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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We would like to make prescribers aware that in patients with untreated multiple myeloma to receive thalidomide in first-line treatment who are older than age 75 years, a 100 mg/day starting dose is now recommended. Prescribers should also be aware that even with a reduced starting dose of thalidomide, this age-group may be at higher risk of serious adverse reactions compared with younger patients (see page 2).

Mycophenolate mofetil (and its active metabolite mycophenolic acid) are associated with a high rate of serious birth defects (23–27% of live births in women exposed during pregnancy compared with 2–3% of live births in the overall worldwide population and with approximately 4–5% of live births in transplant recipients given other immunosuppressants) and an increased risk of spontaneous abortion (45–49% of pregnant women exposed compared with 12–33% with other immunosuppressants). These immunosuppressants should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Pregnancy testing and contraception as appropriate are required before starting treatment. See our article (page 3) for information on additional measures to minimise the risk of exposure to these drugs during pregnancy.

Osteonecrosis of the external auditory canal has been reported very rarely (fewer than 1 in 10 000 patients) with bisphosphonates, mainly in association with long-term therapy (2 years or longer). Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma (see page 4).

Finally this month, a European-wide review by medicines regulators, which included the perspectives of clinician and patient representatives, of antiretroviral medicines for HIV has identified that warnings about lipodystrophy and lactic acidosis routinely applied to these agents may not accurately reflect current scientific understanding and clinical experience. After looking at the appropriateness and applicability of the warnings to these products—with the exception of medicines containing zidovudine, stavudine, or didanosine—product information will no longer include warnings on fat redistribution or lactic acidosis (page 6).

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Thalidomide: reduced starting dose in patients older than age 75 years

Use a lower starting dose of thalidomide in patients with untreated multiple myeloma who are older than age 75 years.

Advice for healthcare professionals:

- In patients older than age 75 years, a 100 mg/day starting dose of thalidomide is now recommended to minimise the risk of adverse drug reactions
- In these patients, the starting dose of melphalan should be 0.1–0.2 mg/kg daily, according to baseline bone-marrow reserve and renal function
- Prescribers should be aware that even with a reduced starting dose of thalidomide, this age-group may be at higher risk of serious adverse reactions compared with younger patients
- Suspected adverse reactions to thalidomide should be reported to us on a Yellow Card

Thalidomide (Thalidomide Celgene) combined with melphalan and prednisone is indicated as first-line treatment of patients with untreated multiple myeloma who are age 65 years or older or who are ineligible for high-dose chemotherapy.

The new recommendation to use a 100 mg/day starting dose of thalidomide in those older than age 75 years of age is based on the results of two randomised phase III studies, one which enrolled patients age 65 years or older, and another which enrolled those age 75 years or older.[1]

In patients older than age 75 years, the melphalan recommended starting dose is 0.1–0.2 mg/kg daily according to baseline bone-marrow reserve, along with a further 50% dose reduction for moderate (creatinine clearance ≥30 but < 50 mL/minute) or severe (creatinine clearance <30 mL/minute) renal insufficiency.

In the phase III study that enrolled patients age 65 years or older, the frequency of serious or fatal adverse reactions was higher in patients older than age 75 years who received thalidomide 100 mg once daily than in younger patients who received thalidomide 200 mg once daily (56.5% vs 46.5% for serious reactions and 10.3% vs 5.3% for fatal reactions, respectively). However, no clinically relevant differences were observed between these age-groups for specific serious adverse reactions, and there were no notable differences in primary causes of death between groups.

The recommended starting dose of thalidomide remains 200 mg once a day for patients age 75 years or younger.

1 Hulin C et al. Efficacy of melphalan and prednisolone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009; 27: 3664–70.

Further information
Letter sent to healthcare professionals, 10 November 2015

Article citation: Drug Safety Update volume 9 issue 4 December 2015: 1.

Mycophenolate mofetil, mycophenolic acid: new pregnancy-prevention advice for women and men

Mycophenolate mofetil and its active metabolite mycophenolic acid are associated with a high rate of serious birth defects and increased risk of spontaneous abortion.

