Zinbryta
(daclizumab beta)

Hepatic risk management guide for physicians

Signs, symptoms, and management of serious hepatic injury

Background

Zinbryta (daclizumab beta) is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with any other DMT is contraindicated or otherwise unsuitable.

It exerts immunomodulatory effects by binding to CD25 (IL-2Rα) and preventing IL-2 binding to CD25. Zinbryta modulates IL-2 signalling by selectively blocking CD25-dependent, high affinity IL-2 receptor signalling, resulting in higher levels of IL-2 available for signalling through the intermediate-affinity IL-2 receptor.

Zinbryta administration can result in serum transaminase elevations and serious hepatic injury which can be unpredictable and could be life-threatening or potentially fatal.

Serious hepatic injury including autoimmune hepatitis requires prompt recognition and action, such as discontinuation of treatment with Zinbryta and potential consideration of additional therapy including prompt referral to a hepatologist.

Purpose of this guide

This guide provides information for physicians on monitoring for hepatic events and management of transaminase elevation and potential serious hepatic injury in patients receiving Zinbryta. It is important that physicians understand and apply the guidance within this document. There is an accompanying patient card and acknowledgement form which provides information on hepatic injury symptoms and actions required if experienced. The physician should discuss the information in the patient card and the acknowledgement form with the patient before prescribing Zinbryta. Both the patient and physician should sign the acknowledgement form to confirm that the discussion has taken place and the patient understands the information that has been given to them.

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Hepatic risk

Treatment with Zinbryta can result in transaminase elevation and serious hepatic injury, which can be unpredictable and could be life-threatening or potentially fatal. Cases of serious hepatic injury occurred early after treatment initiation, in patients having received repeated treatment and several months after discontinuation. Patients may present with signs and symptoms suggestive of hepatic dysfunction, or with elevations in serum transaminase levels.

Hepatic events in daclizumab beta clinical trials

Serious events, including autoimmune hepatitis, hepatitis, and jaundice, were observed in 1.7% of patients. In a clinical trial, a case of fatal autoimmune hepatitis occurred in a patient re-initiating treatment with 300 mg of daclizumab beta after a planned 6 month treatment interruption period.

In clinical trials, serum transaminase elevations occurred at any time during treatment and up to several months after the last dose of daclizumab beta. Most patients had mild elevations that were below and up to 3 times (x) the upper limit of normal (ULN) and resolved spontaneously. An increased incidence of elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was reported in daclizumab beta-treated patients as compared with placebo or interferon beta-1a. The incidence of discontinuation due to medicine-related hepatic disorders was 5% in daclizumab beta-treated patients and 4% in interferon beta-1a patients (please refer to the SmPC for further details).

Management of hepatic risk

The information below is intended as a guide to management of risk of hepatic injury in patients on treatment with Zinbryta.

Serum transaminases and total bilirubin must be monitored at least monthly, as close as possible before each administration and more frequently as clinically indicated during treatment and up to 6 months after the last dose of Zinbryta.

It is important that all healthcare professionals who come into contact with the patient, understand the need for prompt recognition of signs and symptoms that may indicate possible liver injury and take immediate actions.

Actions in case of elevated serum transaminases during treatment and up to 6 months after treatment with Zinbryta:

- If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and bilirubin levels and discontinue treatment with Zinbryta, as appropriate and promptly refer the patient to a hepatologist. Treatment with systemic steroids may be appropriate.
- Treatment discontinuation is recommended in patients who reach ALT or AST >3xULN regardless of bilirubin level.
- Caution should be used when administering medicinal products of known hepatotoxic potential, including non-prescription products, concomitantly with Zinbryta. Obtain information from the patient on the use of concomitant medications, including non-prescription products and herbal supplements.

Prior to initiating treatment with Zinbryta, check the following:

- Perform baseline clinical assessment, including complete medical history and complete list of concomitant medications, including non-prescription products and herbal supplements.
- Obtain serum transaminases and bilirubin levels and screen the patients for Hepatitis B (HBV) and Hepatitis C (HCV). For patients who test positive for HBV or HCV infection, consultation with a physician with expertise in the treatment of HBV or HCV is recommended.
- Zinbryta is contraindicated in patients with pre-existing hepatic disease or hepatic impairment. Treatment initiation is not recommended in patients with history of concurrent autoimmune conditions other than MS.
- Treatment initiation is not recommended in patients with ALT or AST ≥ 2×ULN.

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- Caution should be used when administering medicinal products of known hepatotoxic potential, including non-prescription products and herbal supplements, concomitantly with Zinbryta.
- Educate the patient about the risk of serious hepatic injury and the signs and symptoms that may indicate possible liver problems. Instruct the patient to report immediately any new, persistent or worsening symptoms of possible liver injury to you, or to any emergency care healthcare professionals.
- Ensure that the patient understands the risk of serious hepatic injury associated with the use of Zinbryta and that an informed discussion of benefits and risks occurs.
- Provide the patient with their patient card and the acknowledgement form. Both patient and physician should sign the acknowledgement form and each retain a copy.
- Instruct the patient on the appropriate procedure for seeking medical attention when your clinical practice office is closed.

During therapy with Zinbryta, complete the following:

- Refer to instructions in the separate section above for guidance on what to do in case of elevated serum transaminases.

  Monitor serum transaminases and bilirubin levels at least monthly, as close as possible before each administration and more frequently as clinically indicated during treatment and up to 6 months after the last dose of Zinbryta.
- During patient encounter:
  - Patients should be observed for signs and symptoms of hepatic dysfunction.
  - Question the patient about possible liver-related symptoms and remind them about the signs and symptoms of possible liver problems.
  - **Instruct patient to report immediately any new, persistent or worsening symptoms of possible liver injury to you, or to any emergency care or healthcare professionals.**
  - Remind the patient that symptoms may occur up to 6 months after the last dose.
  - **Question patient about concomitant medications, including non-prescription products and herbal supplements. Caution should be used when administering products of known hepatotoxic potential with Zinbryta.**
  - Remind the patient about the importance of adhering to their liver test schedule.
  - Review liver test results with patient.
  - Review appropriate procedure for seeking medical attention when you are unavailable.

Additional resources

Refer to the Zinbryta patient card and acknowledgement form.

▼ **This medicine is subject to additional monitoring.**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/ risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via MHRA (UK) Yellow Card Scheme.
Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.
If in Ireland, report via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; Email: medsafety@hpra.ie.

Adverse events should also be reported to Biogen on 0800 008 7401 (UK) or 1800 812 719 (Ireland).
E-mail: MedInfoUKI@biogen.com.

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