

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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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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Summary

First on page 2, we ask prescribers to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating systemic vascular endothelial growth factor (VEGF) pathway inhibitors.

On page 5, to minimise further the possibility of mix ups between liposomal, pegylated-liposomal, lipid-complex and conventional formulations of medicines, we ask healthcare professionals to make a clear distinction when prescribing, dispensing, administering, and communicating about these medicines. Medicines with these formulations that have a high risk of medication error will now include their formulation in their name to reduce potentially fatal mix-ups.

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Systemically administered VEGF pathway inhibitors: risk of aneurysm and artery dissection

Before initiating systemic vascular endothelial growth factor (VEGF) pathway inhibitors, carefully consider the risk of aneurysm and artery dissection in patients with risk factors. In patients who receive a systemic VEGF pathway inhibitor, reduce as far as possible any modifiable risk factors such as hypertension.

Advice for healthcare professionals:

- use of systemically administered VEGF pathway inhibitors (see list in background) in patients with or without hypertension may promote the formation of aneurysms or artery dissections
- aneurysms or artery dissections are thought to occur infrequently in patients taking systemic VEGF pathway inhibitors, but some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection
- before initiating a systemic VEGF pathway inhibitor, carefully consider the risk of aneurysm and artery dissection in patients with risk factors such as hypertension, history of aneurysm, smoking, diabetes mellitus, coronary, cerebrovascular or peripheral arterial disease, and hyperlipidaemia; other risk factors include Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, and the use of fluoroquinolones
- in patients who receive a systemic VEGF pathway inhibitor, reduce as far as possible any modifiable risk factors such as smoking and hypertension
- monitor patients for and treat hypertension in accordance with recommendations in the Summary of Product Characteristics for the relevant systemic VEGF pathway inhibitor
- report suspected adverse drug reactions to a VEGF pathway inhibitor to the [Yellow Card Scheme](#) without delay; all suspected adverse drug reactions to black triangle medicines should be reported

European review of cases of aneurysm and artery dissection

A range of systemically administered VEGF pathway inhibitors are authorised for use in the UK (see list in background).

A recent [European review](#) concluded that all systemically administered VEGF pathway inhibitors may promote the formation of aneurysm and artery dissection. The product information for all systemically administered VEGF pathway inhibitors has been updated to include a warning about the risk of aneurysm and artery dissection and to recommend carefully considering these risks before initiating in patients with risk factors, such as hypertension.

Patients who receive a systemic VEGF pathway inhibitor should be monitored and treated for hypertension in accordance with recommendations in the [Summary of Product Characteristics](#) for the relevant systemic VEGF pathway inhibitor.

Action should also be considered for other modifiable risk factors such as smoking. The patient information leaflet for all products will also include advice for patients to inform their doctor or nurse if they have had a previous aneurysm or dissection.

Detailed findings of the review

Before the latest safety review, the product information of four systemic VEGF pathway inhibitors included aortic dissection ([Kisplyx](#)▼ and [Lenvima](#)▼), aneurysm rupture ([Inlyta](#)), or aortic aneurysm and dissection ([Sutent](#)) as side effects. In addition, the product information for all systemic VEGF pathway inhibitors already described the risk of hypertension, which is an important predisposing factor for artery dissection and aneurysm.

As part of the review, a search of the European database of worldwide reports of suspected adverse drug reactions identified 660 case reports of aneurysm or artery dissection for VEGF pathway inhibitors up to 31 December 2018. The most frequently reported adverse events were aortic dissection (n=163), aneurysm (n=146), retinal aneurysm (n=93), aortic aneurysm (n=89), ruptured aortic aneurysm (n=43), intracranial aneurysm (n=34) and aneurysm ruptured (n=31). Fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection.

Of the 529 case reports where medical history was available, most (74%) reported risk factors, most commonly hypertension (49%). Other risk factors reported included diabetes mellitus, hypercholesterolaemia or hyperlipidaemia, a previous history of aortic aneurysm, cardiovascular disease and tobacco use. Aortic dissection and aortic aneurysm were more frequently reported in older patients (aged 65 years or older).

