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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In this issue: we provide advice on new cardiovascular monitoring requirements for **fingolimod** (Gilenya▼) if treatment is interrupted and restarted. We also provide a reminder of existing advice to minimise the risk of cardiovascular adverse events (see article A1).

Also this month: routine monitoring of liver function is now recommended for all patients receiving **lenalidomide** (Revlimid) for multiple myeloma, particularly for patients with a history of, or concurrent, viral liver infection or those receiving concomitant medication associated with a risk of liver injury. This advice follows a number of reports of serious hepatic reactions with lenalidomide use (see article A2).

The European Medicines Agency has recommended that the licence for **Tredaptive** (fixed-dose combination product containing extended-release nicotinic acid [1000 mg]) and laropiprant [20 mg]) should be suspended, after a review showed that the benefits of this product no longer outweigh the risks. Tredaptive has been recalled from 18th January 2013. Patients currently taking Tredaptive should be reviewed at a non-urgent appointment in order to consider the need for alternative treatment options (see article S1 for more information).

And finally: we update you on **roflumilast** (Daxas▼) and the risk of suicidal behaviour which has been reported in patients with and without a history of depression, usually within the first few weeks of treatment. Treatment should be avoided in patients with a history of depression associated with suicidal ideation or behaviour, and discontinued if new or worsening psychiatric symptoms occur (article S2).

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Drug safety advice

A1 Fingolimod (Gilenya▼): bradycardia and heart block – repeat enhanced cardiovascular monitoring when restarting fingolimod after treatment interruption

Starting fingolimod treatment, or re-starting fingolimod after treatment interruption, results in transient decreases in heart rate. In some patients it can also cause transient bradycardias and heart block. This risk is minimised through enhanced monitoring.

Guidance on when enhanced cardiac monitoring is required following treatment interruption has now been updated on the basis of new clinical pharmacology analyses and dose titration data.

The new monitoring advice depends both on the time since treatment started, and how long treatment has been interrupted for (see main article below for details).

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.

Initiation of fingolimod treatment causes a transient reduction in heart rate and a decrease in atrioventricular conduction after the first dose, including the occurrence of heart block.

We first highlighted the need for strengthened monitoring after the first dose of fingolimod in February 2012 and in May 2012 as set out below and provided in more detail in the Summary of Product Characteristics (SPC):

See:
Fingolimod Summary of Product Characteristics [http://www.medicines.org.uk/EMC/medicine/24443/SPC/Gilenya+0.5mg+hard+capsules#CLINICAL_PRECAUTIONS]

- 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.

Because the effects of fingolimod on heart rate and atrioventricular conduction may recur on reintroduction of fingolimod treatment following interruption, we also advised that if fingolimod was stopped for more than 2 weeks for any reason, patients should be monitored in the same way as those starting treatment.

Now, further (unpublished) analyses of clinical pharmacology and dose titration data suggest the risk of these cardiovascular effects depends on the duration of the interruption and also the time since initiation of fingolimod treatment. New advice based on these findings is provided below, along with new advice to repeat the monitoring on day 2 in patients who required pharmacological treatment for symptoms of bradyarrhythmia on Day 1.

New advice

Treatment interruption:
The same first-dose monitoring as for treatment initiation* should be repeated if treatment is interrupted as follows:

- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the next dose of fingolimod should be given as planned without repeating the first-dose cardiovascular monitoring.

Patients should be provided the following simplified advice: 'If you have been taking Gilenya for less than 1 month and you forget to take 1 dose for a whole day, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose.

If you have been taking Gilenya for at least 1 month and have forgotten to take your treatment for more than 2 weeks, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose. However, if you have forgotten to take your treatment for up to 2 weeks, you can take the next dose as planned.

Never take a double dose to make up for a forgotten dose'.

Following pharmacological intervention to treat bradyarrhythmia-related symptoms after first dose:
As per current recommendations, patients requiring pharmacological intervention during the first dose monitoring should be monitored overnight in a medical facility.

