Drug Safety Update

MHRA

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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In this issue, we provide updated advice on all **oral tacrolimus** products. These should now be prescribed and dispensed by brand name only to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection. If a prescriber intends to switch between any oral tacrolimus brand, careful medical supervision and therapeutic monitoring are required (see article A1).

Also this month: care must be taken when dosing with **caffeine citrate** as two products of different strengths are now available. See article A2 for further information.

Febuxostat has been associated with rare but serious reports of hypersensitivity reactions including Stevens-Johnson syndrome. Febuxostat treatment must be stopped immediately if signs of hypersensitivity occur, and not re-started in any patient who has ever developed a hypersensitivity reaction to febuxostat (see article A3).

And finally, see our Stop Press article for a reminder of a possible risk of malignancies with **topical tacrolimus**.

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Drug safety advice

A1 Oral tacrolimus products: prescribe and dispense by brand name only, to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection

The growing number of oral tacrolimus products available on the market increases the potential for inadvertent switching between products, which has been associated with reports of toxicity and graft rejection. Therefore, to ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only.

If a prescriber considers that switching a patient to a different brand of oral tacrolimus would be of benefit, the change requires careful supervision and therapeutic monitoring by an appropriate specialist

Tacrolimus is an immunosuppressant drug which may be given orally to prevent or treat organ transplant rejection. Tacrolimus has a narrow therapeutic index, and even minor differences in blood levels have the potential to cause graft rejection reactions

Oral tacrolimus and inadvertent switching between products
Since 2008, the MHRA has been aware of reports of unintended switching between different pharmaceutical forms of oral tacrolimus products in patients who have been treated with tacrolimus for the prevention of organ transplant rejection. Graft rejection reactions and tacrolimus toxicity have resulted from a small number of these unintended switches between products.

Prescribing oral tacrolimus products
As there are a growing number of tacrolimus products available on the UK market, the Commission on Human Medicines CHM has now advised that the risk of inadvertent switching between the different products may increase.

Therefore, as a precautionary measure, the CHM has updated its advice on the safer use of oral tacrolimus products and recommends that **all oral tacrolimus products should be prescribed and dispensed by brand name only**. This supersedes previous advice regarding the prescribing, dispensing and interchangeability of different tacrolimus products (see Drug Safety Update January 2009, February 2010, and May 2010).

Letter sent to healthcare professionals in May 2012: https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=101781

A letter on the updated advice for oral tacrolimus products was sent to healthcare professionals in May 2012.

The purpose of the new advice is to ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, and to minimise the risk of inadvertent switching between products from different suppliers. As all tacrolimus products are approved in the UK with a brand name, the easiest way to achieve this is to prescribe by brand name only.

Important: careful therapeutic monitoring is recommended for any switching between tacrolimus brands. The currently available brands of oral tacrolimus are:

- Immediate-release capsule taken twice daily (including Adoport, Aletris, Capexion, Evenil, Miloprosan, Prograf, Tacni, Takon, Taliximun, Tamitect and Vivadex)
- Prolonged-release capsule taken once daily (Advagraf)
- Granules for oral solution taken twice daily (Modigraf)

If the exact brand of tacrolimus is not clearly stated on the prescription, the dispensing pharmacist should check with the prescriber to ensure that the appropriate medicine is dispensed.

Changing oral tacrolimus products

This updated recommendation does not preclude patients changing to a different tacrolimus brand if the prescriber considers this to be of benefit to the patient. However, changes between different brands (which may or may not involve changes in dosing regimen), should always be accompanied by careful therapeutic monitoring under the supervision of an appropriate specialist.

Advice for healthcare professionals:

- Prescribers should prescribe oral tacrolimus products by brand name only. When prescriptions have been previously written using the generic name, the brand on which the patient is stabilised should be established to ensure that the patient is supplied with the same product
- If a prescriber intends to switch between any tacrolimus brand, careful medical supervision and therapeutic monitoring are required
- Pharmacists should always dispense the exact brand prescribed. They should contact the prescriber if the prescription is not clear to ensure the appropriate medicine is dispensed
- Patients should be advised to take careful note of the brand name of their usual tacrolimus medicine and should check with their doctor or pharmacist if they receive a different brand or if they have any other questions about the prescription, eg about the dose

Further information:

MHRA information webpage on prescribing and dispensing oral tacrolimus products: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON152758

BNF section 8.2 Drugs affecting the immune response: http://www.medicinescomplete.com/mc/bnf/current/27585.htm

Article citation: Drug Safety Update June 2012 vol 5, issue 11: A1.

A2 Caffeine citrate: two products of different strengths are now available. Care must be taken with dosing, as the two products are not equivalent

Two caffeine citrate products are now available: Peyona▼, which contains 20 mg/mL of caffeine citrate, and a generic product which contains 10 mg/mL of caffeine citrate. Care must be taken with dosing to avoid confusing the two products, as they are not equivalent.

Caffeine citrate solution for infusion or oral administration is authorised for the treatment of primary apnoea of premature newborns. There are two formulations now available: a generic (non-branded) product which contains 10 mg/mL caffeine citrate and a new product called Peyona▼, which contains 20 mg/mL of caffeine citrate.

Care must be taken over which product is being used when dosing with caffeine citrate, as confusing the products may cause dosing errors.

A letter on the safer use of caffeine citrate was sent to healthcare professionals in May 2012.