Based on the available data it is difficult to estimate the magnitude of the risk of aneurysm and artery dissection with systemic VEGF pathway inhibitors, therefore the risk of these adverse reactions is included in the product information with a frequency category of not known. Clinical trial data suggest that the frequency of artery dissection and aneurysm in patients receiving systemic VEGF pathway inhibitors ranges from rare (0.02% of participants) to uncommon (0.15% of participants exposed). The data do not allow for differentiation in the risk of artery dissection and aneurysm between the different systemic VEGF pathway inhibitors and clinical trial data were not available for 6 products.

About artery dissection and aneurysm

The mechanism by which systemically administered VEGF pathway inhibitors can cause aneurysm or artery dissection is unclear but may be due to impairment of vascular wall integrity as well through hypertension or aggravation of pre-existing hypertension. Aortic dissection is a rare but life-threatening event with an estimated annual incidence of between 2.9 to 3.5 cases per 100,000 people.¹ It is usually accompanied by sudden, severe abdominal, chest, or back pain.

Most abdominal aortic aneurysms are asymptomatic, and it is therefore difficult to establish their prevalence, however a national screening programme in the UK that enrolls men at age 65 years suggests a prevalence of about 1.3% in this population.¹

1. [Management of acute aortic dissection](#). *Lancet* 2015; 385: 800–11.

The most common symptom of a ruptured aortic aneurysm is sudden and severe pain in the abdomen or back. Ruptured aortic aneurysms are associated with a high mortality rate.¹

2. [NICE Guideline March 2020](#) (accessed 26/03/20).

The risk of artery dissection or aortic aneurysm is increased in the presence of risk factors such as hypertension, diabetes mellitus, family history of aneurysm, coronary, cerebrovascular or peripheral arterial disease, tobacco use and hyperlipidaemia.^{1,2}

Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease and the use of fluoroquinolones are also risk factors.

Background

Systemically administered VEGF pathway inhibitors authorised in the UK include Avastin, Zirabev ▼ and Mvasi ▼ (bevacizumab); Caprelsa ▼ (vandetanib); Cabometyx ▼ and Cometriq ▼ (cabozantinib); Cyramza (ramucirumab); Fotivda ▼ (tivozanib); Iclusig ▼ (ponatinib); Inlyta (axitinib); Kispix ▼ and Lenvima ▼ (lenvatinib); Nexavar (sorafenib); Ofev and Vargatef (nintedanib); Stivarga (regorafenib); Sutent (sunitinib); Votrient (pazopanib); and Zaltrap (aflibercept).

These medicines are indicated for a variety of cancers, except for Ofev, which is indicated for idiopathic pulmonary fibrosis.

The review concluded that there was insufficient evidence to determine that these risks apply to the two VEGF pathway inhibitors that are administered by intravitreal injection, ranibizumab ([Lucentis](#)) and aflibercept ([Eylea](#)). Both products are authorised for use in ocular diseases.

Report suspected drug reactions on a Yellow Card

Please continue to report any suspected adverse reactions to VEGF pathway inhibitors via the [Yellow Card Scheme](#). Your report will help us safeguard public health.

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Liposomal and lipid-complex formulations: name change to reduce medication errors

Make a clear distinction between liposomal, pegylated-liposomal, lipid-complex, and conventional formulations when prescribing, dispensing, administering, and communicating about these medicines. Medicines with these formulations that have a high risk of medication error will explicitly include 'liposomal', 'pegylated-liposomal' or 'lipid-complex' within their name to reduce potentially fatal medication errors.

Advice for healthcare professionals

- serious harm and fatal overdoses have occurred following confusion between liposomal, pegylated-liposomal, lipid-complex, and conventional formulations of the same drug substance
- **never** interchange liposomal, pegylated-liposomal, lipid-complex, and conventional formulations that contain the same drug substance
- make a clear distinction between liposomal, pegylated-liposomal, lipid-complex, and conventional formulations of the same drug substance when prescribing, dispensing, administering, and communicating about these medicines
- verify the product name and dose before administration and ensure the maximum dose of the specific medicine is not exceeded
- report suspected adverse drug reactions, including medication error with associated harm to a patient, to the [Yellow Card Scheme](#)

New naming recommendations

Some medicines (examples on page 8) are available in liposomal, pegylated-liposomal, or lipid-complex formulations. These formulations can have substantially different dosing and drug release profiles between each other and when compared with conventional formulations of the medicines.