Key updated safety advice for healthcare professionals:

- Mycophenolate mofetil or mycophenolic acid should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection
- Physicians should ensure that women and men taking mycophenolate mofetil and mycophenolic acid understand: the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy
- Mycophenolate mofetil or mycophenolic acid treatment should only be initiated in women of child bearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy
- Mycophenolate mofetil or mycophenolic acid should only be given to women of childbearing potential who are using highly effective contraception
- Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment
- Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products
- Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose

Mycophenolate mofetil (CellCept, a prodrug of mycophenolic acid*) is an immunosuppressive agent used in combination with ciclosporin and corticosteroids for the prevention of acute transplant rejection in patients who have received kidney, heart, or liver transplants.

*This advice has been implemented as a result of a review of CellCept. Product information for other mycophenolate mofetil and mycophenolic acid products will be updated accordingly in due course.

Risk of birth defects and spontaneous abortion

Mycophenolate mofetil is a known teratogen; the most frequently reported congenital malformation is that of the ear. A review of worldwide cases of congenital malformations after exposure during pregnancy has confirmed mycophenolate mofetil as a powerful human teratogen, and showed evidence of an increased rate of congenital malformations and spontaneous abortions compared with other immunosuppressants:

- Spontaneous abortions have been reported in 45–49% of pregnant women exposed to mycophenolate mofetil, compared with 12–33% with other immunosuppressants
- Based on literature reports,[1–3] malformations occurred in 23–27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared with 2–3% of live births in the overall worldwide population, and with approximately 4–5% of live births in transplant recipients treated with other

1 Sifontis NM, et al. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006; 82: 1698–702.

2 Coscia LA, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Cos Clin Transpl 2009: 103–22.

3 Hoeltzenbein M, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. Am J Med Genet A 2012; 158A: 588–96.

immunosuppressants).

- Previously only ear malformations had been recognised, but prospectively gathered data have now identified a range of disorders The following other malformations (including multiple malformations) were most frequently reported:
  - Congenital heart disease, such as atrial and ventricular septal defects
  - Facial malformations, including cleft lip and cleft palate, micrognathia, and hypertelorism of the orbits
  - Eye abnormalities
  - Finger malformations
  - Tracheo-oesophageal malformations
  - Nervous system malformations, such as spina bifida
  - Renal abnormalities

Updated advice on pregnancy testing

Before starting mycophenolate mofetil treatment, women of childbearing potential should have a negative pregnancy test result to exclude unintended exposure of the embryo to mycophenolate.

Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended. The second test should be done 8–10 days after the first one and immediately before starting mycophenolate mofetil. Pregnancy tests should be repeated as clinically required (eg, after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient.

Patients should be instructed not to stop treatment but to consult their physician immediately should pregnancy occur.

Further information
Letter sent to healthcare professionals, 10 November 2015

Reporting of suspected adverse reactions

Suspected adverse reactions to mycophenolate mofetil, including adverse pregnancy outcomes, should be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 9 issue 4 December 2015: 2.

Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported very rarely (fewer than 1 in 10 000 patients) with bisphosphonates, mainly in association with long-term therapy (2 years or longer).

Advice for healthcare professionals:

- The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma
- Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma
- Patients should be advised to report any ear pain, discharge from the

ear, or an ear infection during bisphosphonate treatment

- Report any cases of osteonecrosis of the external auditory canal suspected to be associated with bisphosphonates or any other medicines, including denosumab, on a Yellow Card

Bisphosphonates

Bisphosphonates are used to treat osteoporosis, Paget's disease, and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma. Individual bisphosphonates have different indications (see individual Summaries of Product Characteristics*). The following bisphosphonates are available in the UK:

- Alendronic acid
- Ibandronic acid
- Pamidronate disodium
- Risedronate sodium
- Sodium clodronate
- Zoledronic acid

Osteonecrosis of the external auditory canal

Benign idiopathic osteonecrosis of the external auditory canal is a rare condition that can occur in the absence of antiresorptive therapy and is sometimes associated with local trauma.

Evidence for an association with bisphosphonate treatment

Evidence from the clinical literature and from cases reported to medicines regulators, including one report received via the UK Yellow Card scheme, supports a causal association between bisphosphonates and osteonecrosis of the external auditory canal. Product information is being updated to include advice for healthcare professionals and patients.

