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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This month, we inform you that there have been reports from clinical practice of severe bradycardia or heart block in patients with hepatitis C taking amiodarone (Cordarone X) with the fixed-dose combination of sofosbuvir and ledipasvir (Harvoni▼), and with sofosbuvir (Sovaldi▼) in combination with daclatasvir (Daklinza▼). Avoid concomitant use of amiodarone and the fixed-dose combination of sofosbuvir and ledipasvir, and amiodarone with sofosbuvir and daclatasvir, unless other antiarrhythmics cannot be given—see article 1.

Pomalidomide can cause cardiac failure, interstitial lung disease (ILD) and hepatotoxicity. In patients with cardiac disease or cardiac risk factors, consider the risk of cardiac failure before prescribing pomalidomide and monitor for signs or symptoms during treatment. Carefully assess patients with any acute onset or unexplained worsening of respiratory symptoms to confirm or exclude ILD; stop pomalidomide treatment during assessment. Regularly monitor liver function for the first 6 months of pomalidomide treatment and as clinically indicated thereafter—see article 2.

Two Cochrane systematic reviews suggest that epoetin beta may increase the underlying risk of retinopathy in premature infants. This reinforces the need for monitoring for retinopathy. When reviewing options to prevent anaemia of prematurity, carefully balance the benefit of epoetin beta against its risks, including the possible risk of retinopathy—see article 3.

Finally, in April 2015, letters were sent to healthcare professionals regarding ketoprofen gel, fingolimod (Gilenya▼) and efavirenz (Sustiva)—see article 4 for links to the letters.

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1 **Sofosbuvir with daclatasvir; sofosbuvir and ledipasvir: risks of severe bradycardia and heart block when taken with amiodarone**

Avoid concomitant use of amiodarone (Cordarone X) with ledipasvir-sofosbuvir (Harvoni▼), and amiodarone with sofosbuvir (Sovaldi▼) and daclatasvir (Daklinza▼), unless other antiarrhythmics cannot be given.

When treating patients with both heart rhythm disorders and hepatitis C:

- closely monitor patients taking amiodarone if they start taking the fixed-dose combination of sofosbuvir and ledipasvir, or sofosbuvir in combination with daclatasvir (particularly during the first weeks of treatment)
- only start amiodarone in patients taking either of these antiviral combinations when other anti-arrhythmics are not tolerated or contraindicated; monitor closely (particularly during the first weeks of treatment)
- monitor patients at high risk of bradyarrhythmia continuously for 48 hours in an appropriate clinical setting after starting concomitant amiodarone and antiviral treatment
- monitor patients who have stopped amiodarone within the last few months and need to start taking either of these antiviral combinations – this is due to the long half-life of amiodarone
- advise patients taking amiodarone with either of these antiviral combinations to watch out for signs and symptoms of bradycardia and heart block and get medical help urgently if they experience any of these symptoms:
    - shortness of breath
    - light-headedness
    - palpitations
    - fainting
- please continue to report any suspected adverse reactions to any medicine on a Yellow Card (www.mhra.gov.uk/yellowcard)

Sofosbuvir (Sovaldi▼), daclatasvir (Daklinza▼) and the fixed-dose combination of sofosbuvir and ledipasvir (Harvoni▼) are direct acting antiviral medicines licensed to treat hepatitis C. Amiodarone (Cordarone X) is licensed to treat severe rhythm disorders not responding to other treatments or when other treatments cannot be used.

The MHRA and other EU medicines regulators reviewed the safety of these medicines. This followed 8 reports from EU clinical practice of severe bradycardia or heart block in patients taking amiodarone with the fixed-dose combination of sofosbuvir and ledipasvir, or with sofosbuvir in combination with daclatasvir. Six of the cases occurred within the first 24 hours of starting antiviral treatment. The remaining 2 cases occurred within 2 and 12 days of starting antiviral treatment.

The recommendations from the review are outlined above.

Further information
Letter sent to healthcare professionals in May 2015
https://assets.digital.cabinet-office.gov.uk/media/555c413fed915d7ae5000009/Sovaldi_Harvoni_Daklinza_DHPC_sent_7_May_2015.pdf

European Medicines Agency announcement, April 2015
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/04/news_detail_002313.jsp&mid=WC0b01ac058004d5c1

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2 **Pomalidomide (Imnovid▼): risks of cardiac failure, interstitial lung disease and hepatotoxicity**

New monitoring instructions to detect these side effects as soon as possible.

When using pomalidomide:

- in patients with cardiac disease or cardiac risk factors, use with caution and if used, monitor for signs or symptoms of cardiac failure
- carefully assess patients with any acute onset or unexplained worsening of respiratory symptoms to confirm or exclude interstitial lung disease (ILD); stop pomalidomide treatment during assessment
- if ILD is confirmed, treat appropriately and only resume pomalidomide treatment after thoroughly evaluating the benefits and risks
- regularly monitor liver function for the first 6 months of pomalidomide treatment and as clinically indicated thereafter
- please continue to report suspected adverse drug reactions to pomalidomide or any other medicines on a Yellow Card (www.mhra.gov.uk/yellowcard)

Pomalidomide in combination with dexamethasone is licensed to treat adults with relapsed and refractory multiple myeloma who have received at least two treatments, including lenalidomide and bortezomib, and whose disease has worsened since the last treatment.

A review by the MHRA and other EU medicines regulators concluded that pomalidomide can cause interstitial lung disease (ILD), cardiac failure and hepatotoxicity. This conclusion was based on data from clinical trials, reports from clinical practice and published case reports.[1,2]

Cardiac failure

The review concluded that this side effect is common (ie occurs in between 1/10 and 1/100 patients who take pomalidomide). In most cases, this side effect occurred in patients with cardiac disease or cardiac risk factors and within 6 months of starting pomalidomide. The review also concluded that pomalidomide can cause atrial fibrillation, which may precipitate cardiac failure.

