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 (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, we communicate findings of a cumulative dose-dependent association between cyproterone acetate and the known increased risk of meningioma. Cyproterone for any use is contraindicated for patients with previous or current meningioma. Treatment with high doses for any indication except prostate carcinoma should be restricted to situations in which alternative treatments or interventions are unavailable or considered inappropriate (see page 2).

Next, we issue a reminder of prescribing and vigilance precautions to reduce the risk of bleeding with direct-acting oral anticoagulants (DOACs). We ask all healthcare professionals to remain vigilant for signs and symptoms of bleeding complications during treatment with DOACs, especially in patients with increased risk of bleeding (page 5).

Finally, see page 7 for a summary of letters and alerts sent to healthcare professionals in May 2020. In this article, we provide updates on communications about hydroxychloroquine and dexamethasone in coronavirus (COVID-19) treatment.

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Cyproterone acetate: new advice to minimise risk of meningioma

Risk of meningioma with cyproterone acetate increases with increasing cumulative dose. Use of cyproterone is contraindicated in patients with previous or current meningioma (for all indications) and should only be considered for control of libido in severe hypersexuality or paraphilias in adult men when other interventions are inappropriate.

Advice for healthcare professionals:

- a review has confirmed a cumulative dose-dependent association between cyproterone acetate and the known increased risk of meningioma; the risk is thought to be rare overall, but is highest for doses of 25mg per day and above
- do not use cyproterone for any indication in patients with a meningioma or a history of a meningioma
- be vigilant for symptoms and signs of meningioma (see page 4) in patients taking cyproterone; stop treatment permanently if a meningioma is diagnosed in a patient taking cyproterone
- only use cyproterone for control of libido in severe hypersexuality or paraphilias (sexual deviation) in adult men when other interventions are considered inappropriate
- advice on use of cyproterone in the management of patients with prostate cancer remains unchanged
- for low-dose cyproterone (2mg) in combination with ethinylestradiol, a risk of meningioma has not been demonstrated but since the risk with higher-dose products appears to be cumulative, use is now contraindicated in patients with previous or current meningioma
- report suspected adverse drug reactions associated with cyproterone to the Yellow Card Scheme

Cyproterone acetate and risk of meningioma

Cyproterone acetate is a synthetic progestogen with anti-androgenic activity. High-dose products containing 50–100 milligram (mg) are used in the treatment of prostate cancer (Cyprostat) and hypersexuality disorders (Androcur). Low-dose products containing 2mg cyproterone acetate in combination with 35 microgram (µg) ethinylestradiol (Dianette and Co-cyprindiol) are approved for use in the treatment of acne and hirsutism (see page 4 for full indications). There is also evidence for off-label use of high-dose cyproterone as hormone therapy in gender reassignment and in female patients for conditions related to androgen sensitivity such as acne, hirsutism, and baldness.

The association of high dose (50mg per day) cyproterone acetate with meningioma was first described in 2008 and a warning on the possible risk of meningioma together with a contraindication in patients with meningioma or a history of meningioma was added to the product information for high dose cyproterone products (see Drug Safety Update, October 2009).

New study data for dose-dependent risk

A recent French epidemiological cohort study[1] in women demonstrated that the relationship between cyproterone and meningioma is dose-dependent, and the risk increases with increasing cumulative dose.

1. Weill A, et al. Paris: ANSM. 2019 June.

In the study, patients with a cumulative exposure to cyproterone of between 36g and 60g had an estimated 11-times-higher risk of meningioma than patients with cumulative exposures lower than 3g (see table). A 36g cumulative exposure equates to a daily dose of 100mg cyproterone for 1 year.

Table 1. Incidence and risk of meningioma with cumulative dose of cyproterone

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	Adjusted hazard ratio* (95% confidence intervals)
Slightly exposed (<3g)	4.5 per 100,000	Reference
Exposed to any dose ≥3g	23.8 per 100,000	6.6 (4.0–11.1)
- 12g to 36g	26 per 100,000	6.4 (3.6–11.5)
- 36g to 60g	54.4 per 100,000	11.3 (5.8–22.2)
- more than 60g	129.1 per 100,000	21.7 (10.8–43.5)

*Hazard ratios adjusted based on age as a time-dependent variable and estrogen at inclusion

Review of new data and recommendations

A European review of the new study data concluded that treatment with cyproterone 50mg or 100mg should be restricted to situations in which alternative treatments or interventions are unavailable or considered inappropriate, for all indications except prostate carcinoma. The lowest possible effective dose should be used for all patients. If a patient taking cyproterone at any dose for any indication develops a meningioma, treatment should be stopped immediately and permanently discontinued (see letter sent to healthcare professionals).

