

## 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 (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.



NICE has accredited the process used by the MHRA to produce Drug Safety Update guidance. More information on accreditation can be viewed on the [NICE website](https://www.nice.org.uk/accreditation).

To subscribe to monthly email alerts of Drug Safety Update see: <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/email-signup>

First, new information on the known risks of intraocular inflammation and retinal vascular occlusion with brolucizumab, indicated for neurovascular (wet) age-related macular degeneration (page 2). New advice is included on the minimum interval between maintenance doses and information given on risk factors that may increase the risks of these events.

Second, we issue precautionary advice about paclitaxel formulations used in cancer treatments (page 5), noting that conventional paclitaxel and nab-paclitaxel formulations are not interchangeable and that potential errors in dosing or administration could have consequences for clinical response and increased toxicity or adverse reactions in patients.

On page 7 we summarise recent advice relating to COVID-19 vaccines and medicines published since the December 2021 issue of Drug Safety Update. And on page 9 we include recent letters, recalls and notifications sent to healthcare professionals about medicines and medical devices.

## **Brolucizumab (Beovu ▼): risk of intraocular inflammation and retinal vascular occlusion increased with short dosing intervals**

Maintenance doses of brolucizumab (after the first 3 doses) should not be given at intervals of less than 8 weeks apart.

### **Advice for healthcare professionals:**

- intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions uncommonly associated with intravitreal injection of brolucizumab
- in patients who develop intraocular inflammation or retinal vascular occlusion, discontinue treatment with brolucizumab and manage events promptly
- to reduce the risk of these events, do not administer maintenance doses of brolucizumab (after the first 3 doses) at intervals of less than 8 weeks apart
- closely monitor patients treated with brolucizumab who have a medical history of intraocular inflammation or retinal vascular occlusion (within 12 months before the first brolucizumab injection) since they are at increased risk of developing these adverse reactions post-injection
- intraocular inflammation or retinal vascular occlusion may occur at any time during brolucizumab treatment but occur more frequently during early treatment
- based on observational studies, retinal vasculitis and retinal vascular occlusion after brolucizumab treatment appear to be more frequent in female patients and in patients of Japanese ancestry
- report any suspected adverse drug reactions associated with brolucizumab on a [Yellow Card](#)

### **Advice for healthcare professionals to give to patients and carers:**

- seek advice from your eye care team straight away if you experience a decrease or change in your vision, eye pain, worsening eye redness, or sensitivity to light after your injection of brolucizumab
- these could be symptoms of inflammation in the eye, including a blockage of the blood vessels, which needs to be treated quickly
- always read the information provided about your treatment and talk to your doctor, nurse, or pharmacist if you are concerned about any side effects
- do not stop attending appointments for your brolucizumab treatment without speaking to your eye care team, as stopping could increase your risk of vision loss

## Risk of intraocular inflammation and retinal vascular occlusion

[Brolucizumab](#) (Beovu ▼) is a humanised monoclonal antibody indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD). The recommended dose is 6mg brolucizumab by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, maintenance treatment intervals should be individualised based on disease activity. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered.

Intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions known to be associated with brolucizumab.

In pivotal clinical trials for brolucizumab, intraocular inflammation and retinal vascular occlusive events occurred more frequently in the brolucizumab 3mg and 6mg groups than with the comparator 2mg aflibercept (4.4% of patients in the pooled brolucizumab groups experienced intraocular inflammation versus 0.8% in the aflibercept group; see [EMA public assessment report](#)). Retinal vasculitis and retinal vascular occlusion were subsequently added to the product information as adverse drug reactions in October 2020.

New information on these adverse events, including risk factors and possible mechanism, was considered in a recent European safety review and ophthalmologists were informed of the new recommendations in a [letter in November 2021](#). The [product information of brolucizumab](#) will also be updated to reflect this information.

### Increased risk with 4-weekly dosing intervals during maintenance phase

Preliminary results were recently received from the [MERLIN](#) study. This is a 2-year US multicentre, randomised, double-masked Phase 3A study to assess the safety and efficacy of the recommended dose of brolucizumab (6mg), administered every 4 weeks, compared to aflibercept 2mg every 4 weeks, in patients with neovascular AMD with persistent retinal fluid. The study only recruited patients who had a need for frequent treatment.

In MERLIN, intraocular inflammation, including retinal vasculitis, were reported with a higher frequency in the group receiving brolucizumab 6mg every 4 weeks compared with those receiving aflibercept 2mg every 4 weeks (9.3% versus 4.5%, respectively). Frequency of retinal vascular occlusion was also higher with brolucizumab (2.0% versus 0%, respectively).

In addition, the incidence of intraocular inflammation with 4-weekly dosing of brolucizumab in MERLIN (9.3%) was of a higher frequency than that recorded in the pivotal phase 3 clinical studies using a brolucizumab dosing interval of 6mg every 8 weeks and 12 weeks (4.4%).

