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 10, May 2012

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 new advice on patient groups at high risk of cardiovascular side effects in whom use of **fingolimod** is not recommended, and updated guidance on cardiovascular monitoring requirements after treatment initiation (see article A1).

Also this month: **domperidone** may be associated with a small increased risk of serious ventricular arrhythmia or sudden cardiac death. Non-prescription domperidone products are not recommended for use in patients with underlying cardiac disease, without medical supervision. See article A2 for further information.

Because of the risk of thrombolic events, **strontium ranelate** should not be used in patients with current or previous venous thromboembolism, or in patients with temporary or permanent immobilisation. Prescribers are also advised to be alert to signs and symptoms of rare but serious skin reactions with strontium ranelate, and to be aware of the likely time-to-onset of such events (the first few weeks of treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis and usually within 3 – 6 weeks for drug rash with eosinophilia and systemic symptoms [DRESS]; see article A3).

And finally, cases of keratitis and ulcerative keratitis have been reported with varying frequency following treatment with **epidermal growth factor receptor (EGFR) inhibitors** for cancer indications, such as panitumumab (Vectibix). In some rare cases this has resulted in corneal perforation and blindness. Healthcare professionals should refer patients presenting with symptoms of keratitis to an ophthalmology specialist, and interrupt or discontinue EGFR treatment if ulcerative keratitis is diagnosed (see article A4).

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Drug safety advice

A1 Fingolimod (Gilenya▼): not recommended for patients at known risk of cardiovascular adverse events. New advice for extended early monitoring for those with significant bradycardia or heart block after the first dose

Fingolimod is known to cause transient bradycardias and heart block after the first dose. Fingolimod is now not recommended in patient groups at high risk of cardiovascular adverse events, such as those with significant QT prolongation or history of bradycardia, ischaemic heart disease, cardiac failure, cerebrovascular disease, uncontrolled hypertension, and those receiving antiarrhythmic or heart-rate lowering drugs.

Monitoring advice after the first dose has been updated. All patients should be monitored before, during, and immediately after the first 6 hours of treatment. If the patient's heart rate decreases to its lowest point at the end of the 6-hour treatment period, monitoring should be extended until heart rate increases. Monitoring should also be extended at least overnight if significant atrioventricular block, bradycardia, or QTc prolongation occurs (see below)

Fingolimod (Gilenya) is authorised to treat relapsing-remitting multiple sclerosis in patients whose disease has failed to respond to beta-interferon or is severe and getting worse rapidly. Fingolimod is a sphingosine -1 phosphate receptor ligand.

See:
Drug Safety Update, February 2012:
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON143608

We first highlighted changes to the monitoring advice for fingolimod in February 2012.

We now provide updated advice to avoid use in high risk groups and extend monitoring in some patients. The latest advice follows further review of world-wide data including 15 cases of sudden or unexplained death with fingolimod. Most of the deaths and cardiovascular events had occurred in patients with either a history of cardiovascular problems, such as atrioventricular block or bradycardia, or those who were also taking other medicines. However the data reviewed were not conclusive as to whether Gilenya was the cause of the deaths.

Statement from the European Medicines Agency:
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/04/WC500125690.pdf

The maximum effect of fingolimod on decreasing the heart rate occurred within six hours after the first dose in most patients; this decrease in heart rate can be reversed if necessary by giving atropine or isoprenaline (see statement from the European Medicines Agency).

Updated advice:

<u>Fingolimod is now not recommended in the following high-risk patients:-</u>

a) Those with the following medical conditions:

- 2nd degree Mobitz Type II or higher degree atrioventricular block, sick sinus syndrome, or sino-atrial heart block
- Significant QT prolongation (QTc >470 ms in women, or >450 ms in men)
- History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnea.

b) Those receiving the following antiarrhythmic or heart-rate-lowering drugs:

- Class Ia antiarrhythmics (eg, quinidine, disopyramide) or class III antiarrhythmics

Further information:

Letter sent to healthcare professionals in April 2012:
http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con152562.pdf

BNF section 8.2.4 Other immunomodulating drugs:
http://www.medicinescomplete.com/mc/bnf/current/4789.htm

(eg, amiodarone, sotalol)
- Beta blockers
- Heart rate-lowering calcium channel blockers (eg, verapamil, diltiazem or ivabradine)
- Other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).

In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist is sought prior to initiation of Gilenya treatment. This advice should include, if appropriate, the possibility to switch any concomitant medicine to treatments that are not antiarrhythmic and do not lower the heart rate. If treatment with Gilenya for these patients is considered, monitoring at least overnight following the first dose should be initiated.