In these patients, it is now recommended to repeat the first-dose monitoring* after the second dose of Gilenya.

*Key advice, such as first-dose monitoring requirements and high-risk patients in whom fingolimod is not recommended, is listed in the SPC.

Reporting of suspected adverse drug reactions

- Please report all suspected adverse reactions to fingolimod to the Yellow Card Scheme at http://www.mhra.gov.uk/yellowcard

A letter containing the updated advice was sent to health professionals in January 2013.

See:
Fingolimod SPC [http://www.medicines.org.uk/EMC/medicine/24443/SPC/Gilenya+0.5mg+hard+capsules#CLINICAL_PRECAUTIONS]

Further information:
BNF section 8.2.4 Other immunomodulating drugs [link to http://www.medicinescomplete.com/mc/bnf/current/4789.htm]

Article citation: Drug Safety Update January 2013 vol 6, issue 6: A1.

A2 Lenalidomide (Revlimid): risk of serious hepatic adverse drug reactions – routine monitoring of liver function now recommended

Elevations of liver enzymes occur in 1-10 patients out of every 100 treated with lenalidomide for multiple myeloma in clinical trials; the majority of these are non-serious. Serious (potentially fatal) liver injuries such as acute hepatic failure, toxic hepatitis, hepatocellular hepatitis, and cholestatic hepatitis have been reported overall in <1% of treated patients.

Hepatic function should be routinely monitored (with the same frequency as haematological monitoring*), particularly in patients with a history of, or concurrent, viral liver infection, or when lenalidomide is given at the same time as other medications known to be associated with liver injury.

Lenalidomide (Revlimid) is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Lenalidomide is an immunomodulatory agent similar to thalidomide, and has

antineoplastic, antiangiogenic, and proerythropoietic properties. Lenalidomide was introduced in the UK in June 2007.

Risk of hepatic adverse drug reactions

Suspected adverse hepatic reactions have been reported overall in <1% of patients treated. Of these reactions, abnormal liver investigation results, and clinical signs and symptoms of hepatic disorders are the most common (58.7%). The spectrum of hepatic suspected adverse reactions reported also includes hepatic failure, fibrosis, and cirrhosis (17.2%); and cholestasis and jaundice of hepatic origin (13.8%). The remaining reports (10%) describe non-infectious hepatitis, liver-related coagulation and bleeding disorders, and neoplasms. The outcome was fatal in 5% of cases.

In many of the cases, including most with a fatal outcome, there were confounding risk factors for liver disease such as history of hepatic and renal disorders including viral hepatitis; progression of myeloma; myeloma involvement of the liver; prior chemotherapy; infection or sepsis; and concomitant medications known to cause liver injury, particularly antibiotics.

Out of nine liver biopsies performed in patients with hepatic reactions, six showed histological evidence of drug-induced liver injury. In addition, there have also been a substantial number of cases where liver function has improved on discontinuation of lenalidomide, some cases of positive rechallenge, and some cases of negative rechallenge at a lower dose.

Clinical implications of the evidence for drug-induced liver injury with lenalidomide

The evidence suggests that lenalidomide may be associated with drug-induced liver injury. The most compelling evidence of a causal association derives from the results of liver biopsies, and cases in which there has been a positive dechallenge or a positive rechallenge.

The most common hepatic reactions observed in patients treated with lenalidomide are abnormalities of liver enzymes presenting as hepatocellular injury, and/or with a cholestatic pattern. Elevations of liver enzymes frequently occur relatively soon after the start of treatment with lenalidomide; the median time to onset appears to be 41 days, but reactions have been reported from one day to more than three years after the start of treatment. Early elevations in liver enzymes are usually moderate and may normalise without progression to major liver toxicity.

Serious liver injury due to lenalidomide has been reported in relatively small numbers of patients and appears to be idiosyncratic. Predisposing factors that may increase the risk of serious liver injury with lenalidomide include elevated baseline liver enzymes; pre-existing viral liver disease; concomitant treatment with known hepatotoxic medicines; and older age.

