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HPRA DRUG SAFETY NEWSLETTER

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In this Edition

Daclizumab (Zinbryta) and risk of severe liver injury – EU wide review concludes and confirms further restrictions to reduce risk of liver damage

Unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab (Zinbryta) and for up to 6 months after stopping treatment. A Direct Healthcare Professional Communication (DHPC) was issued by the marketing authorisation holder (MAH) (following approval by the HPRA) in July 2017 to inform relevant healthcare professionals of provisional measures for restriction of use put in place to protect public health while an urgent EU-wide review of daclizumab was on-going.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has now concluded this review. The review found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab and for up to 6 months after stopping treatment. 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 daclizumab had serious liver reaction such as autoimmune hepatitis, hepatitis and jaundice.

Restrictions on use

In view of this risk, the indication for daclizumab 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.

Treatment with daclizumab is contraindicated in patients with pre-existing hepatic disease or hepatic impairment. Treatment initiation is not recommended in patients with alanine transaminase (ALT) or aspartate aminotransferase (AST) 2 or more times the upper limit of normal.

Treatment initiation is not recommended in patients with a history of concurrent autoimmune conditions (except multiple sclerosis). Caution should be used when concomitantly administering medicinal products for known hepatotoxic potential, including non-prescription products and herbal supplements.

New patients should be tested for hepatitis B or C infection before starting treatment and referral to a hepatologist should be considered for those that test positive.

Review of patients

Promptly review any patients who are currently taking daclizumab to assess whether this medicine continues to be appropriate for them. The risks associated with this medicine should be discussed with the patient.

Consider discontinuing therapy if an adequate response to treatment has not been achieved or if continuous monitoring of liver function (at least monthly) is not possible.

Monitor patients' serum transaminase and bilirubin levels at least monthly and as close as possible before

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each administration, and for up to 6 months after stopping treatment. It is recommended that treatment is stopped in patients with ALT or AST levels more than 3 times the upper limit of normal regardless of bilirubin levels.

Promptly refer patients with signs and symptoms of liver damage to a hepatologist.

Exercise caution in patients taking other medicinal products with known hepatotoxic potential, including non-prescription products and herbal supplements.

Discuss the risk of hepatic injury with patients and provide them with a Patient Card. Advise patients to contact their doctor immediately if they develop any symptoms of liver problems, such as unexplained nausea, vomiting, abdominal pain, tiredness, loss of appetite, yellowing of the skin and eyes, and dark urine. An acknowledgement form for patients will be made available by the Marketing Authorisation Holder, to confirm that patients have understood the risk.

Key Message

An urgent EU review of new information on liver safety of daclizumab has concluded and found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment and for up to 6 months after stopping treatment.

In light of the risk, the indication for daclizumab is now restricted to adult patients with relapsing forms of MS who have had an inadequate response to at least two Disease Modifying Therapies (DMTs) for whom treatment with any other DMT is contraindicated or otherwise unsuitable.

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.

Patients with evidence of hepatic injury should be promptly referred to a hepatologist.

All suspected adverse reactions associated with daclizumab should be reported to the HPRA via the various reporting methods available (www.hpra.ie)

Further information on daclizumab (Zinbryta) is available from www.hpra.ie and www.ema.europa.eu

New contraindication for injectable methylprednisolone products containing lactose (Solu-Medrone 40 mg / vial) in patients with cows' milk allergy

Injectable methylprednisolone products containing lactose are authorised for use in a range of different indications including in the treatment of symptoms of severe allergic reactions and other inflammatory conditions. In Ireland, Solu-Medrone Powder and Solvent for Solution for Injection or Concentrate for Solution for Infusion 40mg/vial is the only authorised injectable methylprednisolone-containing product formulated with lactose, and may contain trace amounts of milk proteins.

An EU review was initiated following reports of serious allergic reactions, including bronchospasm and anaphylaxis, in patients allergic to cow's milk treated with injectable methylprednisolone medicines that contain lactose. The majority of patients were younger than twelve years of age. In some reported cases, the adverse reactions were misinterpreted as lack of therapeutic effect in acute allergic conditions, leading to further doses of such products being administered, and a consequent further deterioration in the condition of the patient. Estimates of the prevalence of cow's milk allergy (CMA) varies from 0% to 3% and is higher in children than adults. Allergy to cow's milk proteins is not to be confused with lactose intolerance, which is a non-immunologically mediated reaction to milk caused by a lack of the enzyme lactase in the small intestine, which breaks lactose from milk down into glucose and galactose.

Following consideration of data submitted by the marketing authorisation holders (MAHs), as well as data available in EudraVigilance and the literature, the PRAC has recommended that injectable methylprednisolone-containing medicinal products containing lactose, which potentially contain traces of cow's milk proteins, should not be used in patients with a known or suspected allergy to the proteins in cow's milk., In patients being treated for an allergic reaction with methylprednisolone, if symptoms worse or new allergic symptoms occur, allergic reaction to cows' milk proteins should be suspected.