Updated monitoring advice: For all patients receiving fingolimod, monitoring before, during and after the first dose should include:

Pre-treatment:
- A 12-lead ECG and blood pressure measurement before starting

During the first 6 hours of treatment*:
- Continuous ECG monitoring for 6 hours
- Blood pressure and heart rate measurement every hour

After 6 hours of treatment:
- A further 12-lead ECG and blood pressure measurement

*** If the patient's heart rate at the end of the 6-hour period is at its lowest since fingolimod was first administered, the monitoring should be extended by at least 2 hours and until the heart rate increases.**

Additional criteria for extended monitoring:

In patients with evidence of clinically important cardiac effects during the first 6 hours of fingolimod treatment, monitoring should be extended, including at least overnight monitoring, until resolution. Recommended criteria for extending monitoring include:

The occurrence at **anytime** during the monitoring period after first dose of:
- New-onset 3rd degree atrioventricular block

The presence **at the end** of the monitoring period after first dose of:

- Heart rate less than 45 beats per minute
- QTc interval ≥500 ms
- Persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach) or higher degree atrioventricular block

If fingolimod therapy is discontinued for more than 2 weeks for any reason, the effects on heart rate and atrioventricular conduction may recur on its reintroduction and so the same monitoring precautions as for treatment initiation should apply.

Reporting of suspected adverse drug reactions
- All suspected adverse reactions to fingolimod should be reported to us promptly on a Yellow Card, available at www.mhra.gov.uk/yellowcard

Article citation: Drug Safety Update May 2012 vol 5, issue 10: A1.

A2 **Domperidone: small risk of serious ventricular arrhythmia and sudden cardiac death**

Some epidemiological studies have shown that domperidone may be associated with a small increased risk of serious ventricular arrhythmia or sudden cardiac death. These risks may be higher in patients older than 60 years and in patients who receive daily oral doses of more than 30 mg. Non-prescription domperidone products are not recommended for use in patients with underlying cardiac disease, without medical supervision

Domperidone is a dopamine antagonist with antiemetic properties. In the UK, it is available as a prescription-only medicine (maximum oral dose 80 mg) for the indications of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort, and regurgitation of gastric contents in adults. It is also available without a prescription in pharmacies at lower doses (daily dose 10 mg, maximum dose 40 mg) for the indications of minor gastrointestinal symptoms and nausea and vomiting in patients aged 16 years or older. The duration of non-prescription treatment should not exceed 2 weeks.

Cardiovascular risks

QTc prolongation and ventricular arrhythmia are known cardiac risks for all domperidone-containing products. A recent Europe-wide review of the available data found that domperidone may be associated with a small increased risk of serious ventricular arrhythmia or sudden cardiac death, especially in patients older than 60 years and in patients receiving daily oral doses of more than 30 mg. The Commission on Human Medicines has advised non-prescription domperidone products are not recommended for use in patients with underlying cardiac disease, without medical supervision.

Findings from epidemiology studies

Four epidemiology studies[1,2,3,4] have reported on the relation between domperidone and either sudden cardiac death alone, or on serious ventricular arrhythmia and sudden cardiac death as a combined endpoint. The findings from the two most recent studies[1,2] are summarised below.

Van Noord and colleagues[1] looked at 1304 cases of sudden cardiac death and 13 480 matched controls, of which ten cases were currently exposed to domperidone. For current use of domperidone, the adjusted odds ratio (OR) for a risk of sudden cardiac death was 1.92 (95% CI: 0.78–4.73). Analysis by dose suggested a higher risk for patients prescribed domperidone at higher doses (>30 mg/day), although there were only 4 exposed cases in each group and the 95% confidence intervals overlapped: OR 11.4 (1.99–64.9) for patients prescribed >30 mg/day, compared with 0.99 (0.23–4.23) for patients receiving 30mg/day.

The study by Johannes and colleagues[2] was the largest and most robust study in terms of exposed cases and included 1608 cases and 6428 controls (proton pump inhibitor [PPI] users), of which there were 169 cases and 482 controls with current exposure to domperidone. Compared with users of PPIs, the OR for current domperidone exposure was 1.44 (1.12–1.86). Stratified analyses by age and sex suggested a slightly higher risk for patients older than 60 years (OR 1.47 [1.14–1.91]) compared with those younger than 60 years (OR 1.23 [0.32–4.76]), although the 95% confidence intervals overlapped.

