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

Volume 5, Issue 1, August 2011

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.

NHS Evidence accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

For full details on our accreditation visit **NHS Evidence**

http://www.evidence.nhs.uk/Accreditation

A Europe-wide review has found a small increased risk of bladder cancer in patients taking the antidiabetic pioglitazone. However, the benefits continue to outweigh the risks for those who respond to treatment and in whom there are no identified risk factors for bladder cancer. Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone. Prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Further information is outlined in article A1.

The orphan drug Onsenal▼ (celecoxib) is no longer approved in Europe for the reduction of intestinal polyps in familial adenomatous polyposis (FAP). This follows voluntary withdrawal after a clinical trial, designed to provide evidence for a clinically important benefit, failed to recruit sufficient numbers. Furthermore, other celecoxib medicines are not recommended for the reduction of intestinal polyps in these patients, and they should not be prescribed for this unlicensed indication: the clinical benefit of celecoxib in FAP has not been sufficiently demonstrated and is outweighed by the increased risk of cardiovascular and gastrointestinal side effects (see article A2).

Claire Tilstone, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Pioglitazone: risk of bladder cancer

Use of pioglitazone is associated with a small increased risk of bladder cancer. Healthcare professionals should be aware of new warnings and precautions for use in at-risk patients

Pioglitazone (Actos▼) is an oral treatment for type 2 diabetes, either on its own or combined with other oral antidiabetic agents or insulin. It is also available as a combination tablet with metformin (Competact▼).

Risk of bladder cancer

The potential risk of bladder cancer with pioglitazone was first identified at the time of licensing, observed in male rats in an animal toxicity study that supported the initial licence application. There was no evidence of a similar risk in humans at that time. The marketing authorisation (licence) holder committed to investigate the risk further in animal studies and observational studies in human use.

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has reviewed the results of these studies and other relevant data regularly. After an increase in health professional reports of bladder cancer suspected to be associated with pioglitazone, in March 2011 the EMA initiated a further European-wide review to investigate this safety signal.

Outcome of European review

The review found a small increased risk of bladder cancer in patients taking pioglitazone; however, the benefits continue to outweigh the risks for those who respond to treatment and in whom there are no identified risk factors for bladder cancer.

Observational studies report relative risks ranging from 1.12 to 1.33 when diabetic patients receiving pioglitazone are compared with patients with diabetes receiving other antidiabetic medicines but not exposed to pioglitazone. The increase in absolute risk is therefore likely to be small. Whether the increased risk occurs early in treatment or only after prolonged exposure remains unclear. CHMP stated that the small increased risk could be reduced by appropriate patient selection.

Advice for healthcare professionals:

- Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone
- Prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg, reduction in glycosylated haemoglobin, HbA1c)
- Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age; current or past history of smoking; exposure to some occupational or chemotherapy agents such as cyclophosphamide; or previous irradiation of the pelvic region
- Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone

Further information:

MHRA statement on pioglitazone: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON123285

European Medicines Agency statement on pioglitazone: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/news_detail_001311.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

BNF section 6.1.2.3 Other antidiabetic drugs: http://bnf.org/bnf/bnf/current/4189.htm

Continues…

Call for reporting of suspected adverse reactions

Please report suspected adverse reactions through the Yellow Card Scheme at www.yellowcard.gov.uk. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, and treatment dates.

Article citation: Drug Safety Update Aug 2011 vol 5, issue 1: A1.

A2 Onsenal▼ (Celecoxib) for familial adenomatous polyposis: withdrawal from EU market

Onsenal▼ (celecoxib) is no longer approved in Europe for the reduction of intestinal polyps in familial adenomatous polyposis (FAP). Furthermore, safety and efficacy data do not support the use of celecoxib in this indication and it should not be used for the unlicensed treatment of FAP

Onsenal▼ withdrawal

Celecoxib is a non-steroidal anti-inflammatory drug and cyclo-oxygenase type 2 inhibitor, which is approved for the treatment of symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

Until recently, celecoxib was also authorised as the orphan drug Onsenal▼ for the reduction of intestinal polyps in familial adenomatous polyposis. At the time of approval of Onsenal▼, the licence (marketing authorisation) holder committed to do post-authorisation clinical studies. However, failure to recruit sufficient numbers into a clinical trial designed to provide evidence relating to clinically important benefit has resulted in the licence holder voluntarily withdrawing Onsenal▼.

