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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Further safety information has recently been identified from case reports of prasugrel antiplatelet treatment that describe rare but serious hypersensitivity reactions including, very rarely, angioedema. Some cases have occurred in patients with a known history of hypersensitivity to the antiplatelet agent clopidogrel, but others have no history of clopidogrel exposure. Healthcare professionals should be aware of this risk, and further information is outlined in article A1.

Data from three large controlled clinical trials for lenalidomide have recently shown a signal of an apparent excess of second primary malignancies (mainly haematological) in patients treated for newly diagnosed myeloma, a currently unauthorised indication. However, at present, it is not possible to conclude that the risk has been categorically established or that the risk is equally relevant to the licensed indication. Unlicensed use of lenalidomide is not recommended. Healthcare professionals should be vigilant for the occurrence of second primary malignancies, and should report such events promptly. See article A2 for further information.

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Drug safety advice

A1 Prasugrel (Efient▼): rare but serious hypersensitivity reactions

Prasugrel (Efient▼) has been rarely associated with reports of serious hypersensitivity reactions including, very rarely, angioedema; some of which occurred in patients with a history of hypersensitivity to clopidogrel. Healthcare professionals should be aware of this risk when prescribing prasugrel

Prasugrel is a thienopyridine, belonging to the same class of medicines as clopidogrel, and acts as an inhibitor of platelet activation and aggregation.

Coadministered with aspirin, prasugrel is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (ie, unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction) undergoing percutaneous coronary intervention.

Further safety information has recently been identified from postmarketing case reports describing serious hypersensitivity reactions including, very rarely, angioedema. As at April 2011, nine such cases have been reported worldwide in association with use in approximately 727 000 patients. Some cases have occurred in patients with a known history of hypersensitivity to clopidogrel, but others have no history of clopidogrel exposure. At present, the mechanism for these allergic reactions is unclear. The time to onset of symptoms ranged from immediately after treatment to up to 5–10 days later.

Advice for healthcare professionals:

- prescribers should be aware of the potential risk of rare but serious hypersensitivity reactions with prasugrel and should monitor for signs in all patients, including those with a previous known history of hypersensitivity reactions to thienopyridines
- when prescribing prasugrel, inform patients of the potential risk of hypersensitivity reactions, including angioedema
- suspected adverse reactions to prasugrel should be reported via the Yellow Card Scheme (see www.yellowcard.gov.uk)

Advice for patients taking prasugrel:

- patients should inform their doctor immediately if they experience symptoms suggesting hypersensitivity or allergic reaction (eg, swelling of the face, neck, tongue, lips, or throat; rash; itching; or shortness of breath)

Further information:

Letter for healthcare professionals sent April 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON117263

BNF section 2.9 Antiplatelet drugs: http://bnf.org/bnf/bnf/61/202499.htm?q=prasugrel&t=search&ss=text&p=1

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A2 **Lenalidomide (Revlimid▼): investigation of risk of second primary malignancies in myeloma**

Data from three large controlled clinical trials investigating use in patients with newly diagnosed multiple myeloma have recently shown a signal of an apparent excess of second primary malignancies in patients treated with lenalidomide. Use of lenalidomide in this or other unlicensed indications is not recommended. Healthcare professionals should be vigilant for the occurrence of second primary malignancies, and should report such events promptly

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.

Data from three large controlled clinical trials have recently come to the attention of regulatory authorities in which lenalidomide was given as maintenance treatment for patients with newly diagnosed multiple myeloma. This treatment population falls outside the currently authorised indication for this drug. The data show an apparent excess of second primary malignancies in patients treated with lenalidomide. In these trials, the malignancies were mainly haematological (see table below). On the basis of this observation, a review of the balance of benefits and risks of lenalidomide in its authorised indication is being undertaken in the EU.

For further information on the EU review, see http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/03/news_detail_001225.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

Further information:

Letter for healthcare professionals sent April 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON117263

Yellow Card Scheme: www.yellowcard.gov.uk

European Public Assessment Reports for lenalidomide: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125

BNF section 8.2.4 Other immunomodulating drugs: http://bnf.org/bnf/bnf/61/200218.htm?q=lenalidomide&t=search&ss=text&p=1

Data from controlled clinical trials

These data show a reproducible signal for an excess incidence of second primary haematological and non-haematological malignancies in patients with newly diagnosed multiple myeloma who have been treated with lenalidomide (a currently unauthorised indication) compared with controls.

However, at present, it is not possible to conclude that the risk has been categorically established or that the risk is equally relevant to the licensed indication. More comprehensive data are being obtained. Furthermore, the effects of potential confounding risk factors are unknown, including possible imbalances in molecular or biological markers.

Nevertheless, the new data emphasise the importance of adhering to the licensed indication. Unlicensed use is not recommended, and should only be undertaken after careful individual consideration of potential benefits and risks.

In the light of the new signal, healthcare professionals should consider the possibility of development of new malignancy whenever lenalidomide has been prescribed, and they are encouraged to report any such cases that occur.

Advice for healthcare professionals:

- At present, there is no recommendation to delay, modify, or restrict the use of lenalidomide for patients treated for the indication authorised in the EU
- The use of lenalidomide in unlicensed indications is not recommended; healthcare professionals should carefully consider the balance of risks and benefits of any off-label use
- Current trials of lenalidomide as an experimental drug are under periodic safety monitoring, and the investigation of the signal for second primary malignancies does not affect enrolment or participation in these trials
- Healthcare professionals should be vigilant for the occurrence of second primary malignancies, and should report such events promptly

The table summarises preliminary findings from these three randomised, double-blind, placebo-controlled phase III trials:

Trial (population)	Treatment	Incidence rate of second primary malignancy per 100 patient-years (95%CI)	Notes
1 (patients with newly diagnosed multiple myeloma aged >65 years, n=458)	Lenalidomide combined with melphalan and prednisone, followed by lenalidomide maintenance treatment	3.76 (2.18–6.47)	More cases of second primary malignancies, mainly haematological (including acute myeloid leukaemia and myelodysplastic syndrome)
	Lenalidomide combined with melphalan and prednisone, followed by placebo	3.53 (2.00–6.21)	
	Control group: melphalan combined with prednisone and placebo	2.53 (1.32–4.86)	
2 (patients with newly diagnosed multiple myeloma aged <65 years, n=608)	Lenalidomide consolidation/maintenance treatment immediately after high-dose melphalan and autologous stem-cell transplantation	2.31 (NA)	More cases of second primary malignancies, mainly haematological (including acute myeloid leukaemia, myelodysplastic syndrome, Hodgkin's lymphoma, and B-cell acute lymphoblastic leukaemia)
	Lenalidomide consolidation treatment, followed by placebo maintenance treatment immediately after high-dose melphalan and autologous stem-cell transplantation	0.61 (NA)	
3 (patients with newly diagnosed multiple myeloma aged <65 years, n=426)	Lenalidomide maintenance treatment immediately after high-dose melphalan and autologous stem-cell transplantation	NA	More cases of second primary malignancies, mainly haematological (including acute myeloid leukaemia, myelodysplastic syndrome, Hodgkin's lymphoma, and B-cell acute lymphoblastic leukaemia); crude incidence rate of secondary primary malignancies 8.2% for lenalidomide (n=231) vs 2.2% for placebo
	Placebo maintenance treatment immediately after high-dose melphalan and autologous stem-cell transplantation	NA	

NA=not available.

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Other information from the MHRA

O1 Nicobrevin antismoking preparation: withdrawn from the market

Further information:

Stop-smoking treatments: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice%E2%80%93M%E2%80%93T/Stopsmokingtreatments/index.htm#2; a UK Public Assessment Report on the withdrawal is also available on this webpage (scroll down to 'Other information' at the bottom of the page)

BNF section 4.10.2 Nicotine dependence: http://bnf.org/bnf/bnf/61/3689.htm?q=stop%20smoking&t=search&ss=text&p=1

The Commission on Human Medicines and its Pharmacovigilance Expert Advisory Group considered a review of the risks and benefits of Nicobrevin—a multi-ingredient antismoking preparation containing quinine, menthyl valerate, camphor, and eucalyptus oil. The Commission noted the lack of evidence for efficacy of Nicobrevin as an aid to smoking cessation and the association of quinine and camphor with adverse reactions. Furthermore, none of the antismoking organisations recommend Nicobrevin as an aid to cessation.

The Commission advised that the risks of Nicobrevin outweigh any benefits, and use of an unproven antismoking preparation could delay or deter patients from seeking effective smoking-cessation treatments. Therefore, Nicobrevin has been withdrawn from the UK market. The product licence was cancelled on Jan 31, 2011; UK distribution ceased at the end of August 2010. Various smoking-cessation treatments are available, for further details see link, left.

Article citation: Drug Safety Update May 2011, vol 4 issue 10: O1.