For maintenance treatment, brolucizumab should not be administered more frequently than every 8 weeks.

1 [Khanani AM and others](#). JAMA Ophthalmol. 2021; e214585

### Other risk factors

Two non-interventional retrospective studies ([NCT05082415](#) and [NCT05111743](#)) of large US real-world databases in patients with neovascular AMD aimed to better understand the incidence of these adverse events up to 6 months after initiating treatment with brolucizumab.<sup>1</sup>

The results of these studies suggest that patients with a medical history of intraocular inflammation or retinal vascular occlusion in the year before treatment with brolocizumab are more likely to present with similar events after brolocizumab injection, as compared with patients with neovascular AMD with no history of these events.

In addition, a higher risk of intraocular inflammation (including retinal vasculitis and retinal vascular occlusion) in female patients was observed both in the two retrospective studies and also in the clinical trials (5.3% of female patients and 3.2% of male patients in the pivotal clinical trials). A higher incidence of these events was also seen in patients of Japanese ancestry than in those of non-Japanese ancestry.

### **Evidence that retinal vasculitis and retinal vascular occlusion are immune-mediated events**

The review also considered new data to elucidate the mechanism of these adverse events.

As brolocizumab is a therapeutic protein, there is a potential for immunogenicity and consequently intraocular inflammation. Evidence to support this mechanism comes from a study in 5 patients with neovascular AMD injected with brolocizumab who subsequently developed retinal vasculitis or retinal vascular occlusion. Blood samples from these 5 patients identified a humoral and cellular immune response against brolocizumab 3 to 5 months after the last brolocizumab dose. In samples from 6 control patients who had no signs or symptoms of intraocular inflammation while receiving brolocizumab, anti-drug antibodies, when present, had lower titres. More details of this study can be found in the [letter sent to ophthalmologists](#).

### **Report suspected adverse drug reactions**

Brolocizumab ▼ is a black triangle medicine and all suspected adverse reactions should be reported via the Yellow Card scheme.

Report to 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, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment 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 15, issue 6: January 2022: 1.*

## Paclitaxel formulations (conventional and nab-paclitaxel): caution required due to potential for medication error

Albumin-bound paclitaxel formulations for infusion (nab-paclitaxel; brand names Abraxane, Pazenir) differ from conventional paclitaxel medicines in their authorised indications, pharmacokinetics, recommended dosages, and preparation and administration instructions. Healthcare professionals should use caution when prescribing, dispensing, preparing, and administering any paclitaxel formulations to prevent medication errors, which have the potential to cause harm.

### Advice for healthcare professionals:

- compared with conventional formulations, paclitaxel medicines formulated as albumin-bound nanoparticles (nab-paclitaxel; brand names Abraxane, Pazenir) have **different** authorised indications, pharmacokinetics, dosages, and preparation and administration instructions
- conventional paclitaxel and nab-paclitaxel formulations are **not** interchangeable
- although we have not received reports to suggest harm has occurred in the UK due to a mix-up of these paclitaxel formulations, errors in dosing or administration could have potential consequences for clinical response and increased toxicity or adverse reactions during cancer treatment
- make a clear distinction between paclitaxel formulations when prescribing, dispensing, administering, and communicating about these medicines – use of brand names is advised for nab-paclitaxel formulations
- verify the product name and dose before administration and ensure the specific SmPC instructions are followed for preparation and administration
- report suspected adverse drug reactions, including medication error with associated harm to a patient, to the [Yellow Card Scheme](#)

### Formulations of paclitaxel

Paclitaxel is a member of the taxane group of chemotherapy drugs. Paclitaxel has been available as an anti-cancer medicine since 1993, including under the brand name Taxol. Paclitaxel is indicated for treatment of certain cancers of the ovary, breast, and lung, as well as advanced AIDS-related Kaposi's sarcoma – see example [Summary of Product Characteristics \(SmPC\)](#).

Abraxane was licensed in 2008 and is formulated as paclitaxel bound to albumin in nanoparticles (nab-paclitaxel). Pazenir was authorised in 2019 as bioequivalent to Abraxane. Abraxane and Pazenir are indicated for treatment of certain cancers of the breast, pancreas, and lung – see SmPCs for [Abraxane](#) and [Pazenir](#) for details.

The two nab-paclitaxel medicines are licensed as bioequivalent to each other but have substantially different properties compared with conventional formulations of paclitaxel. As such, there is a warning in the product information and on the packaging for both Abraxane and Pazenir that they should not be substituted for or with other paclitaxel formulations.

Binding of the paclitaxel to albumin in nanoparticles changes how the medicine is transported across cells. As such, recommended doses and administration times are notably different than those for conventional paclitaxel infusions. For example, Abraxane and Pazenir are generally administered intravenously over a 30-minute period, whereas the instructions for conventional paclitaxel are to administer intravenously over a period of 3 hours. Other differences in pharmacokinetic parameters include the plasma clearance rate and volume of distribution.