Overall, the risk of meningioma is still considered to be rare (between 1 in 1,000 patients and 1 in 10,000 people, depending on the dose and duration of treatment). The risk increases with increasing cumulative doses.

Low-dose cyproterone (2mg) in combination with ethinylestradiol (Dianette, Co-cyprindiol), indicated for the treatment in women of acne and/or hirsutism (see page 4 for full indication) has not been shown to be associated with an increased risk of meningioma. However, as an increased risk is still plausible, low-dose combination products are now contraindicated in patients with meningioma or a history of meningioma. A warning regarding the risk of meningioma has also been added to the product information for low-dose cyproterone products.

Reports in the UK

Up to 12 May 2020, there have been 10 Yellow Card reports in the UK describing meningioma, which were suspected to be associated with high-dose cyproterone used in male hypersexuality (4), gender reassignment (4), and female hirsutism (2). The mean age of these cases was 62.1 years, and all had taken cyproterone for a prolonged time (14–36 years where information was provided). There were no reports of meningioma with low-dose cyproterone acetate in combination with ethinylestradiol.

About meningiomas

Meningiomas are the most common intracranial tumours, with an annual incidence of 6 cases per 100,000 in the general population. They arise from the meningeal coverings of the brain and spinal cord and can be single or multiple. Sex hormones are likely to have a role in the development of meningiomas as approximately 70% express progestogen receptors and 30% express estrogen receptors.[2]

2. Blitshteyn S, et al. J Clin Oncol 2008; 26: 279–82

Meningiomas are usually benign, but as they are space occupying lesions, they can put pressure on neurological structures. This can cause a variety of symptoms including changes in vision, hearing loss or ringing in the ears (tinnitus), loss of smell, headaches that worsen with time, memory loss, seizures, or weakness in extremities. Clinicians should be vigilant for these symptoms and signs in patients taking cyproterone, but should also be aware that meningiomas can be asymptomatic.

Background – indications for cyproterone acetate

Cyproterone acetate 50–100mg (Cyprostat, Androcur) is indicated for

- management of patients with prostatic cancer (1) to suppress "flare" with initial luteinising hormone-releasing hormone (LHRH) analogue therapy; (2) in long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred; and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had orchidectomy

- control of libido in severe hypersexuality and/or sexual deviation in the adult male

Cyproterone acetate 2mg combined with ethinylestradiol 35µg (Dianette, Co-cyprindiol) is indicated for treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

Report on a Yellow Card

Please continue to report suspected adverse drug reactions, including for cyproterone acetate to the MHRA via the Yellow Card Scheme.
You can report suspected side effects electronically via:

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

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Direct-acting oral anticoagulants (DOACs): reminder of bleeding risk, including availability of reversal agents

Remain vigilant for signs and symptoms of bleeding complications during treatment with DOACs (apixaban, dabigatran, edoxaban, rivaroxaban), especially in patients with increased bleeding risks. Specific reversal agents are available for dabigatran (Praxbind▼, idarucizumab), and apixaban and rivaroxaban (Ondexxya▼, andexanet alfa).

Advice for healthcare professionals:

- use caution if prescribing direct-acting oral anticoagulants (DOACs) to patients at increased risk of bleeding (for example, older people or people with renal impairment)
- remain vigilant for signs and symptoms of bleeding complications during treatment, especially patients with increased bleeding risk
- remind patients of the signs and symptoms of bleeding and encourage them to always read the patient information leaflet that accompanies their medicines
- ensure patients with renal impairment receive an appropriate dose (see advice and table on page 7) and monitor renal function during treatment to ensure dose remains appropriate
- specific DOAC reversal agents are available for dabigatran, apixaban, and rivaroxaban
- monitor the reversal effects of andexanet alfa using clinical parameters; anti-FXa assays should not be used to measure the effectiveness of andexanet alfa as the results may not be reliable
- report suspected adverse drug reactions associated with DOACs on a Yellow Card, including thromboembolic or haemorrhagic events

Risk of bleeding with DOACs

Direct-acting oral anticoagulants (DOACs) are approved for a variety of uses related to anticoagulation (see full indications on page 7). Available DOACs include the direct factor Xa inhibitors apixaban (Eliquis), edoxaban (Lixiana▼), and rivaroxaban (Xarelto▼) and the direct thrombin inhibitor dabigatran etexilate (Pradaxa).

Use of DOACs increases the risk of bleeding and can cause serious, potentially fatal, bleeds. We continue to receive reports of bleeds, often life-threatening or fatal, in association with DOACs in patients in the UK. In many reported cases, patients have underlying factors that suggest they are at increased risk of bleeding events.