In light of evidence of a risk of serious ventricular arrhythmia and sudden cardiac death, it is important that the following advice is adhered to:

Advice for healthcare professionals:

- Domperidone should be used at the lowest effective dose
- Non-prescription domperidone products are not recommended for use in

References:

1 Van Noord C, et al. Drug Saf 2010; 33: 1003–14

2 Johannes C, et al. Pharmacoepidemiol Drug Saf 2010; 19: 881–88

3 Straus SM, et al. Eur Heart Journal 2005; 19: 2007–12

4 De Bruin ML, et al. Br J Clin Pharmacol 2007; 63: 216–23

patients with underlying cardiac disease, without medical supervision.

- Prescribers should exercise caution for patients who have: existing prolongation of cardiac conduction intervals (particularly QTc); significant electrolyte disturbances; or underlying cardiac diseases such as congestive heart failure, and patients who are known to be taking prescribed medicines for these conditions, particularly for patients older than 60 years and patients who receive daily oral doses of more than 30 mg
- Domperidone should be avoided in patients who are taking concomitant medication known to cause QT prolongation (eg, ketoconazole or erythromycin)
- Patients should be advised to seek prompt medical attention if symptoms such as syncope or tachyarrhythmias appear during treatment

Advice for patients:

- Non-prescription domperidone products are not recommended if you have current heart problems, or have ever had heart problems, including heart failure, a previous heart attack, angina (chest pains), or heart rhythm disorders including a rapid or slow or irregular heartbeat.
- Seek medical attention immediately if you experience symptoms such as an irregular heartbeat or fainting while taking any domperidone product

Further information:

BNF section 4.6 Drugs used in nausea and vertigo: http://bnf.org/bnf/bnf/current/3429.htm?q=domperidone&t=search&ss=text&p=1#_hit

Article citation: Drug Safety Update May 2012 vol 5, issue 10: A2.

A3 Strontium ranelate (Protelos): should not be used in patients with current or previous venous thromboembolism (VTE) or temporary or permanent immobilisation because of risk of VTE. Rare serious skin reactions may occur within the first weeks of treatment

Strontium ranelate (Protelos) is known to increase the risk of venous thromboembolic events (VTE) and should not be used in patients with current or previous VTE, including deep vein thrombosis and pulmonary embolism, or in patients with temporary or permanent immobilisation (eg post-surgical recovery or prolonged bed rest). The need for continued treatment with strontium ranelate should also be re-evaluated in patients over 80 years who have been diagnosed at risk of VTE.

Strontium ranelate is also associated with serious skin and hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS). Although the risk is low, prescribers are advised to be alert to signs and symptoms of serious skin reactions with strontium ranelate. The likely time-to-onset of such events is the first few weeks of treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis and usually within 3 – 6 weeks for DRESS. Early diagnosis and discontinuation of treatment produce the best results, and patients should be advised accordingly

Strontium ranelate (Protelos) is authorised for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures. Strontium ranelate is known to increase the risk of venous thromboembolic events (VTE) and is also associated with serious skin reactions including drug rash with eosinophilia and systemic symptoms (DRESS). Information about these reactions is included in the product information for strontium ranelate.

Risk of venous thromboembolism

The benefits and risks of strontium ranelate have been reviewed following the publication of a study in France which found that cardiovascular events (mostly VTE events) and skin reactions accounted for 52 % and 26 %, respectively, of all post-marketing reports in association with strontium ranelate[1].

The overall risk estimates of VTE with strontium ranelate were unchanged from previous

References:

1. Ranélate de strontium (Protelos): effets indésirables rapporté en France; Presse Med. 2011; 40(10):e453-e462. [*Adverse drug reactions of strontium ranelate (Protelos) in France; study period Jan 2006 to Mar 2009, estimated number of patients exposed 301,951*]

estimates at the time of licensing. However the risk is higher in patients with a history of VTE, as well as in patients who are temporarily or permanently immobilised. The risk of VTE in elderly patients >80 years may also be increased.

Risk of serious skin reactions

The risk of serious hypersensitivity reactions, such as DRESS, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with strontium ranelate is low (the risk of DRESS is rare [>1/10 000, <1/1 000]; the risk of SJS and TEN is very rare [<1/10 000]). However it is important that prescribers and patients are alert for signs and symptoms of these skin reactions, bearing in mind that the highest risk is in the first few weeks of treatment.

