ZINBRYTA if certified by the ZINBRYTA REMS Program.
- I will ensure that prior to dispensing ZINBRYTA, my pharmacy will verify that the prescriber is certified and the patient is authorized to receive ZINBRYTA by contacting the ZINBRYTA REMS Program.
- This pharmacy will ensure that no more than a one month supply of ZINBRYTA is dispensed.
- This pharmacy will ensure any adverse events suggestive of hepatic injury or immune-mediated disorders are reported by Pharmacy to the ZINBRYTA REMS Program.
- This pharmacy will maintain and make available appropriate documentation reflecting that all processes and procedures are in place and are being followed for the ZINBRYTA REMS Program and provide copies of such documentation (including, without limitation, patient-specific information), upon request to Biogen, FDA, or any third party acting on behalf of Biogen or FDA.
- This pharmacy will comply with audits by Biogen, FDA, or a third party acting on behalf of Biogen or FDA to ensure compliance with the ZINBRYTA REMS Program.
- This pharmacy will confirm the authorized representative annually and must recertify in the ZINBRYTA REMS Program if there is a personnel change for that authorized representative.
- I understand that non-compliance with the requirements of the ZINBRYTA REMS Program will result in decertification of my Pharmacy and termination of the authorization to dispense ZINBRYTA.

AUTHORIZED REPRESENTATIVE SIGNATURE

Authorized Representative Signature

Date

Print Name

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Reference ID: 3938318

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Search GO

PRESCRIBERS | PHARMACIES | PATIENTS | FORMS AND RESOURCES

ZINBRYTA REMS Program

What is the ZINBRYTA (daclizumab) Risk Evaluation and Mitigation Strategy (REMS) Program?

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of a drug outweigh its risks. **Due to the risks of severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis, and other immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis, ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program.**

Prescribers

Click here to learn how to prescribe ZINBRYTA:

1. **Become certified** by completing a one-time certification process
2. As you start patients on ZINBRYTA, **counsel and enroll** them into the ZINBRYTA REMS Program, complete the prescription, and order and evaluate baseline liver testing
3. **Perform** ongoing patient monitoring, evaluate **monthly liver testing before each patient's next dose**, and complete the ZINBRYTA REMS Program Patient Status Forms for each patient every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA

Pharmacies

Click here to learn how to dispense ZINBRYTA*:

1. **Designate an authorized representative, become certified**, and **recertify** if there is a change in the authorized representative
2. **Train** staff and **comply** with REMS requirements
3. Before dispensing each dose, **verify** prescriber is certified and patient is authorized to receive ZINBRYTA, and **dispense no more than a one month supply**

Patients

Click here to learn how to receive ZINBRYTA:

1. **Understand the risks** associated with ZINBRYTA
2. **Enroll** in the ZINBRYTA REMS Program by completing the ZINBRYTA REMS Program Patient Enrollment Form with your doctor
3. **Complete** baseline liver testing before your first dose and monthly liver testing before your next dose of ZINBRYTA. A monthly reminder will be sent from the ZINBRYTA REMS Program for liver testing

ZINBRYTA is not available to all pharmacies. If you have any questions about the ZINBRYTA REMS Program or how to obtain ZINBRYTA, call 1-800-456-2255, Monday to Friday, 8:30 AM to 8:00 PM (ET).

Indication

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.

Please see Prescribing Information, including BOXED WARNING, for additional information.

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This site is intended for residents 18 years or older of the United States, Puerto Rico, and US territories.

ZINBRYTA REMS Program: For Prescribers

Prescribers

The requirements for treating with ZINBRYTA (daclizumab)

Please complete this **3-step process** to prescribe ZINBRYTA.

Step 1. Become certified:

Complete the certification process before you prescribe ZINBRYTA

1. **Review** the following educational materials on ZINBRYTA to understand the risks of severe and life-threatening hepatic injury including autoimmune hepatitis, and serious immune-mediated disorders, and the ZINBRYTA REMS Program. Download the:

   - ZINBRYTA Prescribing Information
   - ZINBRYTA REMS Program Overview
   - ZINBRYTA REMS Program Prescriber Training

2. **Complete** the ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form. You must answer all questions in the ZINBRYTA REMS Program Prescriber Knowledge Assessment correctly in order to become certified. Download the:

   - ZINBRYTA REMS Program Prescriber Knowledge Assessment
   - ZINBRYTA REMS Program Prescriber Enrollment Form

3. **Submit** the ZINBRYTA REMS Program Prescriber Knowledge Assessment and the ZINBRYTA REMS Program Prescriber Enrollment Form to complete enrollment. The completed forms should be faxed to the ZINBRYTA REMS Program at **1-855-474-3067**, or mailed to the ZINBRYTA REMS Program at **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**. You will be contacted by the ZINBRYTA REMS Program within 2 business days upon receipt. When contacted, you will receive either:
   - A confirmation of your certification in the ZINBRYTA REMS Program

   OR
   - If necessary, instructions on how to retake the ZINBRYTA REMS Program Prescriber Knowledge Assessment

Once this one-time step has been completed, the ZINBRYTA REMS Program will contact you to finish certification.

