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 (MHRA) is the government agency 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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First, we alert you to important new recommendations following cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir (page 2). It is now recommended that, pending completion of an EU review of this signal, dolutegravir should not be prescribed to women who are trying to become pregnant. Exclude pregnancy in women of childbearing potential with pregnancy testing before starting dolutegravir and advise use of effective contraception throughout treatment.

Next, act on monitoring advice to minimise the uncommon risk of hypercalcaemia following discontinuation of denosumab 120 mg (Xgeva▼) when used for giant cell tumour of bone (page 4). Cases of rebound hypercalcaemia have been reported up 9 months after cessation of denosumab. Monitor patients for signs and symptoms of hypercalcaemia after discontinuation, consider periodic assessment of serum calcium, and re-evaluate the patient's calcium and vitamin D supplementation requirements.

Finally, read study data showing an increased risk of new primary malignancy with Xgeva compared with zoledronic acid when used in the prevention of skeletal-related events in adults with advanced malignancies involving bone (page 6).

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Dolutegravir (Tivicay▼, Triumeq▼, Juluca▼): signal of increased risk of neural tube defects; do not prescribe to women seeking to become pregnant; exclude pregnancy before initiation and advise use of effective contraception

New safety recommendations have been issued while an EU review evaluates cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir.

Advice for healthcare professionals:

- do not prescribe dolutegravir to women who are trying to become pregnant
- exclude pregnancy in women of childbearing potential with pregnancy testing before starting dolutegravir
- advise women of childbearing potential to use effective contraception throughout treatment with dolutegravir
- if pregnancy is confirmed in the first trimester while a woman is taking dolutegravir, switch to an alternative treatment unless there is no suitable alternative
- advise any women taking dolutegravir for HIV to not stop taking their medicine without first consulting their doctor
- report any suspected adverse drug reactions associated with dolutegravir to the Yellow Card Scheme

Signal of increased risk of neural tube defects

An EU review has begun following preliminary results from an observational study suggesting an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception.

The study, which looked at babies born to 11,558 women with HIV in Botswana, showed 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11,173) whose mothers took other HIV medicines. No cases were reported in infants born to women who started dolutegravir later during pregnancy. Final results of the study are expected in about a year. The review will also investigate cases of birth defects in babies born to women who took dolutegravir during pregnancy reported, including two in the USA.

A Direct Healthcare Professional Communication has been sent to healthcare professionals involved in the care of patients with HIV and to patient groups in the UK to advise of these recommendations. The European Medicines Agency has issued information to patients.

Further advice will be communicated as appropriate at the end of the review.

Background

▼Dolutegravir is an integrase inhibitor indicated in combination with other anti-retroviral medicinal products for the treatment of HIV in adults, adolescents, and children older than 6 years. In the EU, dolutegravir has been authorised since 2014. It is marketed on its own as Tivicay and in combination with lamivudine and abacavir as Triumeq or in combination with rilpivirine hydrochloride as Juluca. Further information on these medicines can be found on the EMA website or in the Summaries of Product Characteristics.

Report any suspected adverse drug reactions

Any suspected adverse drug reactions with dolutegravir (Tivicay▼, Triumeq▼, Juluca▼) should be reported without delay on a Yellow Card.

Reporting of suspected side effects in the mother or baby following medicine use in pregnancy is vital for the safe use of medicines. It is quick and easy to report online or via the Yellow Card app (download from the Apple App Store, or Google Play Store).

Further information

- EMA press release. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. 18 May 2018.

- Direct Healthcare Professional Communication. 23 May 2018.

Article citation: Drug Safety Update volume 11 issue 10; June 2018: 1.

Denosumab (Xgeva▼) for giant cell tumour of bone: risk of clinically significant hypercalcaemia following discontinuation

Monitor patients for signs and symptoms of hypercalcaemia after discontinuation of denosumab treatment for giant cell tumour of bone. Cases of rebound hypercalcemia have been reported up to 9 months after cessation of treatment.

Advice for healthcare professionals:

- cases of clinically significant hypercalcaemia (rebound hypercalcaemia) have been reported up to 9 months after discontinuation of denosumab treatment for giant cell tumour of bone
- monitor patients for signs and symptoms of hypercalcaemia after discontinuation, consider periodic assessment of serum calcium, and re-evaluate the patient's calcium and vitamin D supplementation requirements
- advise patients to report symptoms of hypercalcaemia (see list in main text)
- denosumab is not recommended in patients with growing skeletons
- report any suspected adverse reactions to denosumab or other medicines on a Yellow Card

Cases of rebound hypercalcaemia

Cases of clinically significant hypercalcaemia requiring hospitalisation and complicated by acute renal injury have been reported in a clinical trial of adults and skeletally mature adolescents with giant cell tumour of bone.[1] Cases of rebound hypercalcemia were reported up to 9 months after discontinuation of denosumab (for description of selected cases see article). Cases have also been through some national adverse drug reaction reporting schemes. No Yellow Cards have been received of this suspected adverse drug reaction with denosumab in the UK, but continued vigilance is recommended.