## Concerns about the potential for medication error

A healthcare organisation recently contacted the MHRA to enquire whether the packaging of a nab-paclitaxel medicine should more clearly state the formulation. Inadvertent administration of a different paclitaxel formulation could result in a higher dose than intended with increased toxicity, or sub-dosing with subtherapeutic effects. Nab-paclitaxel may be recommended in patients who have developed hypersensitivity to paclitaxel.<sup>1</sup> As such, mix-ups between the two types of formulations may also present the risk of a hypersensitivity reaction, in addition to the risk of underdosing or overdosing.

1 [NHS England](#).  
Version  
1.193;  
page  
108.

As of September 2021, we had not received any cases reported to the Yellow Card scheme for Abraxane and Pazenir suggesting a mix-up with conventional formulations associated with patient harm. Cases of medication error resulting in harm are not always reported to the Yellow Card scheme, and we encourage healthcare professionals to report cases if they occur.

We are working with manufacturers to optimise the safety of these products. In the meantime, we issue this communication on a precautionary basis. We ask healthcare professionals to remain vigilant around these medicines.

## Report suspected reactions on a Yellow Card

Suspected adverse drug reactions (ADR) should be reported 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)

Adverse drug reactions where harm occurs as a result of a medication error are reportable as a [Yellow Card](#) or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment 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](#).

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## COVID-19 vaccines and medicines: updates for January 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the December 2021 issue of Drug Safety Update, up to 13 January 2022.

### Approval of Paxlovid - oral COVID-19 antiviral treatment

We have [approved Paxlovid \(PF-07321332 and ritonavir\)](#) following a rigorous review of its safety, quality and effectiveness by us and expert advice from the government's independent scientific advisory body, the Commission on Human Medicines (CHM).

Paxlovid is an antiviral medicine with a combination of active ingredients, PF-07321332 and ritonavir, that works by inhibiting a protease required for virus replication. Ritonavir slows the breakdown of PF-07321332 in the body, thereby increasing its effectiveness.

Based on the clinical trial data, Paxlovid is most effective when taken during the early stages of infection and so the MHRA recommends its use as soon as possible and within five days of the start of symptoms. It has been authorised for use in people aged 18 and above who have mild to moderate COVID-19 infection and at least one risk factor for developing severe illness. Such risk factors include obesity, older age (>60 years), diabetes mellitus, or heart disease.

Paxlovid may interact with certain other medications. Before it is prescribed, the MHRA is therefore advising that patients' current medications should be carefully reviewed, and appropriate advice given on adjustments that may be needed to their current medications. Additional tests may also be needed for its safe use. For more information, see the contraindications, dosage and interactions sections of the [Summary of Product Characteristics](#).

For more information about Paxlovid (PF-07321332 and ritonavir), see our [Press release](#) and [Decision page](#) which includes the [Summary of Product Characteristics](#) and [Patient Information Leaflet](#).

### Summaries of Yellow Card reporting and other recent MHRA publications

We continue to publish the summaries of the [Yellow Card reporting for the COVID-19 vaccines](#) being used in the UK. 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](#).

We have also recently:

- updated the [Summary of Product Characteristics](#) and [Patient Information Leaflet](#) for Spikevax (COVID-19 Vaccine Moderna) to allow for use of the vaccine as a booster or third dose in individuals 18 years of age and older and for immunocompromised patients, and safety updates (to include diarrhoea and skin reaction as adverse reactions, further information on delayed injection site reactions, minor amendments to the hypersensitivity text, updates to myocarditis and pericarditis sections and updated shelf life and storage instructions)

- advised that the 15 minute observation period after administration of mRNA vaccines (Pfizer/BioNTech and Moderna) can be waived during the emergency response to the Omicron variant. The 15 minute observation window should remain in place for people who may have previously suffered anaphylaxis or other allergic reactions to a food, insect sting, and most medicines or vaccines – see our [Press release](#) for more information on the temporary waiver
- [approved a new paediatric formulation](#) of the Pfizer/BioNTech COVID-19 vaccine for children aged 5 to 11 years, known as Comirnaty 10 micrograms/dose concentrate for dispersion for injection – see the [Decision page](#) for more details
- updated the [product information](#) for Vaxzevria (previously COVID-19 Vaccine AstraZeneca) to allow for the use of the vaccine as a booster or third dose and to include safety information on immune thrombocytopenia (ITP), cerebral venous sinus thrombosis (CVST) without thrombocytopenia, and facial paralysis.
- published the [Public Assessment Report \(PAR\)](#) for Lagevrio (molnupiravir)

We previously included summaries of latest COVID-19 information, including in the [October 2021](#), [November 2021](#) and [December 2021](#) issues of Drug Safety Update.