Step 2. Before you start each appropriate patient on ZINBRYTA:

Enroll the patient in the ZINBRYTA REMS Program

1. **Counsel** your patient about the risks associated with ZINBRYTA and the need for baseline and monthly liver testing before the next dose and share the resources provided below. Download the:

   - ZINBRYTA REMS Program Patient Guide
   - ZINBRYTA REMS Program Patient Wallet Card

2. **Order and evaluate** the baseline liver testing before each patient's first dose of ZINBRYTA.

3. **Complete** the ZINBRYTA REMS Program Patient Enrollment Form and prescription with your patient and provide them with a copy of the finished form. Download the:

   - ZINBRYTA REMS Program Patient Enrollment Form

4. **Submit** the completed form to the ZINBRYTA REMS Program, and then store a copy in the patient's records. Completed forms should be faxed to the ZINBRYTA REMS Program at **1-855-474-3067**, or mailed to the ZINBRYTA REMS Program at **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**. Your patient can expect to be contacted by the ZINBRYTA REMS Program.

Step 3. Once a patient starts on ZINBRYTA:

Perform monthly monitoring and evaluation

1. **Monitor** your ZINBRYTA patients on an ongoing basis. Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Transaminase levels and total bilirubin should be followed monthly for 6 months after the last dose of ZINBRYTA. The patient will be contacted by the ZINBRYTA REMS Program each month to remind them to complete their liver testing.

   If there are changes in the test results, adjust the monitoring and treatment with ZINBRYTA as follows:

Lab values	Recommendations
ALT, AST >5x ULN **OR** Total bilirubin >2x ULN **OR** ALT, AST ≥3 but <5x ULN and total bilirubin >1.5 but <2x ULN	Interrupt ZINBRYTA therapy and investigate for other etiologies of abnormal lab values 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 <2x ULN and total bilirubin is ≤ 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.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

2. **Submit** a completed ZINBRYTA REMS Program Patient Status Form for each patient **every 90 days** during treatment and **every 90 days for 6 months after discontinuation** of ZINBRYTA. Every 90 days, the ZINBRYTA REMS Program will send an individualized Patient Status Form to the certified prescriber for completion. Download the:

   - ZINBRYTA REMS Program Patient Status Form

3. **Report** any adverse events suggestive of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders to the ZINBRYTA REMS Program at **1-800-456-2255**. You may be contacted for more information about these events.

4. **Inform** the ZINBRYTA REMS Program if the patient is no longer under your care or has discontinued ZINBRYTA.

Adobe® Reader® is required to view all of these PDFs. If you do not have it installed, download it free here.

If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call **1-800-456-2255**, *Monday to Friday,* **8:30 AM** *to* **8:00 PM (ET)**.

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ZINBRYTA REMS Program: For Prescribers

Prescribers

The requirements for treating with ZINBRYTA (daclizumab)

Please complete this **3-step process** to prescribe ZINBRYTA.

Step 1. Become certified:

Complete the certification process before you prescribe ZINBRYTA ›

Step 2. Before you start each appropriate patient on ZINBRYTA:

Enroll the patient in the ZINBRYTA REMS Program ›

Step 3. Once a patient starts on ZINBRYTA:

Perform monthly monitoring and evaluation ›

If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call **1-800-456-2255**, *Monday to Friday,* **8:30 AM** *to* **8:00 PM (ET)**.

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ZINBRYTA REMS Program: For Pharmacies

Pharmacies

The requirements for dispensing ZINBRYTA (daclizumab)

ZINBRYTA is not available to all pharmacies. If you have any questions about the ZINBRYTA REMS Program or how to obtain ZINBRYTA, call 1-800-456-2255, Monday to Friday, 8:30 AM to 8:00 PM (ET).

Please complete this **2-step process** to dispense ZINBRYTA.

Step 1. Become certified:

Complete the certification process before you are authorized to dispense ZINBRYTA

1. **Designate** an authorized representative for the pharmacy. He or she will need to review the ZINBRYTA REMS Program Overview and will oversee implementation and ensure compliance with the ZINBRYTA REMS Program requirements. Download the:

   ZINBRYTA REMS Program Overview

2. **Have the authorized representative complete** the ZINBRYTA REMS Program Pharmacy Enrollment Form. Download the:

   ZINBRYTA REMS Program Pharmacy Enrollment Form

3. **Submit** the completed form to the ZINBRYTA REMS Program. Completed forms should be faxed to the ZINBRYTA REMS Program at **1-855-474-3067**, or mailed to the ZINBRYTA REMS Program at **5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709**. You will be contacted by the ZINBRYTA REMS Program to complete certification.

4. **Have the authorized representative ensure** that all relevant staff involved in the dispensing of ZINBRYTA are trained on the ZINBRYTA REMS Program requirements and that a record of training is maintained by the pharmacy.

Step 2. Dispense ZINBRYTA to authorized patients:

Ensure compliance with the ZINBRYTA REMS Program requirements

1. Before dispensing each dose, **verify** that the prescriber is certified and the patient is authorized to receive ZINBRYTA by calling the ZINBRYTA REMS Program at **1-800-456-2255**. **Do not dispense more than a one month supply per patient**.

2. **Ensure** that the pharmacy complies with the procedures required by the ZINBRYTA REMS Program:
   - **Report** any adverse events suggestive of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders to the ZINBRYTA REMS Program at **1-800-456-2255**. You may be contacted for more information about these events.
   - **Maintain** appropriate documentation that all processes and procedures are in place and are being followed so that it can be provided upon request to Biogen, the FDA, or a third party acting on behalf of Biogen or the FDA.
   - **Comply** with potential audits conducted by Biogen, FDA, or a third party acting on behalf of Biogen or the FDA to ensure that all processes and procedures are in place and are being followed.

3. **Recertify** in the ZINBRYTA REMS Program if a new authorized representative is designated by completing and submitting the ZINBRYTA REMS Program Pharmacy Enrollment Form.

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If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call 1-800-456-2255, Monday to Friday, 8:30 AM to 8:00 PM (ET).

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ZINBRYTA REMS Program: For Pharmacies

Pharmacies

The requirements for dispensing ZINBRYTA (daclizumab)

ZINBRYTA is not available to all pharmacies. If you have any questions about the ZINBRYTA REMS Program or how to obtain ZINBRYTA, call 1-800-456-2255, Monday to Friday, 8:30 AM to 8:00 PM (ET).

Please complete this **2-step process** to dispense ZINBRYTA.

Step 1. Become certified:

Complete the certification process before you are authorized to dispense ZINBRYTA ›

Step 2. Dispense ZINBRYTA to authorized patients:

Ensure compliance with the ZINBRYTA REMS Program requirements ›

If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call 1-800-456-2255, Monday to Friday, 8:30 AM to 8:00 PM (ET).

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ZINBRYTA REMS Program: For Patients

Patients

The requirements for receiving treatment with ZINBRYTA (daclizumab)

Work with your doctor to complete this **2-step process** so you can start treatment on ZINBRYTA.

Step 1. Complete enrollment:

Enroll, understand the risks, and complete liver testing before starting treatment

1. **Discuss** the following with your doctor and make sure you understand:
   - The risks of ZINBRYTA including serious liver problems that may lead to death and immune system problems.
   - The baseline liver testing required before your first dose and monthly liver testing required before your next dose.

2. **Receive and read** the ZINBRYTA REMS Program Patient Guide and the ZINBRYTA REMS Program Patient Wallet Card.
   - The ZINBRYTA REMS Program Patient Guide is your comprehensive guide to understanding treatment with ZINBRYTA.
   - The ZINBRYTA REMS Program Patient Wallet Card, which is provided for you to carry during treatment and for up to 6 months after stopping treatment, can be shared with your other doctors.

   Download the:

ZINBRYTA REMS Program Patient Guide

ZINBRYTA REMS Program Patient Wallet Card

3. **Complete** the ZINBRYTA REMS Program Patient Enrollment Form with your doctor who will provide you with a copy of this form. You can expect to be contacted by the ZINBRYTA REMS Program.

4. **Complete** baseline liver testing before your first dose to ensure ZINBRYTA is safe for you to use, as guided by your doctor. You can expect to be contacted by the ZINBRYTA REMS Program each month to remind you to complete your lab tests.

Step 2. Continue treating your relapsing MS:

Complete monthly liver testing before your next dose and report side effects

1. **Complete** your monthly liver testing before your next dose during treatment with ZINBRYTA and for 6 months after you discontinue treatment with ZINBRYTA.

2. **Inform** your doctor of any side effects, reactions, or symptoms you experience after receiving ZINBRYTA.

3. **Carry** your ZINBRYTA REMS Program Patient Wallet Card and tell any of your other doctors that you have been treated with ZINBRYTA.

4. **Notify** the ZINBRYTA REMS Program right away if you change your ZINBRYTA doctor, if your contact information changes, or if you discontinue treatment with ZINBRYTA.

Adobe® Reader® is required to view all of these PDFs. If you do not have it installed, download it free here.

If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call **1-800-456-2255**, *Monday to Friday,* **8:30 AM** *to* **8:00 PM (ET)**.

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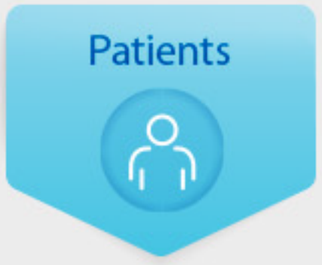
ZINBRYTA REMS Program: For Patients



The requirements for receiving treatment with ZINBRYTA (daclizumab)

Work with your doctor to complete this **2-step process** so you can start treatment on ZINBRYTA.

Step 1. Complete enrollment:

Enroll, understand the risks, and complete liver testing before starting treatment ›

Step 2. Continue treating your relapsing MS:

Complete monthly liver testing before your next dose and report side effects ›

If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call **1-800-456-2255**, *Monday to Friday,* **8:30 AM** *to* **8:00 PM (ET)**.

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ZINBRYTA REMS Program: Forms and Resources

Below are downloadable forms required to become certified and enrolled in the ZINBRYTA (daclizumab) REMS Program.

Prescribers

Materials for Prescribers

Click here to learn more about these resources. Download the:

Prescriber Education and Certification

- ZINBRYTA Prescribing Information
- ZINBRYTA REMS Program Overview
- ZINBRYTA REMS Program Prescriber Training
- ZINBRYTA REMS Program Prescriber Knowledge Assessment
- ZINBRYTA REMS Program Prescriber Enrollment Form
- ZINBRYTA REMS Program Letter for Healthcare Providers

Patient Enrollment

- ZINBRYTA REMS Program Patient Enrollment Form

Continuing Enrolled Patients on Treatment

- ZINBRYTA REMS Program Patient Status Form

Pharmacies

Materials for Pharmacies

Click here to learn more about these resources. Download the:

- ZINBRYTA REMS Program Overview
- ZINBRYTA REMS Program Pharmacy Enrollment Form

Patients

Materials for Patient Counseling

Click here to learn more about these resources. Download the:

- ZINBRYTA REMS Program Patient Guide
- ZINBRYTA REMS Program Patient Wallet Card

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If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call **1-800-456-2255**, *Monday to Friday,* **8:30 AM** *to* **8:00 PM (ET)**.

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Contact Us

ZINBRYTA REMS Program

5000 Davis Drive
PO Box 13919
Research Triangle Park, NC 27709
Phone: 1-800-456-2255
Fax: 1-855-474-3067

If you have any questions about the ZINBRYTA REMS Program or need help enrolling, call **1-800-456-2255**, *Monday to Friday,* **8:30 AM** *to* **8:00 PM (ET)**.

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ZINBRYTA REMS Program

What is the ZINBRYTA (daclizumab) Risk Evaluation and Mitigation Strategy (REMS) Program?

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of a drug outweigh its risks. **Due to the risks of severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis, and other immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis, ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program.**

How does the ZIN

Notable requirements

- Prescribers must be
- Pharmacies must be

ZINBRYTA.

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You are now leaving the ZINBRYTA™ (daclizumab) REMS website.

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Prescri

Click here to learn how to prescribe ZINBRYTA:

1. **Become certified** by completing a one-time certification process
2. As you start patients on ZINBRYTA, **counsel and enroll** them into the ZINBRYTA REMS Program, complete the prescription, and order and evaluate baseline liver testing
3. **Perform** ongoing patient monitoring, evaluate **monthly liver testing before each patient's next dose**, and complete the ZINBRYTA REMS Program Patient Status Forms for each patient every 90 days during treatment and every 90 days for 6 months after discontinuation of ZINBRYTA

Click here to learn how to dispense ZINBRYTA*:

1. **Designate an authorized representative, become certified,** and **recertify** if there is a change in the authorized representative
2. **Train** staff and **comply** with REMS requirements
3. Before dispensing each dose, **verify** prescriber is certified and patient is authorized to receive ZINBRYTA, and **dispense no more than a one month supply**

nts

Click here to learn how to receive ZINBRYTA:

1. **Understand the risks** associated with ZINBRYTA
2. **Enroll** in the ZINBRYTA REMS Program by completing the ZINBRYTA REMS Program Patient Enrollment Form with your doctor
3. **Complete** baseline liver testing before your first dose and monthly liver testing before your next dose of ZINBRYTA. A monthly reminder will be sent from the ZINBRYTA REMS Program for liver testing

ZINBRYTA is not available to all pharmacies. If you have any questions about the ZINBRYTA REMS Program or how to obtain ZINBRYTA, call 1-800-456-2255, Monday to Friday, 8:30 AM to 8:00 PM (ET).

Indication

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.

Please see Prescribing Information, including BOXED WARNING, for additional information.

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/s/

ROBERT TEMPLE
05/27/2016