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 light of new evidence of the risk of transient bradycardias and heart block after the first dose, strengthened cardiovascular monitoring is now recommended for all patients receiving **fingolimod** for multiple sclerosis: see article A1 for advice.

Also this month, **blue dyes** such as Patent Blue V imported from the EU are used in lymphatic mapping for sentinel lymph node biopsy (SLNB) in breast surgery. Patent Blue V does not carry a UK marketing authorisation. On the basis of a clinical study (the ALMANAC trial) and follow-up program (the NEW START program), serious allergic reactions with the use of Patent Blue V in SLNB were estimated at an incidence rate of 0.1%. Since 2007, we have received a total of 26 case reports describing serious allergic reactions or anaphylaxis with use of Patent Blue V. Surgeons are reminded to have competent personnel and emergency facilities available for at least 1 hour after administration of the blue dye (see article A2).

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Drug safety advice

A1 Fingolimod (Gilenya▼): transient bradycardias and heart block after first dose—strengthened cardiovascular monitoring

Because of the risk of transient bradycardias and heart block after the first dose, the recommended level of cardiovascular monitoring of all patients after their first dose of fingolimod has now increased as outlined 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. It is a sphingosine-1 phosphate receptor modulator.

Fingolimod is known to cause transient bradycardias and might be associated with atrioventricular block after the first dose; these are reflected in existing recommendations to observe patients for signs and symptoms of bradycardia in the 6 hours post administration.

The European Medicines Agency (EMA) has started a review of the benefits and risks of fingolimod after becoming aware of new post-marketing evidence about its possible cardiovascular effects after taking the first dose. This includes a 59-year-old patient from the USA with multiple sclerosis who died within 24 hours of taking the first dose of Gilenya. This patient was being treated with metoprolol and amlodipine for hypertension. The exact cause of death is currently unknown. In addition to the unexplained death in the USA, six other unexplained deaths (including three cases of sudden death) after starting treatment with fingolimod have also been reported. As at Feb 6, 2012, we have received four UK reports of suspected adverse reactions with fingolimod, including one case of bradycardia and hypotension occurring 4 hours after the first dose with a drop in heart rate experienced again the following day.

While the review of fingolimod is ongoing, the EMA's Committee for Medicinal Products for Human Use now recommends that the level of cardiovascular monitoring of all patients is increased after their first dose of fingolimod:

For all patients, monitoring during the first 6 hours after first dose should include:

Pretreatment:

- A 12-lead ECG at baseline before starting treatment

During first 6 hours of treatment:

- Continuous ECG monitoring for 6 hours after first dose
- Blood pressure and heart rate measurement every hour
- A further 12-lead ECG 6 hours after taking the first dose

In case of clinically important cardiac effects, monitoring should be extended until resolution. The criteria for extended monitoring beyond the first 6 hours include the following:

- At any time during the 6-hour monitoring, the occurrence of:
  - Symptomatic bradycardia
  - New onset 2nd degree atrioventricular block, Mobitz Type II
  - New onset 3rd degree atrioventricular block
- At the 6-hour timepoint after first dose, the presence of:
  - Heart rate less than 40 beats per minute
  - Decrease in heart rate of more than 20 beats per minute compared with baseline

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- Persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach)

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

Reminder of other cardiovascular safety measures:

- Use of fingolimod should be based on an overall benefit-risk assessment and careful observation during initiation of therapy because of the potential for serious rhythm disturbances. Advice from a cardiologist should be sought before initiating treatment in patients with the following:
  - Sitting heart rate less than 55 beats per minute
  - Concurrent therapy with beta-blockers
  - History of syncope
  - Second degree or higher atrioventricular block
  - Sick-sinus syndrome, ischaemic cardiac disease, congestive heart failure
  - Significant cardiovascular disease

Important drug–drug interactions

- Fingolimod should not be administered with class I or class III antiarrhythmic medicines because these medicines are associated with cases of torsades de pointes in patients with bradycardia
- Caution should be exercised at treatment initiation in patients receiving beta-blockers or other substances which can decrease heart rate because of additive effects on heart rate

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

Further information:

Statement from the European Medicines Agency:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/01/news_detail_001425.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

Letter for healthcare professionals:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON143507

BNF section 8.2.4 Other immunomodulating drugs:
http://bnf.org/bnf/bnf/62/214545.htm?q=fingolimod&t=search&ss=text&p=1

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A2 **Blue dyes in lymph-node imaging: risk of serious allergic reactions**

Blue dyes (eg Patent Blue V, isosulfan blue) used for imaging purposes during surgery are associated with the occurrence of serious allergic reactions, including anaphylaxis. Surgeons are reminded to have competent personnel and emergency facilities available for at least 1 hour after administration of the blue dye

Blue dyes such as Patent Blue V imported from the EU are used in lymphatic mapping for sentinel lymph node biopsy (SLNB) in breast surgery. Patent Blue V does not carry a UK marketing authorisation.

On the basis of a clinical study (the ALMANAC trial)[1] and follow-up program (the NEW START program) serious allergic reactions were estimated at an incidence rate of 0.1%. Since 1975 a total of 70 case reports of allergic reactions with Patent Blue V were reported to us. 58 of these reports have been received since 2007, 26 of which were serious reactions. With currently increasing usage of Patent Blue V in the UK, the number of serious allergic reactions reported to us is also expected to rise.

The UK Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines advised that emergency measures should be available to treat patients that may experience allergic reactions or anaphylaxis.

1 Mansel RE, et al. J Natl Cancer Inst 2006; 98: 599–609.

Further information:

See also a letter for healthcare professionals available at www.mhra.gov.uk/safetyinformation/drugsafetyupdate/CON143611. This letter will also be circulated in partnership with the Association of Breast Surgery (http://www.associationofbreastsurgery.org.uk/)

Prescribers' responsibilities regarding off-label or unlicensed use of medicines: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990

Advice for healthcare professionals:

- Surgeons using blue dyes are reminded to remain aware of the risk of serious allergic reactions, including anaphylaxis
- Competent personnel and emergency facilities should be available for at least 1 hour after administration of blue dye because delayed reactions may occur
- Please report suspected adverse reactions via the Yellow Card scheme (www.mhra.gov.uk/yellowcard), even though blue dyes are unlicensed products, and include the seriousness of the reported reaction

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