Advice for healthcare professionals:

Contraindications:

- Strontium ranelate should not be used in patients with current or previous VTE, including deep vein thrombosis and pulmonary embolism and/or patients with temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest).

Warnings and recommendations:

- The need for continued treatment with strontium ranelate should be re-evaluated in patients over 80 years who have been diagnosed at risk of VTE.
- Patients should be advised of the likely time-to-onset and signs and symptoms of severe skin reactions such as DRESS, SJS or TEN. The highest risk for occurrence of SJS or TEN is within the first few weeks of treatment and usually around 3-6 weeks for DRESS. Symptoms or signs of SJS or TEN include progressive skin rash, often with blisters or mucosal lesions; symptoms of DRESS include rash, fever, eosinophilia and systemic involvement (eg, adenopathy, hepatitis, interstitial nephropathy, or interstitial lung disease).
- Patients should be made aware of the symptoms and likely time-to-onset of severe allergic reactions, including skin rash, and should be advised to stop taking the medicine and seek medical advice immediately. In these patients, strontium ranelate should not be re-introduced

Further information:

Information from the European Medicines Agency:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/03/human_pha_detail_000057.jsp&mid=WC0b01ac058001d126

Letter sent to healthcare professionals in April 2012:
http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con152561.pdf

Article citation: Drug Safety Update May 2012 vol 5, issue 10: A3.

A4 Epidermal growth factor receptor (EGFR) inhibitors: serious cases of keratitis and ulcerative keratitis

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer, such as panitumumab (Vectibix). In rare cases, this has resulted in corneal perforation and blindness. Patients who present with acute or worsening signs and symptoms of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

EGFR promotes cell growth in normal epithelial tissues including the skin and is expressed on a variety of tumour cells. The EGFR inhibitors, cetuximab (Erbitux), erlotinib (Tarceva▼), gefitinib (Iressa▼) and panitumumab (Vectibix▼), are used to treat EGFR-expressing tumours.

Reports of keratitis and ulcerative keratitis

The cornea is covered with a layer of epithelium which may be damaged by treatment with EGFR inhibitors. Patients with a history of keratitis, ulcerative keratitis or severe dry

eye may be particularly at risk. Serious cases of keratitis and ulcerative keratitis (corneal ulceration) have been reported with varying frequency following treatment with an EGFR inhibitor. In rare cases, this has led to corneal perforation and blindness. Ulcerative keratitis must therefore be regarded as an ophthalmological emergency.

This issue was first identified with panitumumab (Vectibix) and a letter sent to healthcare professionals in May 2011. The risk of keratitis and severe keratitis is now considered a class effect for all EGFR inhibitors, and information for all products in this class has been updated with warnings on this risk.

See:
Letter sent to healthcare professionals in May 2011:
http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con120203.pdf

Further information:

BNF section 8.1 Cytotoxic drugs:
http://www.medicinescomplete.com/mc/bnf/current/4758.htm]

Updated product information on keratitis and ulcerative keratitis can be found in individual Summaries of Product Characteristics (see the electronic Medicines Compendium: http://www.medicines.org.uk/emc/).

Advice for healthcare professionals:

- Ulcerative keratitis is an opthalmological emergency
- Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis such as: eye inflammation; increased lacrimation; light sensitivity; blurred vision; eye pain and/or red eye should be referred promptly to an ophthalmology specialist
- If a diagnosis of ulcerative keratitis is confirmed, treatment with the EGFR inhibitor should be interrupted or discontinued.

Patients with a history of keratitis, ulcerative keratitis or severe dry eye may be particularly at risk of ocular damage with EGFR inhibitors.

Article citation: Drug Safety Update May 2012 vol 5, issue 10: A4.

Hot topic

H1 **Antipsychotics: initiative to reduce prescribing to older people with dementia**

There have been increasing concerns over recent years about the use of antipsychotics to treat the behavioural and psychological symptoms of dementia (BPSD). Antipsychotics are associated with an increased risk of cerebrovascular adverse events and greater mortality when used in this population (see Drug Safety Update, March 2009). No antipsychotic (with the exception of risperidone in some circumstances [see Drug Safety Update, March 2009]) is licensed in the UK for the treatment of BPSD; however, antipsychotics are often prescribed off-label for this purpose.

National Dementia Strategy for England

In 2009, in the face of identified shortcomings in the provision of dementia services in the UK and with the increasing challenge to society posed by dementia, the government announced the first National Dementia Strategy for England.[1] The strategy's objective is to ensure significant improvements in dementia services across three key areas: improved awareness; earlier diagnosis and intervention; and a higher quality of care.

