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HPRA DRUG SAFETY NEWSLETTER

66TH EDITION

In this Edition

Eligard (leuprorelin acetate depot injection) - Risk of lack of efficacy due to incorrect reconstitution and administration process

Following identification of a signal of administration errors with Eligard and concerns that such errors may impact on clinical efficacy, this issue was reviewed at EU level by the Pharmacovigilance Risk Assessment Committee (PRAC). A cumulative review of reported global cases identified errors related to storage, preparation and reconstitution of Eligard. Appropriate reconstitution is a critical step in the administration of the product to ensure the effective and safe treatment of patients with prostate cancer. Lack of efficacy may occur due to incorrect reconstitution of Eligard.

Eligard is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

It is available in six-monthly (45mg), three-monthly (22.5mg) and one-monthly (7.5mg) formulations. In the majority of patients, androgen deprivation therapy (ADT) with Eligard results in testosterone levels below the standard castration threshold (<50ng/dL; <1.7 nmol/L); and in most cases, patients reach testosterone levels below <20ng/dL.

Healthcare professionals are reminded of the following:

Advice to Healthcare Professionals

- Appropriate reconstitution of Eligard is a critical step in the administration of the product.
- It is important that all staff involved in the reconstitution and administration of Eligard are familiar with and adhere to the instructions for appropriate methods of reconstitution and administration before using the product.
- Testosterone levels should be measured in suspected cases of maladministration of Eligard.
- The storage conditions for the product have been updated and the product information reflecting this update is available on the HPRA website (www.hpra.ie). The syringe will be modified to simplify reconstitution and administration. The modified syringe (the blue plunger rod design is changing) will be made available as soon as possible.
- A Direct Healthcare Professional Communication (DHPC) was circulated to relevant healthcare professionals in December 2014 and is available on the HPRA website (www.hpra.ie).
- All cases of incorrect storage, reconstitution and administration of Eligard should be reported to the HPRA.

Key Message

* *Further details on Eligard are available at www.hpra.ie*

- There have been global reports of medication errors related to storage, preparation and reconstitution of Eligard.
- Lack of clinical efficacy may occur due to incorrect reconstitution of Eligard.
- Reconstitution instructions in section 6.6 of the SmPC for Eligard must be followed exactly.

Beta interferons - Risk of thrombotic microangiopathy and nephrotic syndrome

Interferon beta-1a and interferon beta-1b are indicated for the treatment of relapsing multiple sclerosis* and in patients with a single demyelinating event with an active inflammatory process. Interferon beta-1b products may also be used in patients with secondary progressive multiple sclerosis with active disease evidenced by relapses.

In July 2014, a European review of interferon beta products* and associated reports of thrombotic microangiopathy (TMA) and nephrotic syndrome was concluded. Cases of thrombotic microangiopathy (TMA), including fatal cases, had been reported during treatment of multiple sclerosis with interferon beta. Most TMA cases presented as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome. Cases of nephrotic syndrome with different underlying nephropathies have also been reported in association with these products. The review could not rule out a causal association between interferon beta products and TMA or nephrotic syndrome.

Advice to Healthcare Professionals

Thrombotic microangiopathy

- TMA may develop several weeks to several years after starting treatment with interferon beta.
- Be vigilant for signs and symptoms of TMA and manage it promptly in line with the advice below.
- Clinical features of TMA include thrombocytopenia, new onset hypertension, fever, impaired renal function and central nervous system symptoms (e.g. confusion and paresis).
- If clinical features of TMA are observed, platelet levels, serum lactate dehydrogenase levels, renal function and red blood cell fragments on a blood film should be performed.
- If TMA is diagnosed, prompt treatment (e.g. plasma exchange should be considered) is required and immediate discontinuation of interferon beta is recommended.

Nephrotic Syndrome

- Nephrotic syndrome may develop several weeks to several years after starting treatment with interferon beta.
- Be vigilant for the development of this condition and manage it promptly in line with the advice below.
- Renal function should be monitored periodically and early signs or symptoms of nephrotic syndrome (e.g. oedema, proteinuria and impaired renal function, especially in high risk groups) should be noted.
- If nephrotic syndrome occurs, it should be treated promptly and consideration should be given to stopping treatment with interferon beta.

The product information (Summary of Product Characteristics (SmPC) and package leaflet (PL)) for all interferon beta products has been updated and will be fully harmonised with information on TMA and nephrotic syndrome.

Key Message

- Cases of TMA including fatal cases have been reported during treatment of multiple sclerosis with interferon beta products.
- Most TMA cases presented as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome.
- Cases of nephrotic syndrome with different underlying nephropathies have also been reported.
- Both TMA and nephrotic syndrome may develop several weeks to several years after starting treatment with interferon beta.
- Be vigilant for the development of these conditions and manage them promptly if they occur.