For this reason, DOACs should be used with caution in patients at increased risk of bleeding such as older people and patients with low body weight or renal impairment. Although routine anticoagulant monitoring is not required for DOACs as it is for vitamin K antagonists, patients (particularly those with an increased bleeding risk) should be made aware of the risk of bleeding and be routinely examined clinically for signs of bleeding or anaemia. Bleeding can occur at any site during treatment with DOACs. Treatment with DOACs should be discontinued if severe bleeding occurs.

DOACs interact with a number of medicines, some of which increase bleeding risk. Refer to product information (Summaries of Product Characteristics linked to above) for advice on use of DOACs with other medicines. Of note, DOACs should not be taken with other anticoagulants. Strong inhibitors of P- glycoprotein or CYP3A4 (or both) increase circulating levels of DOACs therefore may be not recommended or may require DOAC dose reduction.

Dose of DOACs depends on renal function

Exposure to DOACs is increased in patients with renal impairment and it is therefore important that patients receive an appropriate dose depending on renal function. Calculate creatinine clearance (CrCl) in order to determine renal function for dosing of DOACs. Estimated glomerular filtration rate (eGFR) can overestimate renal function and increase the risk of bleeding events (see Drug Safety Update).

Dose adjustment may be necessary if renal function significantly changes during treatment. The product information for dabigatran and edoxaban advises to assess renal function if a decline in function is suspected during treatment (for example, due to hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

DOACs can be used in patients with moderate renal impairment (creatinine clearance of 30mL/min or higher) but a reduced dose may be required depending on the indication. In patients with severe renal impairment (creatinine clearance of lower than 30mL/min) use of dabigatran is contraindicated, while other DOACs should be used with caution or at a reduced dose. Refer to table 1 and product information for specific dosing recommendations.

Table 1. Recommendations for use of DOACs in patients with renal impairment

Severity of renal impairment	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
End stage (<15 CrCl mL/Min)	Contraindicated	Not recommended	Not recommended	Not recommended
Severe (≤29 CrCl mL/Min)	Contraindicated	To be used with caution in some indications; dose reduction is required for other indications	Dose reduction required in all indications	Use with caution in all indications Dose adjustment is required or should be considered in some indications
Moderate (30–50 CrCl mL/Min)	Dose adjustment required or should be considered in some indications	Dose reduction is required in some indications*		Dose adjustment required or should be considered in some indications
Mild (51–80 CrCl mL/Min)	No dose adjustment required		No dose adjustment required	No dose adjustment required
>80 CrCl mL/Min	No dose adjustment required	No dose adjustment required	Should only be used in some indications after a careful evaluation of the individual thromboembolic and bleeding risk	No dose adjustment required

**In patients with serum creatinine ≥1.5mg/dL (133micromole/L) associated with age ≥80 years or bodyweight ≤60kg.*

Management of bleeding and availability of reversal agents

The product information for DOACs includes guidance on the management of bleeds and bleeding complications. Specific reversal agents are available for dabigatran (Praxbind▼, idarucizumab) and apixaban and rivaroxaban (Ondexxya▼, andexanet alfa) but there is currently no specific authorised reversal agent available for edoxaban.

A calibrated quantitative anti-Factor Xa (anti-FXa) assay may help to inform clinical decisions in exceptional situations about use of apixaban, edoxaban, or rivaroxaban, for example in overdose and emergency surgery. However, use of anti-FXa assays should not be used to measure the effectiveness of andexanet alfa as the results may not be reliable. Treatment monitoring should be based mainly on clinical parameters indicative of appropriate response (achievement of haemostasis), lack of efficacy (re-bleeding), and adverse events (thromboembolic events).

Further information about DOACs

DOACs are oral anticoagulants that are increasingly used in UK clinical practice. DOACs are indicated for:

- prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine (2.5mg rivaroxaban only)
- prevention of atherothrombotic events in adult patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events when co-administered with ASA (2.5mg rivaroxaban only)
- prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery (dabigatran, apixaban and rivaroxaban)
- prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age of 75 years and older, diabetes mellitus, prior stroke or transient ischaemic attack (all DOACs)
- treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent events in adults (all DOACs)

DOACs are not recommended in patients with antiphospholipid syndrome. Dabigatran is contraindicated and other DOACs are not recommended in patients with prosthetic heart valves.

Report adverse drug reactions on a Yellow Card

Rivaroxaban (Xarelto▼) and edoxaban (Lixiana ▼) are subject to additional monitoring, and so any suspected adverse drug reactions should be reported to the Yellow Card Scheme. For all DOACs, serious suspected adverse drug reactions, including thromboembolic or haemorrhagic events, should be reported on a Yellow Card.

