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EMA concludes review of Zinbryta and confirms further restrictions to reduce risk of liver damage

Zinbryta to be used in restricted patient group, with strict liver monitoring

The European Medicines Agency (EMA) has concluded its review of the multiple sclerosis medicine Zinbryta (daclizumab) and confirmed further restrictions to reduce the risk of serious liver damage.

The review found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with Zinbryta and for up to 6 months after stopping treatment. In clinical trials, 1.7% of patients receiving Zinbryta had a serious liver reaction.

Zinbryta should now only be used in patients who have had an inadequate response to at least two disease modifying therapies (DMTs) and cannot be treated with any other DMTs. Details of the recommendations for patients and healthcare professionals are given below.

The review of the liver effects of Zinbryta was conducted by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which issued recommendations in October 2017.

The Committee for Medicinal Products for Human Use (CHMP) has now adopted EMA's final opinion, which will be sent to the European Commission for adoption of a legally binding decision.

Information for patients

- Zinbryta can cause serious and life-threatening liver problems in some patients.
- Because of this risk, Zinbryta will now only be given to patients who have tried at least two other disease modifying treatments and cannot be treated with any other such treatments.
- If you are currently on Zinbryta, your doctor will check whether you should continue your treatment or switch to an alternative.
- Your doctor will check your liver regularly (via a blood test), during treatment with Zinbryta and for up to 6 months after stopping treatment. If you do not have your liver checked as required, your prescriptions may be stopped.
- Contact your doctor immediately if you develop any signs and symptoms of liver problems, such as unexplained nausea (feeling sick), vomiting, abdominal pain, tiredness, loss of appetite, yellowing of the skin and eyes and dark urine. Your doctor may stop your treatment and refer you to a liver specialist.

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- Tell your doctor of any medicines you are taking, including non-prescription products and herbal supplements, as these may affect the liver.
- You will be given a form to fill in to show that you understand the risk to the liver and the need for regular check-ups.

Information for healthcare professionals

- Zinbryta can cause unpredictable and potentially fatal immune-mediated liver injury. Several cases of serious liver injury including immune-mediated hepatitis and fulminant liver injury have been reported.
- In clinical trials, 1.7% of patients receiving Zinbryta had a serious liver reaction such as autoimmune hepatitis, hepatitis and jaundice.
- In view of the risk, the indication for Zinbryta is being restricted to adult patients with relapsing forms of multiple sclerosis 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.
- In addition, healthcare professionals are advised of the following measures to minimise risks:
  - Review all patients who are currently taking Zinbryta to assess whether the medicine is still appropriate for them.
  - Monitor patients' serum transaminase and bilirubin levels at least monthly and as close as possible before each administration, and for up to 6 months after stopping treatment.
  - Do not prescribe Zinbryta for patients with pre-existing hepatic disease or hepatic impairment as it is contraindicated in these patients.
  - Screen patients for hepatitis B or C infection before starting treatment in new patients and refer those who test positive to a liver specialist.
  - It is recommended that you do not start treatment in new patients with ALT or AST levels equal to or more than 2 times the upper limit of normal (ULN) or in patients with autoimmune conditions other than multiple sclerosis.
  - It is recommended that you stop treatment in patients with ALT or AST levels more than 3 times the ULN regardless of bilirubin levels.
  - Promptly refer patients with signs and symptoms of liver damage to a specialist.
  - Consider stopping Zinbryta if an adequate response to treatment has not been achieved or the patient fails to follow the requirement for scheduled liver function tests.
  - Exercise caution in patients taking other medicinal products with known hepatotoxic potential, including non-prescription products and herbal supplements.
  - Inform patients about the risk of hepatic injury, how to recognise it and the need for regular monitoring. An acknowledgement form for patients will be made available to confirm that patients have understood the risk.
- These recommendations update provisional measures introduced in July 2017 which were communicated directly to healthcare professionals in the EU. A new written communication will be sent out to healthcare professionals with the updated recommendations.

More about the medicine

Zinbryta is a medicine used to treat certain patients with relapsing forms of multiple sclerosis. Multiple sclerosis is a disease in which inflammation damages the protective sheath around the nerve cells in the brain and spinal cord. Relapsing means that the patient has flare-ups of neurological symptoms.

Zinbryta is available as a solution for injection in pre-filled pens and syringes. It is injected under the skin once a month.

Zinbryta contains the active substance daclizumab and was authorised in the EU in July 2016. More information can be found on the medicine's dedicated page on EMA's website.

More about the procedure

The review of Zinbryta was initiated on 9 June 2017 at the request of the European Commission under Article 20 of Regulation (EC) No 726/2004.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion.

The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.