Interstitial lung disease

Pomalidomide can cause ILD and related events such as pneumonitis. The review concluded that this side effect is common (ie occurrs in between 1/10 and 1/100 patients who take pomalidomide). Onset of respiratory symptoms is usually within 6 months of starting treatment. However, there have been cases where ILD occurred approximately 18 months after starting pomalidomide. ILD usually resolves with steroid treatment and stopping pomalidomide.

Hepatotoxicity

It is already known that pomalidomide can elevate alanine aminotransferase and bilirubin levels. The review found that pomalidomide can also cause serious hepatotoxicity, mainly acute hepatitis. Hepatitis was considered an uncommon side effect (ie occurrs in between 1/100 and 1/1,000 patients who take pomalidomide). There have also been reports of acute liver failure in patients receiving pomalidomide; however the review could not determine if pomalidomide caused the liver failure in these cases. The risk of serious hepatic events appears to be highest in the first 6 months of treatment, therefore regular liver function monitoring is recommended during this period. The available data do not provide sufficient evidence to support specific guidance on monitoring frequency.

1. Veluswamy RR and others. 'Adverse drug reaction: pomalidomide-induced liver injury' Lancet 2014: volume 383, issue 9935, pages 2125-2126
2. Pauff JM and others. 'Post-allograft pomalidomide and reversible hepatotoxicity' Bone Marrow Transplantation 2014: volume 49, pages 1341-1342)

Further information
Letter sent to healthcare professionals in April 2014
https://assets.digital.cabinet-office.gov.uk/media/555c397140f0b666a2000008/Imnovid_DHPC_sent_24_April_2015.pdf

Article citation: Drug Safety Update volume 8 issue 10 May 2015: 2

3 **Epoetin beta (NeoRecormon): increased risk of retinopathy in preterm infants cannot be excluded**

Possible increased risk of retinopathy with epoetin beta in premature infants calls for careful consideration of options for preventing anaemia of prematurity.

When using epoetin beta for preventing anaemia of prematurity:

- consider the benefits and risks, including the possible risk of retinopathy
- monitor the infant for features of retinopathy
- advise parents or carers that their baby's eyes will be carefully monitored for any ill effects
- report suspected side effects to epoetin beta or to any other medicine on a Yellow Card (www.mhra.gov.uk/yellowcard)

Epoetin beta (NeoRecormon) is licensed for the prevention of anaemia of prematurity in infants with a birth weight of 0.75 to 1.5 kg and a gestational age of less than 34 weeks. Epoetin beta is identical to erythropoietin, a hormone that stimulates the production of red blood cells.

Infants born before 31 weeks of gestation, particularly those weighing less than 1.25 kg have an underlying risk of retinopathy of prematurity.[1]

Evidence for retinopathy caused by epoetin beta

A European review has considered the current evidence for retinopathy associated with epoetin beta treatment of anaemia of prematurity. Two Cochrane systematic reviews assessed the effectiveness of treatment of anaemia with erythropoietin in premature and/or low birth weight infants. One focused on treatment started within 7 days after birth,[2] the other studied treatment started 8 to 28 days after birth.[3] The systematic reviews also considered adverse effects, including retinopathy of prematurity.

Taken together, the two systematic reviews suggest that epoetin beta may increase the underlying risk of retinopathy in premature infants.

The summary of product characteristics will be amended to include this possible risk of retinopathy. The European review of available data concluded that more data are needed to draw a firm conclusion about erythropoietin and the risk of retinopathy of prematurity. However, the available data show that an increase in the underlying risk of retinopathy in premature infants with early epoetin use cannot be excluded.

Article citation: Drug Safety Update volume 8 issue 10 May 2015: 3

1. Matthew MRK and others. 'Retinopathy of prematurity: are we screening too many babies?' Eye 2002: Volume 16, issue 5 pages 538–542
2. Ohlsson A, Aher SM. 'Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants' Cochrane Database of Systematic Reviews 2014: Issue 4: article number: CD004863
3. Aher SM, Ohlsson A. 'Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants' Cochrane Database of Systematic Reviews 2014: Issue 4, article number: CD004868

4 **Letters sent to healthcare professionals in April 2015**

In each issue of Drug Safety Update we summarise drug safety letters sent to healthcare professionals that are not linked to their own Drug Safety Update article. In April 2015, letters were sent regarding:

- Ketoprofen gel and risk of photosensitivity reactions: reminder of risk minimisation measures – sent on 20 April 2015
- Efavirenz (Sustiva): discontinuation of the Sustiva 30 mg/ml oral solution formulation by the end of October 2015 – sent by Bristol-Myers Squibb on 23 April 2015
- Fingolimod (Gilenya ▼): first reported case of progressive multifocal leukoencephalopathy (PML) in a multiple sclerosis patient taking fingolimod without previous treatment with natalizumab or other immunosuppressive medicines – sent by Novartis on 29 April 2015

Ketoprofen gel: https://assets.digital.cabinet-office.gov.uk/media/555c335ce5274a74ca000009/Ketoprofen_DHPC_sent_20-04-2015.pdf
Efavirenz: https://assets.digital.cabinet-office.gov.uk/media/555c3376ed915d7ae2000002/Sustiva_DHCP_sent_23_April_2015.pdf
Fingolimod: https://assets.digital.cabinet-office.gov.uk/media/555c338ced915d7ae5000007/Gilenya_DHPC_sent_29_April.pdf

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