Any suspected adverse drug reactions associated with any medicine used in patients with confirmed or suspected COVID-19, including medicines to manage long-term or pre-existing conditions such as DOACs, should be reported to the COVID-19 Yellow Card reporting site. By reporting suspected side effects of any medicines used in the context of COVID-19, healthcare professionals can provide valuable evidence to inform decisions on the safe and effective use of medicines as the pandemic evolves.

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Letters and drug alerts sent to healthcare professionals in May 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.

Hydroxychloroquine
On 8 June 2020, we instructed UK clinical triallists using hydroxychloroquine to treat or prevent coronavirus (COVID-19) to suspend recruitment of participants until further data which justifies continuation have been provided, and any additional safety measures have been implemented.

On 17 June, we received a request from the University of Oxford to recommence recruitment to the 'COPCOV' trial investigating hydroxychloroquine in prevention of COVID-19.

The submitted justifications and supporting information were reviewed by us with independent advice obtained from the Commission on Human Medicines (CHM).

On 26 June, it was agreed that sufficient risk mitigation measures had been taken to support recruitment of further participants. These measures included those already in place and additional requested steps including enriching the data collection for comorbidities, additional DSMB oversight, and a specific interim analysis.

Please see our website for more information.

Dexamethasone
On 16 June 2020, the Chief Medical Officer (CMO) issued an alert (see alert on Central Alerting System) confirming that dexamethasone has been demonstrated to have a clear place in the management of hospitalised patients with COVID-19. There were no excess harms identified in using 6mg once per day (either by mouth or by intravenous injection) of dexamethasone in the patient population. Dexamethasone was not used in pregnant women.

Clinicians should therefore consider dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation. Out of hospital treatment is not appropriate.

See Drug Safety Update article from May 2020 on using the new dedicated COVID-19 Yellow Card site to report suspected side effects in COVID-19 treatment.

Supply-related letters – May 2020

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

- Ativan 4mg/ml Solution for Injection (Lorazepam): Temporary supply of a different presentation and changes to the instructions - US product
- Calrecia, 100mmol/l, solution for infusion (calcium chloride): Interim Supply of stock to Mitigate Supply Disruption
- Sirturo▼100mg (bedaquiline): Interim Supply of Irish Stock to Mitigate Supply Disruption
- Pancuronium bromide 2mg/ml: Temporary supply of alternative US product 10mg/10ml (1mg/ml) multiple-dose fliptop glass vials
- Clozaril 25 mg tablets (clozapine): interim Supply of Danish and Swedish Stock to Mitigate Supply Disruption
- Verorab (Rabies Vaccine, Inactivated) Important information for healthcare professionals due to import of Verorab due to a shortage of UK licensed Rabies Vaccine
- Benlysta▼ (belimumab) pre-filled pen: short-term availability of pen for subcutaneous (SC) administration during COVID-19 pandemic in the UK for existing patients receiving belimumab for injection intravenous (IV) administration– letter for England, letter for Scotland
- Clenil Modulite 100mcg (beclometasone): release of batches of different appearance and without dose indicator; actions needed from dispensers

Supply-related letters – June 2020

Up to 15 June 2020, we are aware of the following letters sent or provided to relevant healthcare professionals to support the supply of medicines in the UK:

- 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 blisters foil

Reminder of Emerade recall alerts

Class 2 Medicines Recall: Emerade 500 micrograms solution for injection in pre-filled syringe, PL 33616/0015 (EL(20)A/23. Issued 18 May 2020. We remind healthcare professionals that Emerade 500 microgram pre-filled syringes (pens) were recalled from patients due to an error in one component of the auto-injector believed to cause some pens to fail to activate and deliver adrenaline. See summary in May 2020 Drug Safety Update.

Other drug alerts issued in May 2020

Company led drug alert - Duavive (conjugated oestrogen/bazedoxifene acetate) 0.45mg/20mg Modified Release Tablets – EU/1/14/960/001. Issued 27 May 2020. As a precautionary measure, batches from wholesalers are being recalled due to out-of-specification results from ongoing stability studies. An evaluation of the foil laminate pouch identified oxygen levels above the specified limits, resulting in lower dissolution results for bazedoxifene acetate.

Class 4 Medicines Defect Information: Sodium Benzoate (Amzoate) 2g in 10 mL Sterile Solution for injection, EL (20)A/24. Issued 28 May 2020. The carton label on sodium benzoate (Amzoate) 2g in 10mL sterile solution for injection incorrectly states the concentration of disodium edetate (excipient) as 0.1% w/v (10mg in 1mL) instead of 0.1% w/v (10mg in 10mL). Healthcare professionals are advised to exercise caution when dispensing and administering the product.

See all Drug Alerts and Medical Device Alerts from the MHRA.

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