The government commissioned the Banerjee Report (Time for Action, an independent review of the use of antipsychotics in elderly people with dementia) as part of the strategy.[2] The report concluded that antipsychotic use was too high in patients with

See:
Drug Safety Update, March 2009:
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088116

Off-label use of medicines; Drug Safety Update, April 2009:
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990

1 Department of Health. Living well with dementia: A National Dementia Strategy. Feb 3, 2009:
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_094051.pdf

2 Department of Health. The use of antipsychotic medication for people with dementia: Time for action. A report for the Minister of State for Care

dementia, and that the associated risks outweighed the benefits in most of these patients because these drugs seemed to have only a limited positive effect in managing dementia symptoms.[3] More recently, the Prime Minister has launched a challenge to improve the care of people with dementia[4].

The Report also concluded that antipsychotics seemed to be used too often as a first-line response to difficult behaviour in dementia (most often agitation), rather than as a considered second-line treatment when other non-pharmacological approaches have failed (see NICE guidelines for dementia[5]). On the basis of these findings, the government pledged to reduce by two-thirds the use of antipsychotics for people with dementia by November 2011.

Current prescribing

Currently available prescribing data suggest that there has been an encouraging overall reduction in the proportion of elderly people with dementia being prescribed antipsychotics in the UK since 2007. However, further work is needed to change prescribing habits as the reductions identified to date fall short of the hoped-for levels. The NHS Information Centre is carrying out a national survey and local information (such as the Prescribing Observatory for Mental Health survey[6]) is important in changing practice.

The Alzheimer's Society, Department of Health, Dementia Action Alliance, and the Royal College of General Practitioners have produced a number of documents to support healthcare and social-care professionals in implementing the actions required to realise the objectives of the National Dementia Strategy.

A best practice guide[7] is available to help determine the best treatment and care for people with BPSD, with an emphasis on alternatives to drug treatment. It includes clinical checklists, information about prevention of BPSD, and information about specific interventions, together with pathways for determining appropriate treatment for someone who has a current antipsychotic prescription and someone who does not.

Advice for healthcare and social-care professionals:

For prescribers considering using antipsychotics in patients without a current prescription:

- Carefully consider, after a thorough clinical examination including an assessment for possible psychotic features (such as delusions and hallucinations) whether a prescription for an antipsychotic drug is appropriate—see appropriate pathway in best-practice guide[7]

For prescribers considering continuing antipsychotics in patients with a current prescription:

- Identify and review patients who have dementia and are on antipsychotics, with the purpose of understanding why antipsychotics have been prescribed
- In consultation with the patient, their family and carers, and clinical specialist colleagues such as those in psychiatry, establish: whether the continued use of antipsychotics is appropriate; whether it is safe to begin the process of discontinuing their use; and what access to alternative interventions is available.
- Consult the best-practice guide[7]

Article citation: Drug Safety Update May 2012 vol 5, issue 10: H1.

Services by Professor Sube Banerjee. October 2009: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_108302.pdf

3 Ballard, C, Howard R. Neuroleptic drugs in dementia: benefits and harm. Nat Rev Neurosci 2006; 7: 492–500

4 Older People & Dementia team (DH). **Prime Minister's challenge on dementia** Delivering major improvements in dementia care and research by 2015: http://www.dh.gov.uk/dementia

5 NICE/SCIE. Dementia: Supporting people with dementia and their carers in health and social care, 2006: http://www.nice.org.uk/CG42

6 Prescribing Observatory for Mental Health (2011). Topic 11a baseline executive summary: Prescribing antipsychotic medication for people with dementia. CCQI108 (data on file)

7 Alzheimer's Society. Optimising treatment and care for people with behavioural and psychological symptoms of dementia: A best practice guide: http://alzheimers.org.uk/site/scripts/download_info.php?downloadID=609

Further information:

NHS Information Centre survey on dementia: http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/national-dementia-and-antipsychotic-prescribing-audit

National Dementia Strategy: www.dh.gov.uk/en/SocialCare/NationalDementiaStrategy/index.htm

Dementia Action Alliance: www.dementiaaction.org.uk

Royal College of General Practitioners: www.rcgp.org.uk

BNF section 4.2.1 Antipsychotic drugs: http://www.medicinescomplete.com/mc/bnf/current/3209.htm?q=Antipsychotic%20drugs&t=search&ss=text&p=1#_hit