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 inform of recent safety recommendations for the medicine bendamustine, used for haematological cancers. Studies show an increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML). We advise that skin examinations should be performed periodically in patients on bendamustine-containing regimens. We also advise that PML should be considered in the differential diagnosis for patients on bendamustine with new or worsening neurological, cognitive, or behavioural signs or symptoms. See page 2 for new safety advice.

On page 5, we include a summary of recent MHRA advice relating to COVID-19 vaccines and medicines up to 18 March 2021. And on page 6 we include letters and medicines recalls and notifications sent to healthcare professionals in February 2021.

Bendamustine (Levact): increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML)

Periodically perform skin examinations in patients on bendamustine-containing regimens and consider PML in the differential diagnosis for patients on bendamustine with new or worsening neurological, cognitive, or behavioural signs or symptoms.

Advice for healthcare professionals:

- in clinical studies, an increased risk from background for non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) has been observed in patients treated with bendamustine-containing therapies
- periodically perform skin examinations in patients on bendamustine-containing regimens, particularly in patients with risk factors for skin cancer – these include people with lighter natural skin colour; skin that burns, freckles or reddens easily; a large number of moles; and a personal or family history of skin cancer
- very rare cases of PML have also been reported in patients being treated with bendamustine usually in combination with rituximab or obinutuzumab
- consider PML in the differential diagnosis for patients on bendamustine with new or worsening neurological, cognitive, or behavioural signs or symptoms
- if PML is suspected, undertake appropriate diagnostic evaluations, and suspend treatment until PML is excluded
- report suspected adverse drug reactions associated with bendamustine on a Yellow Card

Review of non-melanoma skin cancer and PML

Bendamustine is an anti-cancer medicine authorised for certain patients with chronic lymphocytic leukaemia, non-Hodgkin's lymphomas, or multiple myeloma (see full indication in Background).

Patients treated with bendamustine have an existing increased risk for non-melanoma skin cancer due to their underlying disease and age. However, two published trials (BRIGHT[1] and GALLIUM[2]) show a higher number of cases of non-melanoma skin cancer with bendamustine-containing regimens than with other treatments used for lymphoma.

A European review of safety data has recommended these risks be added to the Summary of Product Characteristics alongside advice to periodically monitor patients for skin changes. Advice will also be added to the Patient Information Leaflet to state that patients should contact their doctor if they notice worrying skin changes. Advice on the NHS website about changes to moles may be helpful for this discussion.

1 Flinn IW and others. J Clin Onc 2019; 37: 984–91,

2.Hiddemann W and others. J Clin Onc 2018; 36: 2395–404.

In addition, very rare cases of progressive multifocal encephalopathy (PML) have been reported in patients on bendamustine-containing regimens. Although concomitant treatment was present in all cases where information was provided, a temporal relationship with bendamustine was evident in most cases and an increased risk of PML is thought plausible. These risks have been added to the product information and patients should be directed to the patient information leaflet to be aware of signs and symptoms of PML.

If PML is suspected, treatment with bendamustine should be suspended until PML is ruled out. Evaluation of PML includes, but is not limited to, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham viral DNA).

Non-melanoma skin cancer: evidence from clinical trials

The BRIGHT trial is a completed, phase 3, open-label, randomised, parallel-group study of first-line treatments for patients with advanced indolent non-Hodgkin's lymphoma or mantle cell lymphoma.[1] The trial compared outcomes in patients assigned to bendamustine plus rituximab versus alternative chemotherapy regimens (R-CHOP/R-CVP[3]).

In this trial, 14 of 221 (6.3%) patients treated with bendamustine plus rituximab and 5 of 215 (2.3%) patients treated with R-CHOP/R-CVP were reported to develop squamous cell carcinoma or basal cell carcinoma.

3 Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP).

The GALLIUM trial was an open-label, randomised parallel-group study of previously untreated follicular lymphoma (grade 1 to 3a; stage III or IV disease).[2] The trial compared outcomes in patients randomised to receive either obinutuzumab or rituximab plus a chemotherapy backbone with bendamustine or alternative chemotherapy regimens (R-CHOP/R-CVP).

This study took into account all malignancies occurring more than 6 months after first study drug intake. Basal cell carcinoma was reported in 16 of 676 patients (2.4%) receiving bendamustine versus 1 of 513 patients receiving CHOP/CVP. There were also increases in the number of reports of squamous cell carcinoma in patients receiving bendamustine, while no cases were reported in patients receiving CHOP/CVP.

Cases of PML

The European review of safety data also identified an increase in reporting of cases of PML when bendamustine-containing therapy is used. During the period reviewed (7 January 2018 to 6 January 2020), 42 cases of PML worldwide were reported, 11 of which were fatal. This compared to 9 cases in the previous period (7 January 2017 to 6 January 2018).

Concomitant treatment was present in all cases, with most receiving rituximab or obinutuzumab alongside bendamustine. However, a temporal relationship with bendamustine was evident in most cases. In 31 of the cases, bendamustine-containing therapy was the latest treatment before onset.

A contributory role of bendamustine to the development of PML is thought possible. It is known that bendamustine can cause prolonged lymphopenia and CD4-positive T-cell depletion. This effect is more pronounced when bendamustine is combined with rituximab.