Letter sent to healthcare professionals in May 2012: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON152832

Further information:

BNFC section 3.5.1 Respiratory stimulants: http://www.medicinescomplete.com/mc/bnfc/current/129103.htm

Advice for healthcare professionals:

- Two formulations of caffeine citrate solution are now available: Peyona▼, which contains 20 mg/mL caffeine citrate, and a non-branded product which contains 10mg/mL caffeine citrate. Take careful note of which product is being used, to avoid dosing errors
- Caffeine citrate is for use in neonatal Intensive Care Units only and treatment must be initiated under the supervision of a physician experienced in neonatal intensive care
- Healthcare professionals should also pay special attention to the contraindications, warnings and precautions for use when prescribing and administering caffeine citrate products
- During treatment with any caffeine citrate product, measurement of baseline caffeine levels, monitoring of plasma caffeine concentrations, as well as dose adjustments during treatment, are advisable, particularly in cases of insufficient response or toxic effects, or in infants who are at an increased risk of elevated plasma concentrations (eg, very premature infants or those who have hepatic or renal impairment)
- It is also advisable to measure baseline caffeine levels in infants whose mothers have ingested large quantities of caffeine prior to delivery or infants who previously have been treated with theophylline

Please remember to report suspected adverse reactions to caffeine citrate on a Yellow Card at www.mhra.gov.uk/yellowcard

Article citation: Drug Safety Update June 2012 vol 5, issue 11: A2.

A3 **Febuxostat (Adenuric▼): stop treatment if signs or symptoms of serious hypersensitivity (eg, serious skin reactions or systemic hypersensitivity) occur**

There have been rare but serious reports of hypersensitivity reactions, including Stevens-Johnson syndrome and acute anaphylactic shock, with febuxostat (Adenuric▼). Febuxostat must be stopped immediately if hypersensitivity occurs, and must not be re-started in patients who have ever developed a hypersensitivity reaction to febuxostat.

Febuxostat (Adenuric▼) is a non-purine, xanthine oxidase inhibitor licensed for the treatment of chronic hyperuricaemia in adults, in whom urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Since its launch in 2009 there have been rare but serious reports of hypersensitivity reactions to febuxostat, some associated with systemic symptoms. These have included rare reports of Stevens-Johnson syndrome and acute anaphylactic shock (frequency ≥1/10 000 to <1/1000).

In most cases, the reactions occurred during the first month of treatment. Some, but not all, of the patients experiencing hypersensitivity reactions to febuxostat were reported to have a prior history of hypersensitivity to allopurinol and/or renal disease

A letter on this safety issue was sent to healthcare professionals in May 2012 and the product information has been updated with relevant warnings.

Letter sent to healthcare professionals in May 2012: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON152832

Further information:

BNF section 10.1: Drugs used in rheumatic diseases and gout: http://www.medicinescomplete.com/mc/bnf/current/204954.htm

Advice for healthcare professionals:

- Febuxostat treatment should be stopped immediately if signs or symptoms of serious hypersensitivity reactions occur – early withdrawal is associated with a better prognosis.
- If a patient has ever developed a hypersensitivity reaction with febuxostat, including Stevens-Johnson syndrome, febuxostat must not be re-started at any time.
- Most cases of hypersensitivity to febuxostat occur during the first month of treatment
- Patients should be advised of signs and symptoms of severe hypersensitivity or Stevens-Johnson syndrome. These include: infiltrated maculopapular eruption; generalised or exfoliative rashes; skin lesions; facial oedema, fever, haematologic abnormalities such as thrombocytopenia, a single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis), progressive skin rashes associated with blisters or mucosal lesions and eye irritation
- A prior history of hypersensitivity to allopurinol and/or renal disease may indicate potential hypersensitivity to febuxostat

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Stop press

S1 Tacrolimus ointment (Protopic): reminder of a possible risk of malignancies including lymphomas and skin cancers

Tacrolimus ointment (Protopic) is used to treat moderate to severe atopic dermatitis flares, and to maintain flare-free intervals, in adults and adolescents age 16 years and older, who do not respond to, or are intolerant of, conventional therapies such as topical corticosteroids.

Protopic is available in two strengths containing tacrolimus 0.03% and 0.1%, respectively. The lower strength ointment can be used to treat moderate to severe atopic dermatitis in children of 2 years and above, as well as adults and adolescents. The higher strength ointment is licensed only for use in patients aged 16 years and older.

Risk of malignancies

Healthcare professionals are reminded that tacrolimus may be associated with a possible risk of malignancy. Benign as well as malignant neoplasms including Epstein-Barr virus-associated lymphoproliferative disorders and skin malignancies have been reported in association with oral (systemic) tacrolimus treatment.

Cases of malignancies, including lymphomas and skin cancers have also been reported in patients using topically applied tacrolimus since it was licensed in 1999. In addition, findings from epidemiological studies have suggested a possible increased risk of cutaneous T-cell lymphoma in patients treated with topical calcineurin inhibitors, including tacrolimus ointment [1-3].

Healthcare professionals must remember that Protopic should not be prescribed to patients younger than 2 years, and that the use of Protopic in children aged 2 – 16 years is restricted to the lower strength 0.03% ointment only.

References:

1. Hui RL et al. *Ann Pharmacother* 2009; **43** (12):1956-1963

2. Schneeweiss S et al. *Dermatology* 2009; **219**(1): 7-21

3. Arana A et al. Presentation at the annual meeting of the International Society for Pharmacoepidemiology, Brighton, UK 2010

Further information:

Letter to health professionals sent in May 2012:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON152832

BNF section 13.5.3: Drugs affecting the immune response:
http://www.medicinescomplete.com/mc/bnf/current/119636.htm

In addition, Protopic should not be applied to lesions that are considered to be potentially malignant or pre-malignant, or used in patients with congenital or acquired immunodeficiencies, or in patients on therapy that causes immunosuppression.

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