Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we inform you that there have been reports of thrombotic microangiopathy and nephrotic syndrome linked to interferon beta treatment. Be vigilant for early signs or symptoms of these conditions (see below) and treat these conditions promptly if they occur—see article A1.

From October 2014 Dexamethasone 4 mg/ml injection (Organon Laboratories Limited) will be replaced with a new formulation called Dexamethasone 3.8 mg/ml solution for injection (Aspen Pharma Trading Limited). As a result, the storage conditions, presentation, and packaging will change—see article A2.

We remind you that basiliximab is indicated for preventing acute organ rejection only for allogeneic renal transplantation. The clinical trials that have been done in heart transplantation did not prove basiliximab to be effective. Furthermore, serious cardiac side effects were observed more frequently with basiliximab than with other induction agents—see article S1.

Also, don't miss the latest drug safety advice!

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Drug safety advice

A1 Interferon beta: risk of thrombotic microangiopathy and risk of nephrotic syndrome

There have been reports of thrombotic microangiopathy and nephrotic syndrome linked to interferon beta treatment. Be vigilant for early signs or symptoms of these conditions (see below) and treat these conditions promptly if they occur

Interferon beta-1a and interferon beta-1b are immunomodulatory drugs indicated for the treatment of remitting relapsing multiple sclerosis.

A European review was triggered by reports of thrombotic microangiopathy and nephrotic syndrome associated with interferon beta treatment. The review suggested that there may be an association between interferon beta treatment and thrombotic microangiopathy and between interferon beta treatment and nephrotic syndrome.

Thrombotic microangiopathy
Thrombotic microangiopathy is a serious condition characterised by occlusive microvascular thrombosis and secondary haemolysis. It is the hallmark of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. Early clinical features include thrombocytopenia, new onset hypertension, and impaired renal function. Laboratory findings suggestive of thrombotic microangiopathy include decreased platelet counts, increased serum lactate dehydrogenase, and schistocytes (red blood cell fragmentation) on a blood film. Thrombotic microangiopathy may occur weeks to years after starting interferon beta treatment.

Cases of thrombotic microangiopathy, including fatal cases, have been reported during interferon beta treatment. To date, we have received 13 Yellow Card reports[1] of thrombotic microangiopathy, haemolytic uraemic syndrome, or thrombotic thrombocytopenic purpura linked to interferon beta treatment.

A European review is investigating a potentially increased risk of thrombotic microangiopathy with a new formulation of Rebif (interferon beta-1a) compared with an old formulation of Rebif.[2] The old formulation is not currently available in the UK. We will communicate the outcome and any updated advice once the review is finished.

Nephrotic syndrome
Nephrotic syndrome is a kidney disorder characterised by proteinuria, hypoalbuminaemia, and oedema.

Cases of nephrotic syndrome with different underlying nephropathies have been reported during interferon beta treatment. These nephropathies included collapsing focal segmental glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis, and membranous glomerulopathy. Nephrotic syndrome may occur weeks to years after starting interferon beta treatment.

To date, we have received five Yellow Card reports[1] of nephrotic syndrome linked to interferon beta treatment.

Advice for healthcare professionals:

Thrombotic microangiopathy:

- Be vigilant for signs and symptoms of thrombotic microangiopathy. Clinical features of thrombotic microangiopathy include:
    - thrombocytopenia
    - new onset hypertension
    - fever

1. Yellow Card reports are reports of suspected adverse drug reactions (ADRs) taken from all spontaneous and study sources. Spontaneous reports are those submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug.

2. Hunt D et al *N Engl J Med* 2014; 370:1270-1

    - central nervous system symptoms (eg, confusion and paresis)
    - impaired renal function
- If you observe clinical features of thrombotic microangiopathy, test blood platelet levels, serum lactate dehydrogenase levels, and renal function. Also test for red blood cell fragments on a blood film
- If thrombotic microangiopathy is diagnosed, treat promptly (consider plasma exchange) and stop interferon beta treatment immediately

Nephrotic syndrome:

- Monitor renal function periodically
- Be vigilant for early signs or symptoms of nephrotic syndrome such as oedema, proteinuria, and impaired renal function especially in patients at high risk of renal disease
- If nephrotic syndrome occurs, treat promptly and consider stopping interferon beta treatment
- Please report any suspected adverse reactions to interferon beta or any other medicine via a Yellow Card (www.mhra.gov.uk/yellowcard).

Article citation: Drug Safety Update October 2014 vol 8, issue 3: A1.

A2 **Dexamethasone 4 mg/ml injection (Organon Laboratories Limited): reformulation with changes in name, concentration, storage conditions, and presentation**

From October 2014 Dexamethasone 4 mg/ml injection (Organon Laboratories Limited) will be replaced with a new formulation called Dexamethasone 3.8 mg/ml solution for injection (Aspen Pharma Trading Limited). As a result, the storage conditions, presentation, and packaging will change

Dexamethasone 4 mg/ml injection is indicated for general and local glucocorticoid injection therapy (eg, joint inflammation) and for any acute condition in which intravenous glucocorticoids may be life-saving (eg, severe asthma, severe allergic reactions, and cerebral oedema).

