Drug Safety Update

MHRA

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 provide updated information on the risk of second primary malignancy with lenalidomide for multiple myeloma. Current available evidence suggests that there may be a small increased risk of second primary malignancy in patients treated with lenalidomide for the authorised indication of relapsed or refractory myeloma. Overall, in trials this was compensated by greater overall survival and progression-free survival. Healthcare professionals should remain vigilant for this risk – see article A1.

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Drug safety advice

A1 Lenalidomide (Revlimid▼): risk of second primary malignancy—update

Clinical trials investigating use of lenalidomide in patients with newly diagnosed multiple myeloma have shown a four-fold increased risk of second primary malignancy (including: haematological malignancies such as acute myeloid leukaemia, Hodgkin's disease, and B-cell lymphocytic leukaemias; myelodysplastic syndrome; solid tumours; and melanomas). There seems to be a smaller increased risk of second primary malignancy in patients treated with lenalidomide for relapsed or refractory myeloma—the authorised indication. Healthcare professionals should consider the possibility of second primary malignancy in patients treated with lenalidomide

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, which has antineoplastic, antiangiogenic, and antierythropoietic properties.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON117323

In May 2011 we published an article in Drug Safety Update on the preliminary investigation of a signal from clinical trials in which lenalidomide was given as maintenance treatment for patients with newly diagnosed multiple myeloma. Importantly, this treatment population falls outside the currently authorised indication. The data showed an apparent excess of second primary malignancy in patients treated with lenalidomide (including: haematological malignancies such as acute myeloid leukaemia, Hodgkin's disease, and B-cell lymphocytic leukaemias; myelodysplastic syndrome; solid tumours; and melanomas).

Following this, a Europe-wide review relating to the risk of second primary malignancy in patients treated for the authorised indication of relapsed or refractory multiple myeloma has been conducted, in order to determine the balance of risks and benefits of lenalidomide, taking into consideration the availability of alternative treatment options for these patients (which were not available when the licence was granted for lenalidomide).

Risk of second primary malignancy in patients with relapsed or refractory myeloma

To date, there have been eight case reports (from the pivotal clinical trials of 353 patients assigned lenalidomide and 350 controls that supported the license application for lenalidomide) of invasive second primary malignancy (excluding non-melanoma skin cancer), one of whom had died as a result of the reported second malignancy and four of whom had died from other causes; three remained alive. The incidence of invasive second primary malignancy (excluding non-melanoma skin cancer) for lenalidomide-exposed patients was 1.71 versus 0.91 per 100 patient-years for the control group).

The incidence of second primary malignancy (including non-melanoma skin cancer) in lenalidomide-treated patients was 3.98 per 100 patient-years compared with 1.38 per 100 patient-years for controls. Non-invasive second primary malignancies comprise basal-cell or squamous-cell skin cancers. Most invasive second primary malignancies were solid tumours (incidence rate 1.28 per 100 patient-years).

The available evidence suggests that there may be a small increased risk of development of second primary malignancy. Overall in the trials this was compensated by greater overall survival and progression-free survival in patients treated with lenalidomide for relapsed or refractory myeloma. The balance of benefits and risks for lenalidomide remains favourable in its licensed indication.

Continues…

Risk of second primary malignancy in patients newly diagnosed myeloma

In clinical trials of newly diagnosed multiple myeloma (unauthorised indication), a four-fold increased incidence of second primary malignancy has been observed in patients receiving lenalidomide (7.0 %) compared with controls (1.8%). The median follow-up for participants with newly diagnosed myeloma in clinical trials ranges from 27.2 months to 36.5 months.

The available data do not allow identification of potential risk factors for the development of second primary malignancy, therefore, the possibility of second malignancy should be considered in all patients treated with lenalidomide.

Further information:

Letter for healthcare professionals sent Oct 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON134744

European Public Assessment Reports for lenalidomide: http://www.emea.europa.eu/humandocs/PDFs/EPAR/revlimid/H-717-en6.pdf

BNF section 8.2.4 Other immunomodulating drugs: http://bnf.org/bnf/bnf/current/200217.htm

Advice for healthcare professionals:

- Use of lenalidomide in unlicensed indications is not recommended unless it takes place as part of a clinical trial
- Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated
- Healthcare professionals should report all suspected adverse reactions, including second primary malignancy promptly to us via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

Article citation: Drug Safety Update Nov 2011 vol 5, issue 4: A1.

Yellow Card Scheme update

Y1 Yellow Cards which made a difference—high-dose rosuvastatin and rhabdomyolysis

Yellow Cards: helping safeguard public health

The Yellow Card Scheme principally acts as an early-warning system for identifying previously unrecognised adverse drug reactions (ADRs). It also provides valuable information on recognised ADRs, allowing us to identify and refine the understanding of risk factors that may affect the clinical management of patients.

The value of the Scheme has been demonstrated many times and it has helped to identify numerous important safety issues, many of which were not recognised as being related to a particular medicine until we received information on Yellow Cards.

Making a difference: Yellow Cards reporting rhabdomyolysis with rosuvastatin

In March 2003, rosuvastatin (Crestor) was launched in the UK. Consistent with other statins, muscle toxicity was recognised as a dose-related adverse reaction to rosuvastatin, leading in rare cases to rhabdomyolysis. The Summary of Product Characteristics for Crestor contained the warning:

> *…As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. uncomplicated myalgia and myopathy, have been reported in Crestor-treated patients. Rare cases of rhabdomyolysis have been reported in subjects receiving rosuvastatin 80 mg in investigational clinical trials which were occasionally associated with impairment of renal function. All cases improved on cessation of therapy.*

In September 2003, we received the first reports of suspected rhabdomyolysis with rosuvastatin treatment. By February 2004, the rosuvastatin dose was reported to be at 40 mg or higher in four of the five reports received, and the reporting rate (taking prescribing data into account) was higher than expected relative to historical data with other statins.

See also information in Current Problems in Pharmacovigilance, Oct 2004: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007447

This finding led to a thorough review of all available data sources and to the following update to prescribing advice in June 2004:

- The highest licensed dose (40 mg) was contraindicated in patients with predisposing risk factors for muscle toxicity
- Specialist supervision was recommended when the 40 mg dose is initiated
- Patients who were already taking 40 mg treatment were recommended to have a review of their treatment.

In this example, a small number of Yellow Card reports of rhabdomyolysis with high-dose rosuvastatin, combined with data on the drug's usage levels, provided enough evidence for us to trigger a full review that led to action to protect public health.

Reporting of ADRs is vital to enable us to identify potential drug-safety issues. Please report, even if you are unsure whether a reaction is linked to a medicine. Show your support for the Yellow Card Scheme by reporting adverse reactions and you can help make medicines safer.

Report online at www.mhra.gov.uk/yellowcard

Article citation: Drug Safety Update Nov 2011 vol 5, issue 4: Y1.

Stop press

S1 **Paracetamol: reminder of updated dosing recommendations for children**

We recently informed you that updated dosing recommendations for paediatric paracetamol liquids had been developed to ensure children receive optimum dosing for their age.

See Drug Safety Update July 2011: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON123113

Products labelled with the new recommendations are now entering the market, and we would like to remind you of the updated dosing regimens which can be accessed via the margin weblink.

Access the accompanying report: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON134919

Furthermore, a detailed report on this update to liquid paracetamol medicines is also available (see margin weblink).

Further information:
BNF section 4.7.1 Non-opioid analgesics: http://bnf.org/bnf/bnf/current/3457.htm

Article citation: Drug Safety Update Nov 2011 vol 5, issue 4: S1.