See [guidance on COVID-19 for all our latest information](#), including after publication of this article.

## Reporting Yellow Cards

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the dedicated [Coronavirus Yellow Card reporting site](#) or via the Yellow Card app.

As these products are under additional monitoring this includes all suspected ADRs associated with these vaccines. This will allow quick identification of new safety information.

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

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected adverse events.

*Article citation: Drug Safety Update volume 15, issue 6: January 2022: 3.*

## Letters and medicine recalls sent to healthcare professionals in December 2021

### Letters

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

- [Spikevax▼ \(also known as COVID-19 Vaccine Moderna\): potential mismatch between printed Patient Information Leaflets \(PILs\) and vial labels and cartons as Moderna makes the tradename transition](#)
- [Ronapreve▼ \(casirivimab and imdevimab\) 120 mg/ml solution for injection or infusion: important information for healthcare professionals about the expiry date of the 6 ml vial packs](#)
- [Lymphoseek \(tilmanocept\) 50 micrograms kit for radiopharmaceutical preparation: temporary 6 month extension of shelf life of LOT 347446](#)
- [Evorel Sequi \(estradiol, norethisterone acetate\): discrepancy in Marketing Authorisation Number on the Evorel 50 pouch \(PL 49105/0006\) within the Evorel Sequi carton \(PL 49105/0010\) for a limited number of new batches](#)
- [Orencia \(abatacept\) 125 mg/mL ClickJect Pen: supply Issue](#)

### Medicine Recalls and Notifications

In December 2021, recalls and notifications for medicines were issued on:

[Class 2 Medicines Recall: Intrapharm Laboratories Ltd, Mydrilate 0.5% Eye Drops 5ml, EL \(21\)A/35](#). Issued 8 December 2021 A batch of Mydrilate (cyclopentolate hydrochloride) 0.5% Eye Drops 5ml is being recalled as a precautionary measure due to out of specification results identified during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

[Class 2 Medicines Recall: Novartis Pharmaceuticals UK, Lucentis 10 mg/ml solution for injection in pre-filled syringe EL \(21\)A/36](#). Issued 13 December 2021. A batch of Lucentis (ranibizumab) 10 mg/ml solution for injection in pre-filled syringe 5ml is being recalled due to a defective plunger stopper. The Marketing Authorisation Holder has received increased numbers of customer complaints that the plunger in this batch is difficult to press down. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

[Class 4 Medicines Defect Information: SmofKabiven Central emulsion for Infusion, Fresenius Kabi Ltd, EL \(21\)A/37](#). Issued 16 December 2021. Batches of SmofKabiven central emulsion for Infusion have been identified that incorrectly state the amount of glucose anhydrous in the energy content section as 150mg. The correct value of 125mg glucose anhydrous (42% glucose as monohydrate) is stated in the rest of the product information, including the Summary of Product Characteristics, outer carton and on the infusion bag ingredients. Healthcare professionals are advised to exercise caution when administering this product particularly when calculating patient nutritional requirements.

[Class 2 Medicines Recall: Wockhardt UK Ltd, Heparin sodium 1,000 I.U./ml solution for injection or concentrate for solution for infusion, EL \(21\)A/38](#). Issued 20 December 2021. A batch of heparin sodium 1,000 I.U./ml solution for injection or concentrate for solution for infusion is being recalled as a precautionary measure due to out of specification results identified during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

[Class 4 Medicines defect information: Benylin Chesty Coughs Original \(P\) and Benylin Chesty Coughs Non-Drowsy \(GSL\), EL\(21\)A/39](#). Issued 21 December 2021. Batches of Benylin chesty coughs original (diphenhydramine hydrochloride and levomenthol) and Benylin chesty coughs non-drowsy (guaifenesin and levomenthol) have been identified with incorrect product information. The product labelling in affected batches states an incorrect alcohol content of 0.25mg or 0.7mg in each 5ml, where the correct alcohol content for both products is 198mg per 5ml. The safety advice on the label regarding the amount of alcohol contained in these products is low and will not have any noticeable effects is correct.

[Company led medicines recall: Dermaved Sensitive Cream \(unlicensed medicine\), CLMR \(21\)A/09](#). Issued 30 December 2021. A batch of Dermaved sensitive Cream is being recalled. This product is supplied by Dermaved online only. This is an unlicensed skin medication, and the affected batch has been identified to contain low levels of clobetasol propionate, a strong steroid which is only available as a prescription treatment for skin conditions.

### **Medical Device Safety Information**

A recent MHRA Device Safety Information page has been published on:

- [Rheovalves disposable needle-free valves: stop using specific lots due to risk of breakage in patient.](#)

For all of the latest safety notices from the MHRA on drugs and medical devices, see [Alerts and recalls for drugs and medical devices](#).

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