Following reports of serious medication errors (some leading to deaths), liposomal and lipid-complex medicines with a high risk of medication error will explicitly include the qualifier 'liposomal', 'pegylated-liposomal', or 'lipid-complex' within their name. [This recommendation](#) aims to reduce the risk of mix-up between different formulations of these medicines. The product information and labelling of new injectable liposomal-formulated medicines will also include reference to 'dispersion', which is the accepted descriptor term for these types of formulations.

For medicines administered topically or via non-injectable routes, 'liposomal', 'pegylated-liposomal' or 'lipid-complex' will only be added to the name if a clear risk to patient safety has been identified.

Actions required from healthcare professionals

Although the new naming recommendations will help to reduce serious and fatal medication errors, healthcare professionals must remain vigilant around these medicines.

1. [Lipid-based drug products - errors due to confusion with conventional products: USA, 1998, 9 and 10.](#)

Prescribers should be explicit in which medicine they are prescribing when stating the product and the dose. Electronic prescribing and dispensing tools enable a clear distinction between available formulations, and it is the responsibility of the prescriber to ensure that the correct medicine is selected. These formulations should be clearly distinguished when communicating with colleagues about these medicines. The dose should be verified against the selected product before administration.

Examples of reported medication errors

Errors due to the mix-up between these different formulations of medicines are well documented.¹

Doxorubicin – medication errors

A recent European review of worldwide data identified 5 reported cases of mix-up between liposomal and conventional doxorubicin (one of which reported as an adverse reaction with a fatal outcome).

Amphotericin B – medication errors

We are currently aware of 3 fatal overdoses in the UK caused by administering conventional amphotericin B instead of the liposomal or lipid-complex formulations. In 2018 we advised that [particular care must be taken](#) in prescribing and dispensing the correct parenteral formulation of amphotericin B.

New naming recommendations

Examples of affected medicines includes those containing **amphotericin, daunorubicin, doxorubicin, cytarabine and irinotecan**. This list is not exhaustive, and the new naming convention will also apply to similarly formulated products licensed in the future. The following are examples of name changes:

Formulation	Original Name of the medicine	Amended name of the medicine
Pegylated-liposomal doxorubicin	Caelyx 2 mg/ml Concentrate for Solution for Infusion	Caelyx pegylated-liposomal 2 mg/ml Concentrate for Solution for Infusion
Liposomal doxorubicin	Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion	Myocet liposomal 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion.
Conventional doxorubicin	Doxorubicin Accord 2 mg/ml Concentrate for Solution for Infusion	Unchanged
Liposomal amphotericin*	AmBisome 50 mg Powder for dispersion for infusion	AmBisome Liposomal 50 mg Powder for dispersion for infusion
Lipid-complex amphotericin*	Abelcet 5mg/mL Concentrate for Suspension for Infusion	Abelcet LipidComplex 5mg/mL Concentrate for Dispersion for Infusion
Conventional amphotericin*	Fungizone 50mg Powder for Sterile Concentrate	Unchanged

*Amphotericin products, while now complying with the new naming convention, have contained formulation particulars and equivalency/interchangeability warnings on the label in the UK for several years.

Report any suspected adverse drug reactions

Any suspected adverse drug reactions (ADR), including medication errors with associated harm to a patient, should be reported to the Yellow Card Scheme. Report on the [Yellow Card website](#) or via the Yellow Card app (download via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices).

Medication errors resulting in harm should be reported to the [Yellow Card Scheme](#). Report medication errors or near misses without harm to patients via local risk management systems that feed into the [National Reporting and Learning System](#).

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Letters and drug alerts sent to healthcare professionals in June 2020

Coronavirus (COVID-19) updates

Healthcare professionals are reminded that the MHRA continue to provide guidance related to coronavirus (COVID-19), including for medicines, on our [dedicated guidance page](#).

[Lopinavir-ritonavir: RECOVERY trial finds no clinical benefit in COVID-19](#)

Comparison of 1596 patients randomised to lopinavir-ritonavir with 3376 patients randomised to usual care found no significant difference in the primary endpoint of 28-day mortality. The trial arms for these medicines have subsequently closed.

[Remdesivir for patients hospitalised with COVID-19 \(adults and children of 12 years and older\)](#)

An interim clinical commissioning policy to define routine access to remdesivir in the treatment of COVID-19 across the UK. This follows confirmation of a [Conditional Marketing Authorisation \(CMA\) by the European Medicines Agency \(EMA\)](#) for the use of remdesivir in the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. The Early Access to Medicines Scheme (EAMS) put in place in May 2020 has now ended. See [SPC for remdesivir](#).