A total of 29 reports indicative of osteonecrosis of the external auditory canal in association with bisphosphonates have been identified worldwide, including 11 cases reported in the clinical literature.[1–7] Cases have been reported with use of both intravenous or oral bisphosphonates for both cancer-related or osteoporosis indications; there is currently insufficient evidence to determine whether there is any increased risk with higher doses used for cancer-related conditions. Most cases were associated with long-term bisphosphonate therapy for 2 years or longer, and most cases had possible risk factors including: steroid use; chemotherapy; and possible local risk factors such as infection, an ear operation, or cotton-bud use. Bilateral osteonecrosis of the external ear canal was reported in some patients, as was osteonecrosis of the jaw.

The number of cases of osteonecrosis of the external auditory canal reported in association with bisphosphonates is low compared with the number of cases reported of bisphosphonate-related osteonecrosis of the jaw, a well-established side effect of bisphosphonates.[†]

Evidence for an association with denosumab treatment

The available data do not support a causal relation between osteonecrosis of the external auditory canal and denosumab. However, this possible risk is being kept under close review, given that denosumab is known to be associated with osteonecrosis of the jaw.

Article citation: Drug Safety Update volume 9 issue 4 December 2015: 3.

*Summaries of Product Characteristics can be found here on the MHRA website or on the website of the European Medicines Agency, depending whether the medicine has a national or European licence, respectively.

1 Bast F, et al. Bilateral bisphosphonate-associated osteonecrosis of the external ear canal: a rare case. HNO. 2012; 60: 1127–29 [in German].

2 Froelich K, et al. Bisphosphonate-induced osteonecrosis of the external ear canal: a retrospective study. Eur Arch Otorhinolaryngol 2011; 268: 1219–25.

3Kharazmi M, et al. Bisphosphonate-associated osteonecrosis of the auditory canal. Br J Oral Maxillofac Surg 2013; 51: e285–87.

4Polizzotto MN, et al. Bisphosphonate-associated osteonecrosis of the auditory canal. Br J Haematol 2006; 132: 114.

Salzman R, et al. Osteonecrosis of the external auditory canal associated with oral bisphosphonate therapy: case report and literature review. Otol Neurotol 2013; 34: 209–13.

6 Thorsteinsson AL, et al. Bisphosphonate-induced osteonecrosis of the external auditory canal: a case report. J Clin Med Case Reports 2015; 2: 3.

7 Wickham N, et al. Bisphosphonate-associated osteonecrosis of the external auditory canal. J Laryngol Otol 2013; 127 (suppl 2): S51–53.

[†]Patient reminder cards about the risk of osteonecrosis of the jaw are being introduced for intravenous bisphosphonates and denosumab. The cards will become available at different times for individual products. They are now available for the following products: Prolia (denosumab); Xgeva (denosumab); Aclasta (zoledronic acid); Zometa (zoledronic acid); zoledronic acid 5 mg generics and zoledronic acid 4 mg generics. The cards can be viewed here.

Antiretroviral medicines: updated advice on body-fat changes and lactic acidosis

With the exception of medicines containing zidovudine, stavudine, or didanosine, product information will no longer include warnings on fat redistribution or lactic acidosis.

Advice for healthcare professionals:

- Product information for antiretrovirals will be updated to reflect current knowledge about lipodystrophy (including lipoatrophy) and lactic acidosis, so that patients and healthcare professionals can decide on treatment based on the most up-to-date advice
- There are no new risks or safety concerns associated with antiretrovirals. Patients can be reassured that previous information about the risk of lipodystrophy and lactic acidosis for several medicines is no longer considered relevant
- Patients should continue to take their medicine(s) as prescribed
- Patients who have any questions should discuss them with their healthcare professional

Background

Warnings regarding lipodystrophy and lactic acidosis were introduced in product information for antiretrovirals for HIV treatment in the early 2000s in line with clinical findings. Class warnings for lactic acidosis applied only to nucleoside and nucleotide analogue medicines, whereas lipodystrophy warnings applied to all antiretroviral agents.

An assessment of a licence application for a new fixed-dose combination product called Triumeq (dolutegravir, abacavir, and lamivudine) identified that class warnings about lipodystrophy and lactic acidosis were being routinely applied to antiretroviral agents for HIV, but that they may not accurately reflect current scientific understanding. An EU-wide review therefore looked at the appropriateness and applicability of the warnings to these products.

Lipodystrophy

The review of the risk of lipodystrophy included lipoatrophy, lipoaccumulation, and changes in weight and metabolism.