European review of celecoxib in FAP

The European Medicines Agency has reviewed the available data after concerns that celecoxib may continue to be used unlicensed in the treatment of FAP. The review concluded that the clinical benefit of celecoxib in FAP has not been sufficiently demonstrated and is outweighed by the increased risk of cardiovascular and gastrointestinal side effects from celecoxib use at high dose and long term in patients with FAP.

Further information:
See letter for healthcare professionals sent April 2011:
www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON117263

European Medicines Agency statement on Onsenal withdrawal:
www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/04/news_detail_001236.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1
European Medicines Agency conclusion on use of celecoxib in FAP:
www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/05/WC500106524.pdf

Advice for healthcare professionals:

- Celecoxib is not recommended for the reduction of intestinal polyps in FAP and should not be prescribed for this unlicensed indication
- Patients who are taking Onsenal▼ should consult their doctor as soon as possible to discuss alternative treatment options

Call for reporting

Please report suspected adverse reactions through the Yellow Card Scheme at www.yellowcard.gov.uk. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, and treatment dates.

Article citation: Drug Safety Update Aug 2011 vol 5, issue 1: A2.

Stop press

S1 **Vimpat▼ (lacosamide) 15 mg/mL syrup: recall due to quality defect**

Vimpat 15 mg/mL syrup for the treatment of partial-onset seizures will be recalled because of a quality defect in some batches, leading to an uneven distribution of the active substance lacosamide.

The recall will begin on Sept 15, 2011, to allow sufficient time for patients to be switched to suitable alternatives (see advice below). The precipitate consists of the active substance lacosamide and is not a contamination. This quality defect affects only the syrup.

Further information:

European Medicines Agency statement on Vimpat 15 mg/mL recall: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2011/07/human_pha_detail_000035.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d126

BNF section 4.8.1 Control of epilepsies: http://bnf.org/bnf/bnf/current/3575.htm

Advice for healthcare professionals:

- Doctors should contact their patients to switch them to Vimpat film-coated tablets if possible
- A 10 mg/mL oral solution currently authorised in the USA and undergoing authorisation in the EU may be made available on a named-patients basis for those who cannot take the tablets
- Do not start any new patients on Vimpat 15 mg/mL syrup
- Suspected adverse reactions to Vimpat should be reported on a Yellow Card at www.yellowcard.gov.uk

Advice for patients:

- Patients are advised not to stop the medication or change the dose without speaking to their doctor

Article citation: Drug Safety Update Aug 2011 vol 5, issue 1: S1.

S2 **Traditional Chinese Medicines containing Lei Gong Teng (*Tripterygium wilfordii*): risk of serious side effects**

We are advising consumers not to use unlicensed herbal products that contain the herbal ingredient Lei Gong Teng (*Tripterygium wilfordii*, also known as Thunder God Vine or Seven-step vine) because of concerns about serious side effects on fertility and on the liver, kidneys, immune system, blood, and heart. We have received a Yellow Card report indicating a potential serious adverse effect which could be associated with consumption of Lei Gong Teng.

This product is available over the internet and may also be available in some traditional Chinese medicine outlets in the UK. Promoted mainly as a natural herbal product for rheumatoid arthritis, other autoimmune diseases, and psoriasis, it is sold either as a dried herb for preparation as a tea or in tablet form.

Further information:

See our website: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Herbalmedicines/Herbalsafetyupdates/Allherbalsafetyupdates/CON123310

Advice for healthcare professionals:

- Healthcare professionals are asked to remain vigilant and advise anyone currently using this product to stop taking it
- Report any suspected adverse reactions to Lei Gong Teng on a Yellow Card at www.yellowcard.gov.uk

Article citation: Drug Safety Update Aug 2011 vol 4, issue 1: S2.