Lactose-containing methylprednisolone medicines will be reformulated to remove any trace of milk proteins. Companies have been asked to take steps towards lactose-free formulations by 2019. In the meantime, a Direct Healthcare Professional Communication has been sent to communicate the new restriction and warnings.

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Advice to Healthcare Professionals

- Solu-Medrone Powder and Solvent for Solution for Injection or Concentration for Solution for Infusion 40 mg/vial is the only strength of Solu-Medrone available on the Irish market which uses lactose produced from cows' milk as an excipient and may contain trace amounts of milk proteins.
- Serious allergic reactions have been reported in patients allergic to cows' milk proteins.
- Do not use injectable methylprednisolone medicines that contain lactose in patients with a known or suspected allergy to cow's milk.
- Healthcare professionals should consider allergy to cow's milk in case the symptoms of patients treated for acute allergy condition worsen or if new allergic symptoms occur. Administration of the product should be stopped in these patients, and the patient's condition should be treated accordingly.
- A warning that the product must not be used in patients allergic to cow's milk will be added to the product information and implemented on the vial and outer packaging to improve identification of the concerned products.

Key Message

Injectable methylprednisolone products containing lactose of bovine origin may cause serious allergic reactions in patients allergic to cow's milk proteins when treated for allergic reactions.

Injectable methylprednisolone products containing lactose of bovine origin (i.e. Solu-Medrone Powder and Solvent for Solution for Injection or Concentrate for Solution for Infusion 40 mg / vial) are now contraindicated in patients with a known or suspected allergy to cow's milk.

Further details on Solu-Medrone Powder and Solvent for Solution for Injection or Concentrate for Solution for Infusion 40 mg / vial are available on www.hpra.ie

Warning about the use of Xofigo (radium-223 dichloride) in combination with Zytiga (abiraterone acetate) and prednisone or prednisolone: ongoing clinical trial shows an increased risk of death and fractures

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) is investigating an increased risk of death and fractures reported in an ongoing clinical trial with Xofigo (radium-223 dichloride) when used in combination with abiraterone acetate (Zytiga) and prednisone/prednisolone as compared with abiratone acetate and prednisone/ prednisolone used in combination with placebo.

The randomised clinical trial in asymptomatic or mildly symptomatic patients with chemotherapy naïve bone-predominant metastatic castration-resistant prostate cancer (CRPC) is investigating the safety and efficacy of Xofigo given in combination with abiraterone acetate and prednisone/ prednisolone compared to placebo given in combination with abiraterone acetate and prednisone/prednisolone. Xofigo is currently approved for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Preliminary data analysed by the independent data monitoring committee responsible for overseeing the trial showed a death rate of 27% (109 out of 401 patients) for the Xofigo combination compared with 20% (82 out of 405 patients) for the placebo combination. Fractures also occurred more frequently in patients receiving the Xofigo combination versus the placebo combination (24% versus 7%). Patients in this study are no longer being treated with Xofigo and are being monitored closely.

The PRAC will further evaluate the data from this study as well as other available data to fully assess any impact on the authorised use of Xofigo. However while the review is ongoing, healthcare professionals are advised not to use Xofigo in combination with abiraterone acetate and prednisone/prednisolone to treat patients with metastatic castration-resistant prostate cancer.

A Direct Healthcare Professional Communication (DHPC) has been circulated by the Marketing Authorisation Holder (following approval by the HPRA) to relevant healthcare professionals.'

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Key Message

Preliminary data from an ongoing clinical trial indicate increased death rate and fracture rate for patients receiving Xofigo in combination with abiraterone acetate (Zytiga) and prednisone/prednisolone versus those receiving placebo in combination with abiraterone acetate and prednisone/prednisolone.

Healthcare professionals are advised not to use Xofigo in combination with abiraterone acetate and prednisone/prednisolone to treat patients with metastatic castration-resistant prostate cancer while a full review is ongoing.

All suspected adverse reactions associated with Xofigo should be reported to the HPRA via the various reporting methods available (www.hpra.ie).

Further information is available on www.ema.europa.eu

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Eligard (leuprorelin acetate)	Medication errors associated with leakage due to overtightening of the safety needle.
Xofigo (radium-223-dichloride)	Increased risk of death and fractures in a randomized clinical trial with Xofigo used in combination with abireterone acetate and prednisolone/prednisone.
Gadolinium Contrast Agents	Updated recommendations following review of gadolinium retention in brain and other tissues.
Litak (cladribine)	Risk of progressive multifocal leukoencephalopathy (PML).
Zinbryta (daclizumab)	Restrictions of use due to the risk of fulminant liver failure.

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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