Dexamethasone 4 mg/ml injection has been reformulated to harmonise the formulations available within the EU market and to improve the manufacturing process. Aspen Pharma Trading Limited has taken over the licence from Organon Laboratories Ltd. All orders placed from October 2014 onwards will be supplied with the new formulation called Dexamethasone 3.8 mg/ml solution for injection (PL 39699/0060; Aspen Pharma Trading Limited). The old formulation, Dexamethasone 4 mg/ml injection (PL 00065/0106R; Organon Laboratories Limited), will no longer be available.

The reformulation will result in the following changes:

- **Concentration:** the concentration of the active substance in the reformulated product will be 3.8 mg/ml dexamethasone, which is equivalent to 5.0 mg/ml of dexamethasone sodium phosphate. The dose recommendations have not changed. However, due to the change in concentration, the dilutions will need to be amended. A dosing card has been developed to help administer the reformulated product (see further information below).

- **Storage conditions:** the reformulated product must be stored in the refrigerator at 2 to 8°C to reduce the potential for particle formation. The old formulation is associated with a very low risk of particle transfer to patients; no serious safety concerns are associated with the use of the old formulation.

- **Presentation:** the reformulated product will be available in a glass vial containing 1 ml of solution for injection.

- **Packaging:** the carton of the reformulated product will be clearly marked “New formulation”, “Change in concentration”, and “Store in a refrigerator”.

Further information
Dosing card
http://www.mhra.gov.uk/idcm2/groups/dsu/documents/publication/con464226.pdf
Patient information leaflet and technical information leaflet
http://www.mhra.gov.uk/idcm2/groups/dsu/documents/publication/con464228.pdf
Summary of product characteristics
http://www.mhra.gov.uk//idcm2/groups/dsu/documents/publication/con464227.pdf Letter sent to healthcare professionals in September 2014
http://www.mhra.gov.uk/idcm2/groups/dsu/documents/publication/con464229.pdf

Advice for healthcare professionals:

- Take the new concentration of dexamethasone (3.8 mg/ml) into account when diluting the product for use (see dosing card in further information on the left)
- Store the reformulated product in a refrigerator at 2 to 8°C
- Use up your stocks of the old formulation before using the new formulation
- Consult the new summary of product characteristics, technical information leaflet, and dosing card for further information

Article citation: Drug Safety Update October 2014 vol 8, issue 3: A2.

Stop press

S1 **Basiliximab indicated for renal transplantation only; efficacy and safety not shown in heart transplantation**

Basiliximab (Simulect) is indicated for preventing acute organ rejection only for allogeneic renal transplantation in patients receiving organ transplantation for the first time.

A European regulatory review investigated the safety and efficacy of basiliximab for off-label use in heart transplantation. This review was triggered by three unexplained deaths in Sweden in patients who received basiliximab for heart transplantation. All three patients had signs and symptoms of thromboembolic events and potential cardiac disorders.

The review found no adequately powered randomised studies of basiliximab in heart transplantation. The clinical trials that have been done in heart transplantation did not prove basiliximab to be effective. Furthermore, serious cardiac side effects such as cardiac arrest, atrial flutter, and palpitations were observed more frequently with basiliximab than with other induction agents. Therefore a new warning has been included in the basiliximab product information regarding the lack of proven safety and efficacy in heart transplantation (see link to the left).

Further information
Basiliximab summary of product characteristics
https://www.medicines.org.uk/emc/medicine/12889

Letter sent to healthcare professionals in September 2014
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con465930.pdf

Call for reporting
Please continue to report all suspected adverse drug reactions to us on a Yellow Card (www.mhra.gov.uk/yellowcard).

Article citation: Drug Safety Update October 2014 vol 8, issue 3: S1.

O1 **Drugs and driving: clarification for Wales, Scotland, and Northern Ireland**

In July we reported on a new offence of driving with certain controlled drugs above specified limits in the blood. This new offence will be enforceable in England, Wales, and Scotland[1] but not Northern Ireland where the introduction of a similar offence is under consideration. The new offence does not replace any existing offences of driving whilst impaired by drugs, including licenced medicines.

Please continue to warn patients of any potential driving impairment caused by a medicine and the need for caution.

Drug Safety Update article on drugs and driving from July:
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON432898

1. The date of enforcement depends on approval of regulations by the Scottish Parliament

Further information
Information leaflet to give to patients
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con437439.pdf

Guidance from the Department for Transport:
https://www.gov.uk/government/collections/drug-driving

Article citation: Drug Safety Update October 2014 vol 8, issue 3: O1.