



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



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.**



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



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.



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

ALT, AST >5x ULN
OR
Total bilirubin >2x ULN
OR
ALT, AST >3 but <5x ULN
and total bilirubin >1.5
but <2x ULN

Recommendations

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 \leq 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.



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

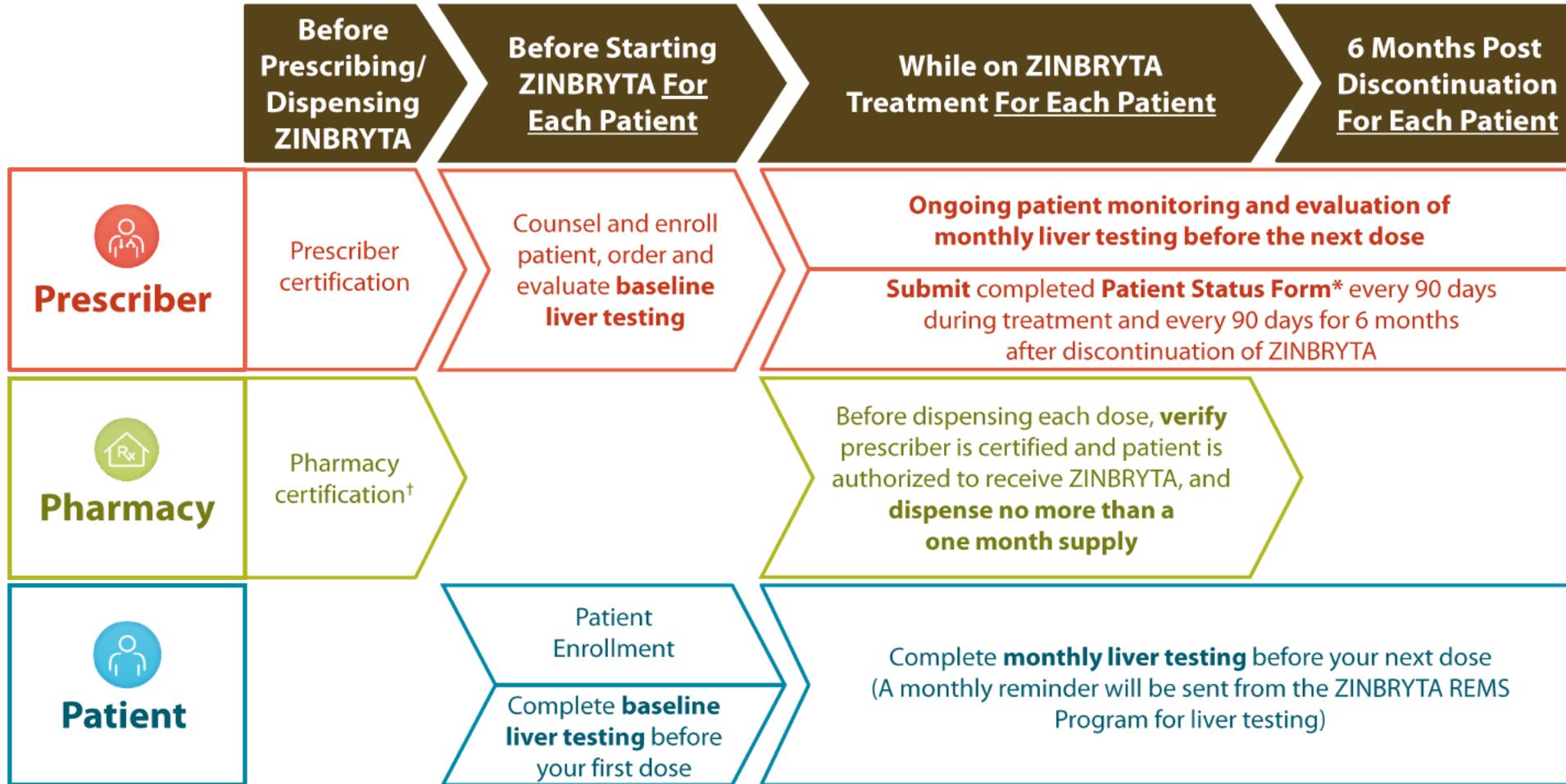


What Is the ZINBRYTA REMS Program?

- 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.



Requirements and Roles of Prescribers, Pharmacies, and Patients



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



How Does a Prescriber Become Certified in the Program?



Before prescribing ZINBRYTA

- 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
- 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
- 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



How Does a Prescriber Enroll Appropriate Patients in the Program?



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



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.



Overview of ZINBRYTA REMS Program Forms



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.

Please submit this completed form to the ZINBRYTA REMS Program via fax or mail:
1-855-474-2067 5000 Davis Drive, PO Box 13919, Research Triangle Park, NC 27709
If you have any questions regarding the ZINBRYTA REMS Program, call: 1-800-455-2255

Zinbryta™
(daclizumab)
50 mg Subcutaneous Injection

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 Waiver 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.



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

Unknown

Prescriber Name Prescriber Number

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.

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