See:

Updated lenalidomide Summary of Product Characteristics [link to: http://www.medicines.org.uk/EMC/medicine/19841/SPC/Revlimid/]

and Patient Information Leaflet [link to: http://www.medicines.org.uk/EMC/medicine/19842/PIL/Revlimid/].

Further information:

Letter for healthcare professionals sent December 2012 [link to: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con218766.pdf]

Report suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

European Public Assessment Report for lenalidomide (Revlimid): [link to:

Advice for healthcare professionals:

- Routine monitoring of liver function with the same frequency as haematological monitoring* is recommended for patients receiving lenalidomide. This is particularly important in patients with a history of, or concurrent, viral liver infection, or when lenalidomide is given at the same time as other medications known to be associated with liver injury.
- Prescribers should consider the possibility of lenalidomide-induced liver injury in patients presenting with otherwise unexplained deterioration of liver function.
- Impairment of liver function generally resolves when lenalidomide treatment is stopped. Once abnormal liver function parameters return to baseline, resumption

http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&mid=WC0b01ac058001d124]

BNF section 8.2.4 Other immunomodulating drugs [link to http://www.medicinescomplete.com/mc/bnf/current/PHP5713-lenalidomide.htm]

of treatment with lenalidomide at a lower dose may be considered.

- Reminder advice: lenalidomide is excreted predominantly by the kidney. It is important to adjust the dose of lenalidomide in patients with renal impairment to avoid high plasma levels which may increase the risk of severe hepatotoxicity, as well as haematological side effects.

*The haematological monitoring recommendations for lenalidomide are as follows: a complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.

Article citation: Drug Safety Update January 2013 vol 6, issue 6: A2.

Stop press

S1 **Tredaptive (combined niacin-laropiprant) – no longer for prescribing as preliminary HPS2-THRIVE trial failed to show benefit outweighs risks**

See:

EMA press release, December 2012 [http://www.emea.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/12/news_detail_001686.jsp&mid=WC0b01ac058004d5c1]

HPS2-THRIVE study [http://www.ctsu.ox.ac.uk/research/mega-trials/hps2-thrive]

Tredaptive is a fixed-dose combination product containing extended-release nicotinic acid (1000 mg) and laropiprant (20 mg), which has been indicated for the treatment of dyslipidemia, particularly in patients with combined mixed dyslipidemia and in patients with primary hypercholesterolemia. It has been used in combination with a statin when the cholesterol-lowering effect of statin treatment alone is not sufficient, or alone in patients unable to take statins. Recent use of Tredaptive in the UK has been less than 3000 patients.

A European review of Tredaptive (and similar medicines available outside the UK) was started in December 2012 after new data from a large, long-term study (HPS2-THRIVE) involving over 25 000 patients suggested that the benefits of these medicines did not outweigh the risks.

New data show risks outweigh benefits

The preliminary results of the study indicated that adding Tredaptive to simvastatin did not provide significant additional benefit in reducing the risk of major vascular events such as heart attack and stroke, compared with statin therapy alone. In addition, a higher frequency of non-fatal but serious adverse events was seen in patients taking Tredaptive with simvastatin, compared with patients taking simvastatin alone. These events included bleeding (intracranial and gastro-intestinal), myopathy, infections and new-onset diabetes.

UK healthcare professionals were sent a letter highlighting the new information on Tredaptive in December 2012, and advised not to start any new patients on the drug.

EMA press release, January 2013 [http://www.emea.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/01/news_detail_001694.jsp&mid=WC0b01ac058004d5c1]

In the light of the latest evidence, the benefit-risk balance for Tredaptive is considered negative, and the medicine has been recalled. A letter informing healthcare professionals of this decision was circulated in January 2013.