Background

Bendamustine is indicated for:

- first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
- indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen
- first-line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide- or bortezomib-containing treatment

Report on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Report suspected side effects to medicines, vaccines or medical device and diagnostic adverse incidents used in coronavirus (COVID-19) using the dedicated Coronavirus Yellow Card reporting site or the Yellow Card app. See the MHRA website for the latest information on medicines and vaccines for COVID-19.

Article citation: Drug Safety Update volume 14, issue 8: March 2021: 1.

COVID-19 vaccines and medicines: updates for March 2021

A summary of advice recently issued by the MHRA relating to coronavirus (COVID-19), up to 18 March 2021.

We previously included a summary of latest advice in the January 2021 and February 2021 issues of Drug Safety Update. Here we include a summary of key MHRA advice issued up to 18 March 2021 and since the publication of the February 2021 edition of Drug Safety Update.

In February 2021 we published the first summaries of the Yellow Card reporting for the COVID-19 vaccines being used in the UK. This report is being updated weekly. The data continues to confirm that the vast majority of reported side effects are mild and short-lasting, reflecting a normal immune response to vaccines – including a sore arm and fatigue.

The report summarises information received via the Yellow Card scheme and will be published regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

The MHRA encourages anyone to report any suspicion or concern they have beyond the known, mild side effects on the Coronavirus Yellow Card reporting site.

We have also recently:

- released a statement on 18 March about the COVID-19 Vaccine AstraZeneca and venous thromboembolism following a rigorous scientific review of all the available data
- updated the information leaflets for the AstraZeneca and Pfizer/BioNTech COVID-19 vaccines to provide a more detailed description of the “flu like illness”. These types of reactions reflect the acute immune response triggered by the body to the vaccines, are typically seen with most types of vaccine and tend to resolve within a day or two. If other COVID symptoms are experienced or fever is high and lasts longer than 2 or 3 days, vaccine recipients should stay at home and arrange to have a test
- published the Public Assessment Report for the COVID-19 Vaccine Moderna

See guidance on COVID-19 for all our latest information, including after publication of this article.

Article citation: Drug Safety Update volume 14, issue 8: March: 2.

Letters and drug alerts sent to healthcare professionals in February 2021

Letters

In February 2021, the following letters were sent or provided to relevant healthcare professionals:

- Alkindi (hydrocortisone granules in capsules for opening): risk of acute adrenal insufficiency when switching from crushed or compounded oral hydrocortisone formulations to Alkindi – see accompanying Drug Safety Update, February 2021

- AmBisome (Liposomal Amphotericin B) 50 mg Powder for dispersion for infusion: identify and dispose of co-packaged Sartorius 5µm Minisart Filters due to potential to release fibres during use – see also the medicines defect notification

- Soprobec (beclometasone dipropionate) 200 micrograms per actuation pressurised inhalation solution: change in the colour of plastic actuator and protective cap

Medicines Recalls and Notifications

As of February 2021, the MHRA has replaced ‘Drug alerts’ and ‘company led drug alerts’ with ‘medicines recalls’ and ‘medicine notifications.’ No further safety communications will be issued with the ‘alert’ terminology unless they are National Patient Safety Alerts – see article for further information on the changes to the classification system.

Class 3 Medicines Recall: Intrapharm Laboratories Ltd, Kolanticon Gel 500ml, EL (21)A/01. Issued 03 February 2021. A single batch of Kolanticon Gel 500ml has been identified with lumpy product consistency. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 2 Medicines Recall: Grünenthal Ltd, Palexia 20 mg/ml Oral Solution (PL 21727/0054). Issued 08 February 2021. Specific batches of Palexia 20 mg/ml Oral Solution have been identified as at risk for microbial contamination with Burkholderia contaminans. All remaining stock within expiry should be quarantined and returned. Pharmacists should contact all patients dispensed this product between December 2017 and February 2021 to determine if they possess affected batches and arrange return to the pharmacy as appropriate.

Class 4 Medicines Defect Information, AmBisome Liposomal 50 mg Powder for dispersion for infusion, (PL 16807/0001), EL (21)A/03. Issued 11 February 2021. The Minisart 5µm sterile filters co-packaged in several batches of AmBisome Liposomal 50mg Powder for dispersion for infusion have been identified as defective. There is no quality issue associated with the AmBisome powder, but the Minisart filters may release fibres and particles which pose a potential risk of thromboembolism. In identified batches, the Minisart filters should be removed and disposed of appropriately. Alternative 5 micron filters should be used. See also accompanying letter for healthcare professionals.

Class 2 Medicines Recall: Eaststone Limited, MidaBuc - Midazolam (as HCL) 10mg/mL Oromucosal Solution, EL (21)A/04. Issued 16 February 2021. A single batch of MidaBuc (Midazolam 10mg/mL oromucosal solution) is being recalled due to underfilled or empty bottles. Stop supplying the batch immediately, quarantine remaining stock and return to supplier.

Class 3 Medicines Recall: SyriMed, Clonidine hydrochloride 50micrograms/5ml Oral Solution, EL (21)A/05. Issued 17 February 2021. A single batch of Clonidine hydrochloride 50 micrograms/5ml oral solution has been identified with defective child-lock container closures due to an issue with bottle capping during manufacture. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Article citation: Drug Safety Update volume 14, issue 8: March: 3.