Use the [dedicated COVID-19 Yellow Card site](#) to report suspected side effects in COVID-19 treatment. See [Drug Safety Update article from May 2020](#) for details.

Safety letters – June 2020

In June 2020, the following letters were sent or provided to relevant healthcare professionals related to safety procedures:

- [Ondexxya: signal of erroneous assay results for levels of antifactor Xa activity with use of andexanet alfa](#)
- [5-Fluorouracil \(i.v.\), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe and fatal toxicity](#)
- [Flucytosine: Updated recommendations for the use in patients with dihydropyrimidine dehydrogenase \(DPD\) deficiency](#)
- [Myalepta \(metreleptin\) 5.8 mg vial: inconsistency in the English-language package leaflet \(PL\)](#)
- [Viaflex Specials products containing sodium chloride, heparin sodium, potassium chloride and magnesium sulfate: incorrect information on the primary and secondary labels](#)
- [Brinzolamide 10mg/Timolol Maleate 5mg eye drops: omission of legal category of prescription only medicine \(POM\) on packaged cartons in the UK](#)

Supply-related letters – June 2020

In June 2020, the following letters were sent or provided to relevant healthcare professionals to support the supply of medicines in the UK:

- [Diprivan 10 mg/ml \(1%\) Emulsion for Injection or Infusion \(propofol\): Interim supply of Stock to Mitigate Supply Disruption](#)
- [Belvo 250 mg gastro-resistant tablets: extension of shelf life for two batches](#)
- [EpiPen \(Adrenaline\) Auto-Injector 0.3 mg: supply of a batch \(no. 9FM766\) with US-labelled auto-injectors packaged in UK cartons with a UK leaflet](#)
- [Semglee ▼ 100 units/ ml x 3ml prefilled pens \(Insulin glargine\): Interim Supply of Polish Stock to Mitigate Supply Disruption](#)
- [Finomel emulsion for infusion \(1435ml - 1101320\): interim supply of Belgian stock to mitigate supply disruption \(42% glucose solution, a 10% amino acid solution with electrolytes, and a 20% lipid emulsion\)](#)
- Adoport (tacrolimus) 2mg capsules: limited number of packs with [Italian](#), [Spanish](#), [Dutch](#), and [Nordic](#) blister foil

Drug alerts – June 2020

[Class 2 Medicines Recall: Epistatus \(Midazolam\) 10mg/mL Oromucosal Solution \(Multi Dose Bottles\), EL \(20\)A/25](#). Issued 8 June 2020. Specific batches of Epistatus (Midazolam) 10mg/mL Oromucosal Solution (multi-dose bottles) are being recalled due to a potentially faulty and incorrectly engaged child-resistant container closure.

[Class 4 Medicines Defect Information: Depo-Provera 150mg/mL Injection \(1mL Vial\) EL \(20\)A/26](#). Issued 30 June 2020. There is the typographical error in active ingredient stated on the label on the vial. The active ingredient should be “medroxyprogesterone acetate” (a long acting contraceptive) however, it is stated as “methylprednisolone acetate” (a corticosteroid). The outer carton and leaflets (Patient leaflet and Healthcare Professional leaflet) list the correct active ingredient

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Medical Device Alerts issued in June 2020

In this monthly update, we highlight selected Medical Device Alerts and notices that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see [Alerts and recalls for drugs and medical devices](#).

- [Philips HeartStart XL Defibrillator/Monitor – therapy selector switch may fail \(MDA/2020/018\)](#). Issued 30 June 2020. Manufactured by Philips – the rotary therapy selector switch may fail resulting in unexpected device behaviours which could lead to a delay or failure in delivering therapy.
- [Philips HeartStart MRx Monitor/Defibrillators - may fail to deliver therapy without alerting the user to a fault in the event of internal damage \(MDA/2020/016\)](#). Issued 17 June 2020. The Philips HeartStart MRx Monitor/Defibrillator MRx may fail to identify a fault and alert the user in the event of internal damage suffered during a drop or due to severe mechanical shock.
- [Results from laboratory-based tests for COVID-19 antibodies using capillary blood sample collection kits may not be reliable \(MDA/2020/015\)](#). Issued 8 June 2020. This covers issues with both laboratory based tests for COVID-19 antibodies (unvalidated sample type) and capillary blood sample collection kits (unvalidated for home use)

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