Lipoatrophy

Lipoatrophy was previously considered to be associated with nucleoside reverse transcriptase inhibitors (NRTIs). The review noted that lipoatrophy was associated with reduced mitochondria levels in fat cells, and related only to substances with a high risk of mitochondrial toxicity—ie, zidovudine, stavudine, and possibly didanosine.[1,2] However, lipoatrophy was not seen in regimens with other NRTI products: instead, treatment was associated with fat gain from improved HIV infection control.[3–5]

Lipoaccumulation

There was no clear evidence that disproportional body-fat redistribution was related to antiretroviral treatment.[6]

1 Nolan D, et al. Contribution of nucleoside-analogue reverse transcriptase inhibitor therapy to lipoatrophy from the population to the cellular level. Antivir Ther 2003; 8: 617–26.

2 Cherry CL, et al. Tissue-specific associations between mitochondrial DNA levels and current treatment status in HIV-infected individuals. J Acquir Immune Defic Syndr 2006; 42: 435–40.

3 Hammond E, et al. Human immunodeficiency virus treatment-induced adipose tissue pathology and lipoatrophy: prevalence and metabolic consequences. Clin Infect Dis 2010; 51591–99.

4 McComsey GA, et al. Changes in fat mitochondrial DNA and function in subjects randomized to abacavir-lamivudine or tenofovir DF-emtricitabine with atazanavir-ritonavir or efavirenz: AIDS Clinical Trials Group study A5224s, substudy of A5202. J Infect Dis 2013; 207: 604–11.

5 Van Vonderen MG, et al. Zidovudine/lamivudine for HIV-1 infection contributes to limb fat loss. PLoS ONE 2009: 4: e647.

6 Moyle GJ, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. AIDS 2006; 20: 2043–50.

Blood-lipid levels: changes in weight and metabolism

Warnings of increased levels of blood lipids were previously included in the product information for protease inhibitors and for nucleoside and nucleotide analogues. Protease inhibitors were also thought to be associated with a risk of hyperglycaemia. Effects on blood lipids and glucose may occur with any HIV medicine.[7]

Summary

Consistent with current HIV treatment guidelines,[8,9] product information will be amended to advise that weight gain and metabolic changes (such as lipid and glucose increases) may occur during treatment with any HIV medicine. However, these changes are partly linked to underlying disease control and lifestyle in addition to antiretroviral treatment. Warnings for lipoatrophy and lipoaccumulation will be retained only for zidovudine, stavudine, and didanosine.

Lactic acidosis

Warnings about the risk of lactic acidosis were previously applicable only to nucleoside and nucleotide analogues. The review looked at evidence from observational studies,[10,11] published case reports, and data from licence holders of antiretroviral medicines. The risk of lactic acidosis was considered to differ across the class, being most strongly associated with zidovudine, stavudine, and didanosine.

Therefore, in line with current evidence, warnings about lactic acidosis will be removed for nucleoside and nucleotide analogues, with the exception of products that contain zidovudine, stavudine, or didanosine. For combination medicines, any warnings still relevant to any of the active substances will remain in the medicine's product information.

7 De Wit S, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Diabetes Care 2008; 31: 1224–29.

8 European AIDS Clinical Society. Guidelines, version 8.0 October 2015. http://www.eacsociety.org/files/2015_eacsguidelines_8.0-english_revised-20151104.pdf

9 British HIV Association. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. http://www.bhiva.org/documents/Guidelines/Monitoring/hiv_971_EV.pdf

10 Boubaker K, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. Clin Infect Dis 2001; 33: 1931–37.

11 Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. AIDS 2007; 21: 2455–64.

Further information
European Medicines Agency. Updated advice on body fat changes and lactic acidosis with HIV medicines

Article citation: Drug Safety Update volume 9 issue 4 December 2015: 4.

Letters sent to healthcare professionals in November 2015

A summary of letters sent to healthcare professionals in November 2015:

- Thalidomide: reduced starting dose in patients older than age 75 years (see also page 2)
- Mycophenolate mofetil (CellCept): pregnancy-prevention advice (see also page 3)
- Nicorandil (Ikorel): second-line treatment for angina; risk of progressive ulceration
- InductOs: supply shortage
- Dimethyl fumarate (Tecfidera): new measures to minimise the risk of progressive multifocal leukoencephalopathy

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