The Summary of Product Characteristics for Xgeva has been updated to include risk of hypercalcaemia following discontinuation of treatment for giant cell tumour of the bone. This adverse event is thought to occur uncommonly, with an estimated frequency of occurring in fewer than 1 in every 100 patients receiving denosumab.

Symptoms of hypercalcaemia include excessive thirst, fatigue, drowsiness, confusion, loss of concentration, depression, nausea, vomiting, constipation, and muscle and/or bone pain.

Clinically significant hypercalcaemia is a known risk after stopping denosumab treatment in patients with growing skeletons; denosumab is not recommended in this patient group.

1.Uday S, et al. Osteonecrosis of the Jaw and Rebound Hypercalcemia in Young People Treated With Denosumab for Giant Cell Tumor of Bone. *J Clin Endocrinol Metab* 2018; **103:** 596–603.

About denosumab

Denosumab 120 mg (Xgeva▼) is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity. See Summary of Product Characteristics.

Denosumab 120 mg is also indicated for the prevention of skeletal-related events with advanced malignancies involving bone (see June 2018 Drug Safety Update on risk of new primary malignancy).

Denosumab is also associated with the risk of hypocalcaemia usually occurring in the first weeks of treatment, although it can occur later (see Drug Safety Update articles from September 2014 and October 2012).

Denosumab 60 mg (Prolia) is indicated for the treatment of osteoporosis and bone loss. For full indication see Summary of Product Characteristics.

Report any suspected adverse drug reactions

The Medicines and Healthcare products Regulatory Agency continually monitors the safety of all medicines. All suspected adverse reactions associated with Xgeva▼, including after stopping treatment, should be reported to the Yellow Card Scheme.

Article citation: Drug Safety Update volume 11, issue 11; June 2018: 2.

Denosumab (Xgeva▼) for advanced malignancies involving bone: study data show new primary malignancies reported more frequently compared to zoledronate

A pooled analysis has shown an increased rate of new primary malignancies in patients given Xgeva (1-year cumulative incidence 1.1%) compared with those given zoledronic acid (0.6%), when used in the indication of the prevention of skeletal-related events with advanced malignancies involving bone. No treatment-related pattern in individual cancers or cancer groupings were apparent.

Risk of new primary malignancy

A recent EU review of Xgeva has added into the product information the risk of new primary malignancy when used for the prevention of skeletal-related events in adults with advanced malignancies involving bone. A letter has been sent to healthcare professionals about this risk.

In a pooled analysis of four phase III studies in patients with advanced malignancies involving bone, new primary malignancy was reported more frequently in patients treated with Xgeva (denosumab 120 mg, once a month) compared to zoledronic acid (4 mg, once a month) during the primary double-blind treatment phases of these studies.

New primary malignancy occurred in 54 (1.5%) of 3,691 patients treated with Xgeva (median exposure of 13.8 months; range: 1.0–51.7 months) and in 33 (0.9%) of 3,688 patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0-50.8 months). The cumulative incidence at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid. No treatment-related pattern in individual cancers or cancer groupings were apparent.

Background

Denosumab 120 mg (Xgeva▼) is indicated for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone.

Denosumab 120 mg is also indicated for adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see June 2018 Drug Safety Update).

Denosumab 60 mg (Prolia) is indicated for the treatment of osteoporosis and bone loss. For full indication see Summary of Product Characteristics.

Report any suspected adverse drug reactions

The Medicines and Healthcare products Regulatory Agency continually monitors the safety of all medicines. All suspected adverse reactions associated with Xgeva▼ should be reported to the Yellow Card Scheme.

Article citation: Drug Safety Update volume 11, issue 11; June 2018: 3.

Letters sent to healthcare professionals in May 2018

In May 2018, letters were sent to healthcare professionals about:

- Azithromycin: increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation (HSCT) patients treated with azithromycin
- Lynparza▼(Olaparib): Risk of medication errors with new pharmaceutical form
- Xgeva▼ (denosumab): risk of new primary malignancy
- Lymphoseek (tilmanocept) radiopharmaceutical preparation: temporary extension of shelf life of lot F03016002
- ReoPro (abciximab) 2 mg/mL solution for injection or infusion: indefinite supply shortage
- Tivicay▼ (dolutegravir), Triumeq▼ (dolutegravir, abacavir, lamivudine), Juluca▼ (dolutegravir, rilpivirine): neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception

You still have time to complete this 10-minute survey to tell us your views on the way medicines safety issues are communicated and how we might improve this to better support safe and effective use.

Article citation: Drug Safety Update volume 11, issue 11; June 2018: 4.

Medical Device Alerts issued in May 2018

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

An alert was recent issued by MHRA on:

- JM103 and JM105 Jaundice Meters – risk of misinterpretation of measurement in hyperbilirubinemia cases

You are also reminded of the actions from the following alert, highlighted in Drug Safety Update last month:

- Home use and Point of Care blood glucose monitoring system: Accu-Chek Aviva, Accu-Chek Performa and Accu-Chek Inform II test strips – risk of strip error messages and false high and low blood glucose results

Article citation: Drug Safety Update volume 11, issue 11; June 2018: 5.