** The following interferon beta products are authorised for the treatment of multiple sclerosis. Further details available at www.hpra.ie:*

Avonex (interferon beta-1a), Rebif (interferon beta-1a), Betaferon (interferon beta-1b), Extavia (interferon beta-1b), Plegridy (peginterferon beta-1a).

Mycophenolate mofetil (CellCept) and Mycophenolic acid (Myfortic) - New warnings about the risks of hypogammaglobulinaemia and bronchiectasis

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA concluded a review of case reports and published studies which showed that mycophenolate mofetil in combination with other immunosuppressants can cause hypogammaglobulinaemia and bronchiectasis.

The active pharmacological form of mycophenolate mofetil is mycophenolic acid and therefore the warnings regarding these risks applies to all products that contain mycophenolic acid as their active ingredient such as CellCept and Myfortic.

Advice to Healthcare Professionals

Hypogammaglobulinaemia

- Hypogammaglobulinaemia associated with recurrent infections has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.
- Patients who develop recurrent infections should have their serum immunoglobulins measured.
- In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered. In some of the reported cases, switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal.

Bronchiectasis

- There have been published reports of bronchiectasis in patients receiving mycophenolate mofetil in combination with other immunosuppressants.
- Patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, should be investigated promptly.
- In some of the confirmed cases of bronchiectasis, switching mycophenolate mofetil to an alternative immunosuppressant resulted in an improvement in respiratory symptoms.

Key Message

- A review of case reports and published studies showed that mycophenolate mofetil (as the active mycophenolic acid) in combination with other immunosuppressants can cause hypogammaglobulinaemia and bronchiectasis.
- Patients who experience recurrent infections should have their serum immunoglobulins measured and patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, should be investigated properly.
- In some of the confirmed cases of hypogammaglobulinaemia and bronchiectasis, switching mycophenolate mofetil to an alternative immunosuppressant resulted in improvement in symptoms.
- A Direct Healthcare Professional Communication (DHPC) was circulated by the Marketing Authorisation Holders (MAHs) for CellCept and Myfortic to relevant healthcare professionals in December 2014 and is available from the HPRA website (www.hpra.ie).
- The product information (SmPC and PL) for these products will be updated shortly with the respective warnings.
- Healthcare professionals should report any suspected adverse reactions associated with mycophenolate mofetil and mycophenolic acid to the HPRA.

* *Further details on CellCept and Myfortic are available at www.hpra.ie and www.ema.europa.eu/ema/*

Tecfidera (dimethyl fumarate) - Progressive Multifocal Leukoencephalopathy (PML) in a patient with severe and prolonged lymphopenia

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently advised that Healthcare Professionals and Patients should be informed about the first case of progressive multifocal leukoencephalopathy (PML) in a patient treated with Tecfidera (dimethyl fumarate). This fatal case of PML, in the setting of severe prolonged lymphopenia, was reported in a patient receiving Tecfidera for 4.5 years. Lymphopenia is a known adverse drug reaction of Tecfidera and patients undergoing treatment should be monitored regularly, with regular complete blood counts (CBC), including lymphocytes.

Tecfidera is authorised in the EU for treatment of adult patients with relapsing remitting multiple sclerosis. Based on this new information, healthcare professionals should be aware of the following:

Advice to Healthcare Professionals

- Lymphopenia is a known adverse reaction of Tecfidera and patients undergoing treatment should be monitored regularly. Complete blood counts (CBC), including lymphocytes, should be checked regularly and at close intervals, as clinically indicated.
- Prolonged lymphopenia may be associated with an increased risk of PML.
- Patients should be appropriately informed about the risk of PML.
- Patients receiving Tecfidera who experience lymphopenia should be monitored closely and frequently for signs and symptoms of neurological dysfunction.
- When PML is suspected, Tecfidera should be discontinued immediately.

Key Message

- A fatal case of PML, in the setting of severe prolonged lymphopenia has been reported in a patient receiving Tecfidera for 4.5 years. This is the first case of PML associated with Tecfidera and has been reviewed by PRAC.
- Patients should have complete blood counts, including lymphocytes, monitored regularly and at close intervals, as clinically indicated.
- Patients experiencing lymphopenia while being treated with Tecfidera should be monitored closely and frequently for signs and symptoms of neurological dysfunction.
- Tecfidera should be stopped immediately if PML is suspected.
- All suspected adverse reactions associated with Tecfidera should be reported to the HPRA (www.hpra.ie).

* *Further details on Tecfidera are available at www.hpra.ie and www.ema.europa.eu/ema/*

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

PRODUCT	SAFETY ISSUE
Procoralan **(ivabradine hydrochloride)**	New contraindication and recommendations to minimise the risk of cardiovascular events and severe bradycardia.
Cellcept **(mycophenolate mofetil) and Myfortic (mycophenolic acid)**	New warnings about the risks of hypogammaglobulinaemia and bronchiectasis.

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

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority