

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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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.



The MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

This month, we have important information for professionals who work in the field of cancer.

Articles on p2 and p3, respectively, provide advice about a risk of hepatitis B reactivation in patients receiving treatment with BCR-ABL tyrosine kinase inhibitors or pomalidomide.

And our article on p4 informs you of interim steps to take to help minimise the risk of serious or potentially fatal infection with the use of idelalisib, after new findings from clinical trials outside its currently authorised drug combinations or indicated populations.

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1 BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation

Patients should be tested for hepatitis B virus before starting treatment with BCR-ABL tyrosine kinase inhibitors.

Advice for healthcare professionals:

- Test patients for infection with hepatitis B virus (HBV) before starting treatment with BCR-ABL tyrosine kinase inhibitors
- Consult experts in liver disease and in the treatment of HBV before starting treatment with BCR-ABL tyrosine kinase inhibitors in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV during treatment
- Patients who are carriers of HBV who require treatment with BCR-ABL tyrosine kinase inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after stopping
- Suspected adverse reactions to pomalidomide should be [reported to us on a Yellow Card](#)

BCR-ABL tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib) are used in the treatment of chronic myeloid leukaemia or Philadelphia chromosome positive acute lymphoblastic leukaemia. Full details of authorised indications are given in individual Summaries of Product Characteristics.*

Cases of HBV reactivation

An EU-wide review has shown that cases of HBV reactivation can occur in patients who are chronic carriers of the virus after they have received a BCR-ABL tyrosine kinase inhibitor. Some cases resulted in acute liver failure or fulminant hepatitis, leading to liver transplantation or death. The review assessed cases from clinical studies and cases of suspected adverse drug reactions reported by healthcare professionals and in the literature.

Case reports suggest that HBV reactivation may occur at any time during treatment with a BCR-ABL tyrosine kinase inhibitor. Some patients had a history of hepatitis B, whereas for others the serological status at baseline was unknown. On HBV reactivation, an increase in viral load or positive serology was diagnosed.

The risk of HBV reactivation is considered a class effect of BCR-ABL tyrosine kinase inhibitors; however, the mechanism and frequency of virus reactivation during exposure are currently unknown.

Article citation: Drug Safety Update volume 9 issue 10 May 2016: 1

*Summaries of Product Characteristics are available on the [European Medicines Agency website](#) for dasatinib, nilotinib, bosutinib, and ponatinib, and on the [MHRA website](#) for imatinib.

Further information
[Letter sent to healthcare professionals](#) 11 April 2016

EU Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on [updates to product information for BCR-ABL tyrosine kinase inhibitors](#)

2 Pomalidomide (Imnovid▼): risk of hepatitis B reactivation

Before starting treatment with pomalidomide, establish hepatitis B virus status in all patients.

Advice for healthcare professionals:

- Hepatitis B virus status should be established before starting treatment with pomalidomide
- For patients who test positive, consultation with a physician with expertise in the treatment of hepatitis B is recommended
- Previously infected patients should be closely monitored for signs and symptoms of active infection throughout pomalidomide treatment
- Suspected adverse reactions to pomalidomide should be [reported to us on a Yellow Card](#)

1 Yang JD, et al. [Hepatitis B reactivation in patients with multiple myeloma and isolated positive hepatitis B core antibody: a call for greater cognizance](#). *Ann Hepatol* 2014;13: 461–65.

2 Danhof S, et al. [Long-term disease control by pomalidomide- /dexamethasone-based therapy in a patient with advanced multiple myeloma: a case report and review of the literature](#). *Case Rep Oncol* 2015; 8: 189–95.

Further information
[Letter sent to healthcare professionals](#) 22 April 2016

Pomalidomide (Imnovid▼) combined with dexamethasone is indicated for adults with relapsed and refractory multiple myeloma who have received at least two previous treatment regimens, including lenalidomide and bortezomib, and who have shown disease progression on the last therapy.

Risk of hepatitis B reactivation

A review by EU medicines regulators of clinical studies and cases of suspected adverse drug reactions reported by healthcare professionals and in the literature^{1,2} has concluded that pomalidomide can cause hepatitis B reactivation.

The review assessed cases worldwide up to 7 August 2015 and identified 5 patients who developed hepatitis B reactivation while receiving treatment with pomalidomide. 2 cases resulted in acute liver failure, 1 of which had a fatal outcome. 4 cases occurred within a month of starting pomalidomide.

Article citation: Drug Safety Update volume 9 issue 10 May 2016: 2

3 Idelalisib (Zydelig▼): interim measures following signal of serious infection and deaths related to infection found in clinical trials

There are new interim treatment recommendations for idelalisib for chronic lymphocytic leukaemia and follicular lymphoma in light of new findings from clinical trials outside its currently authorised drug combinations or indicated populations.

Interim advice for healthcare professionals

Indications

Chronic lymphocytic leukaemia

- Do not start as first-line treatment in patients who have 17p chromosome deletion or *P53* mutation
- For patients who have a 17p deletion or *P53* mutation who are already receiving idelalisib first line, clinicians should carefully consider the balance of benefits and risks for the individual (see below), and should decide whether to continue treatment
- Idelalisib combined with rituximab can be started or continued in patients who have received at least one previous line of therapy
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Follicular lymphoma

- Idelalisib monotherapy can be started or continued in adults with disease refractory to two previous lines of treatment

New measures to minimise risk for all patients

- Inform patients of the risk of serious and fatal infections (see below)
- Do not start treatment in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection
- All patients should receive prophylactic treatment for *Pneumocystis jirovecii* pneumonia throughout idelalisib treatment
- There should be regular clinical and laboratory screening for cytomegalovirus infection. Stop treatment in patients with evidence of infection or viraemia
- Monitor patients for signs and symptoms of respiratory disease throughout treatment and advise them to promptly report any new respiratory symptoms
- Monitor absolute neutrophil counts in all patients at least every 2 weeks for the first 6 months of treatment, and at least weekly in those with a count fewer than 1000 per mm³ (further guidance is provided in a [table in a letter to healthcare professionals](#))

Reporting of suspected adverse reactions

- Suspected adverse reactions to pomalidomide should be [reported to us on a Yellow Card](#)

Interim results from clinical trials

3 phase III clinical trials have shown a signal of increased mortality associated with idelalisib. The trials were assessing the addition of idelalisib to standard therapy in first-line chronic lymphocytic leukaemia and to the treatment of relapsed indolent non-Hodgkin lymphoma (small lymphocytic lymphoma)—ie, outside its currently authorised drug combinations or indicated populations. The relevance of these findings for the licensed uses of idelalisib is [currently under assessment](#).

The trials showed increased numbers of deaths in the idelalisib treatment group compared with placebo (7.4% vs 3.5%, respectively). The excess deaths were mainly due to infections, including *P jirovecii* and cytomegalovirus, and respiratory events (some of which may have been related to infection).

The precautionary measures outlined above should be followed while there is further investigation of the implications of these findings for the medicine's authorised uses. Further advice will be communicated as appropriate at the end of the [review](#).

Further information

[Letter sent to healthcare professionals](#) 23 March 2016

Article citation: Drug Safety Update volume 9 issue 10 May 2016: 3

4 Letters sent to healthcare professionals in April 2016

In April 2016, letters were sent to healthcare professionals regarding:

- canagliflozin-containing medicines ([Invokana](#) ▼, [Vokanamet](#) ▼): risk of lower limb amputation (primarily of the toe)
- BCR-ABL tyrosine kinase inhibitors ([imatinib](#) ▼, [dasatinib](#), [nilotinib](#), [bosutinib](#) ▼, [ponatinib](#) ▼) and risk of hepatitis B reactivation: screen patients for hepatitis B virus before treatment – see also the article above
- pomalidomide ([Imnovid](#) ▼): hepatitis B virus status to be established before initiating treatment - see also the article above
- retigabine ([Trobalt](#)): risk acquired vitelliform maculopathy

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