Further information:

BNF section 2.12: Lipid-regulating drugs
http://www.medicinescomplete.com/mc/bnf/current/PHP1700-tredaptive.htm

Advice for healthcare professionals

- Tredaptive has been recalled since 18th January 2013
- Patients currently taking Tredaptive should make a non-urgent appointment to discuss their treatment options with their doctor.

Article citation: Drug Safety Update January 2013 vol 6, issue 6: S1.

S2 **Roflumilast (Daxas▼): risk of suicidal behaviour – avoid use in patients with previous or existing psychiatric symptoms and discontinue treatment if new or worsening symptoms are identified**

Roflumilast (Daxas▼) is a phosphodiesterase-type-4 (PDE4) inhibitor used for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis. It is indicated for adult patients with a history of frequent exacerbations as 'add-on' to bronchodilator treatment. The recommended dose is one 500 microgram tablet daily.

From clinical trial data, roflumilast is known to be associated with an increased risk of psychiatric disorders such as:

- insomnia (in 100 -1000 out of every 10 000 patients)
- anxiety (in 10 -100 out of every 10 000 patients)
- nervousness and depression (in 1 - 10 out of every 10 000 patients).

Rare instances of suicidal ideation and behaviour, including completed suicide, have been also observed in patients using roflumilast (in 1-10 out of 10 000 patients). A recent review of postmarketing data (unpublished) has found that cases of suicidal behaviour have also been reported postmarketing, and suggests that suicidal behaviour was seen in patients with and without a history of depression, usually in the first weeks of treatment.

If patients have existing psychiatric symptoms, or if concomitant treatment is intended with other medicines likely to cause psychiatric symptoms, roflumilast treatment should only be started or continued after careful assessment of the benefits and risks.

Advice for healthcare professionals:

Further information:

BNF section 3.3: Phosphodiesterase type-4 inhibitors
http://www.medicinescomplete.com/mc/bnf/current/PHP1891-phosphodiesterase-type-4-inhibitors.htm

- Roflumilast is not recommended for patients with a history of depression associated with suicidal ideation or behaviour.
- Patients and caregivers should be asked to notify the prescriber and their healthcare provider of any changes to behaviour or mood, and any suicidal ideation. Such symptoms include preoccupation with suicidal thoughts, and self-harm.
- Roflumilast should be discontinued if new or worsening psychiatric symptoms or suicidal behaviour are identified.

Article citation: Drug Safety Update January 2013 vol 6, issue 6: S2.

Other information from the MHRA

O1 Learning about Yellow Card reporting and pharmacovigilance

See:

Pharmacovigilance learning module [http://learning.bmj.com/learning/module-intro/.html?locale=en_GB&moduleId=10042344]

We have collaborated with BMJ Learning to develop a multimedia learning module, 'Pharmacovigilance—identifying and reporting adverse drug reactions'.

Using scenario-based learning, supported by video clips, the course explains the importance of continuous monitoring for adverse reactions and the MHRA's Yellow Card Scheme for reporting suspected adverse reactions; when and how to submit a Yellow Card; and how to keep informed about adverse reactions.

This online course is approved for one hour of CPD/CME credit. A certificate of completion is available on passing a short assessment exercise at the end. The course is free of charge and any health professional can participate by registering on the BMJ Learning website.

Article citation: Drug Safety Update January 2013 vol 6, issue 6: O1.

O2 New MHRA Twitter channel on safety of medicines

See:

@MHRAmedicines [https://mobile.twitter.com/MHRAmedicines]

The MHRA is pleased to announce the launch of a new Twitter channel, **@MHRAmedicines**, dedicated to medicines' safety information. On this channel we will be notifying you when Drug Safety Update is published, and you may also find other safety messages and alerts for medicines and vaccines here too.

The medicines safety Twitter channel will work alongside our Devices safety, Herbals safety and Press and Corporate Twitter channels to help our audience stay more up-to-date with targeted information and messages. We will of course continue to publish all of this information on our website and issue email alerts as appropriate.

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