

Initial REMS approval: 05/2016

BLA 761029 ZINBRYTA™ (daclizumab)

Alpha subunit, Interleukin-2 antagonist

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## **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.

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](http://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](http://www.zinbrytarems.com)). The REMS Program Website must include the capability 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 compliance 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 initial 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.